EFFECTIVENESS OF TREATING TO THE TARGET OF REMISSION STRATEGIES IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS

Laura Steunebrink

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CHAPTER 1

General introduction

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease, with heterogeneity in disease activity as well as progressive joint damage, persistent pain, loss of function and impaired quality of life [1]. RA may present at any age, occurs in an estimated 0.5-1.0% of the general population, and is more frequent in females than in males [2,3].

The disease course of RA is progressive with alternating periods of flares and remission. Permanent remission also occurs, but rarely. Without treatment, RA may lead to severe joint deformations and permanent loss of function. Reported rates of radiographic progression have varied enormously, with previous systematic reviews showing that 39–73% of early RA patients develop one or more erosions in the first 5 years [4,5].

Over the last decades, several major therapeutic changes have impacted the course and severity of RA. The disease is now often recognized earlier and effective treatment often starts before joint destruction has occurred [6]. Nowadays, RA is a more manageable disease than 20 years ago, severe joint damage has become rare and achieving remission and subsequent tapering of medication is now feasible. However, long-term remission is relatively rare and most patients still experience poor long-term outcomes, considerable economic losses and work disability. Since there is no cure for this disease yet, the goal of treatment is still long-term suppression of the inflammatory process in order to achieve sustained clinical remission.

Early recognition and the window of opportunity

After early recognition by general practitioners (GPs) and the identification of RA by a rheumatologist, the next step is to start adequate treatment as soon as possible. It has been shown that delay in initiation of effective treatment is associated with more progression of joint damage [7] and that starting treatment as soon as possible is associated with better clinical results and less joint damage. The evidence from trials using early intensive disease modifying anti-rheumatic drug (DMARD) strategies introduced the concept of a ‘window of opportunity’ and gave rise to early RA (ERA) clinics, supported by the feasibility of long-term remission, as well as improved functional and radiographic outcomes of starting treatment early [6,8–10]. The window of opportunity represents a very early phase of the disease in which therapeutic modification is thought to be more successful, because of an incomplete advanced stage of the disease processes. This window of opportunity has been suggested to encompass the first 12 weeks after symptom onset [6].

Treat to target strategy (T2T)

Although not a new concept to medicine [11], the concept of ‘Treat to Target’ was formally published in 2010 as being integral to the RA treatment paradigm [12]. Treat to target (T2T) had previously been applied successfully in disease domains such as hypertension or diabetes [12]. Central to the T2T concept is the selection of an outcome domain (e.g. hypertension), outcome measure (e.g. sphygmomanometer) and outcome target (e.g. <140mmHg). The outcome domain is then systematically measured and treatment is intensified each time the target is not met.

Likewise, a protocolled T2T strategy provides guidance for the management of RA in daily clinical practice. Treatment strategies in RA have shifted towards early diagnosis, close monitoring of disease activity and intensive use of DMARDs aimed at inducing rapid and sustained suppression of disease activity [13–15]. According to the 2010 EULAR recommendations, we need to strive for a target of remission of disease activity within 3 months. To achieve remission within 3 months, patients should be monitored strictly (‘tight control’), every 1 to 3 months, using a validated measure of RA disease activity, such as the DAS28, and if the target of remission is not reached, treatment should be intensified [15]. Rheumatologists strive to reach the predefined therapeutic goal as soon as possible. Treating RA with DMARDs according to a T2T strategy has been shown to be more effective than traditional routine care [16–18].

The principle of T2T has now become the standard treatment approach in rheumatology and is supported by a number of clinical trials, such as FIN-RACo [9,19], TICORA [20], CAMERA [21,22], CIMESTRA [23,24], and BeSt [25,26]. The T2T approach was arguably first introduced in the TICORA trial, in which intensive outpatient management of patients with RA was compared with routine care [20]. The CAMERA trial subsequently confirmed improvement of clinical efficacy using intensive management [21]. This study made use of a strict protocol and a computerized decision program [21]. The BeSt study was the first trial to compare different initial treatment strategies with a treat-to-target approach in their follow-up [26]. The DREAM cohort study was the first to demonstrate that treat-to-target was feasible in daily clinical practice [17]. The tREACH trial demonstrated the clinical efficacy of induction combination DMARD therapy versus methotrexate (MTX) monotherapy and different glucocorticoid (GC) bridging therapies [27,28]. The FIN-RACo group compared the efficacy and tolerability of a DMARD combination with a single drug treatment [9]. The CareRA trial compared the efficacy and safety of different initial DMARD combinations and GC bridging schemes in high-risk patients with early RA [29]. The CARDERA trial addressed the merits of intensive therapy with conventional

drugs in early active RA, assessing the relative benefits of two DMARDs, adding prednisolone to one DMARD, or using two DMARDs with prednisolone [30]. All of these studies had a T2T strategy design. Recent treat to target studies suggest that clinical remission is now an achievable therapeutic goal in RA in both randomized controlled trials and in daily clinical practice [16,17,31–33]. Chapter 3 examines 1-year remission rates of a new T2T protocol for patients with early RA in daily clinical practice.

Disease activity

According to the EULAR recommendations, the primary target for the treatment of RA should be clinical remission, i.e. the essential absence of activity of the disease [15]. To evaluate disease activity and treatment success, different composite scores can be used. A high score generally means high disease activity and a need to intensify treatment. Most disease activity scores were developed during the 1990s, the first composite score was the disease activity score (DAS). New disease activity measures were developed since then, including adapted and simplified versions of the original DAS, like the disease activity score in 28 joints (DAS28) [34], the clinical disease activity index (CDAI) [35] and the simplified disease activity index (SDAI) [36]. The DAS28 [37] arguably seems to be most appropriate in daily clinical practice [38]. The DAS28 [39] is a widely used and valid index measure of RA disease activity in individual RA patients. The DAS28 consists of four measures: a tender joint count (TJC) and a swollen joint count (SJC), both from 28 evaluated joints, along with the erythrocyte sedimentation rate (ESR), and a visual analogue scale (VAS) of patient's general health (GH) [39], and is calculated according to the following formula:

$$0.56\sqrt{(TJC28)} + 0.28\sqrt{(SJC28)} + 0.70\ln(ESR) + 0.014(VAS \text{ of GH})$$

Regular evaluation of disease activity can give a good overview of the course of disease activity over time and the response to treatment in daily clinical practice. The European League Against Rheumatism (EULAR) has formulated criteria by which patients can be classified as having high disease activity ($DAS28 > 5.1$), moderate disease activity ($3.2 > DAS28 \leq 5.1$), low disease activity ($2.6 \leq DAS28 \leq 3.2$) or remission ($DAS28 < 2.6$). The EULAR response criteria were classified as followed: good responders were patients with an improvement of > 1.2 and a present score of ≤ 3.2 ; moderate responders were patients with an improvement of > 0.6 to ≤ 1.2 and a present score of ≤ 5.1 , or an improvement of > 1.2 and a present score of > 3.2 ; non responders were patients with an improvement of ≤ 0.6 , or patients with an improvement of > 0.6 to ≤ 1.2 and a present score of > 5.1 [40] (Table 1).

Table 1: *The EULAR response criteria using DAS and DAS28*

Disease activity level	DAS at endpoint	DAS28 at endpoint	Improvement in DAS or DAS28 from baseline		
			>1.2	> 0.6 and ≤ 1.2	≤ 0.6
<i>Low</i>	≤ 2.4	≤3.2	Good	Moderate	None
<i>Moderate</i>	>2.4 and ≤3.7	>3.2 and ≤5.1			
<i>High</i>	>3.7	>5.1			

*Data from[40,41]

Monotherapy versus combination therapy

The available treatments in rheumatology have also changed during the last decades. In the past century, the pyramid model had been accepted as the conventional treatment strategy for RA patients, in which only non-steroidal anti-inflammatory drugs (NSAIDs) were used in early or mild disease [42]. The present century came with new treatments that were developed as a result of the unmet need of effective treatment options and new insights in the pathogenesis of the disease. Conventional synthetic DMARDs need approximately three to six months to be fully effective, and during this period joint damage may already have developed. Subsequently, the reverse pyramid model became more and more popular, in which more aggressive medication was prescribed early in the disease course before damage already was effectuated.

Rheumatologists can now use four types of DMARDs: 1. classical or conventional synthetic (cs)DMARDs, 2. biological (b)DMARDs, 3. targeted synthetic (ts)DMARDs and 4. corticosteroids. Currently, the goal of therapy is not only symptom relief and early remission, but in particular the prevention of long-term structural damage and functional decline. Nowadays, treatments start with the use of DMARDs as soon as possible after the diagnosis is made. Many trials in patients with recent-onset RA, often defined as a symptom duration of less than two years, have shown that early introduction of DMARDs more effectively suppresses disease activity, preserves functional ability and slows radiographic damage than delayed start of treatment [7,43].

Of the csDMARDs, MTX has been the most commonly used drug to treat RA since the 1980s. MTX remains the first-line treatment choice according to recent EULAR guidelines [15]. MTX has also been called the anchor drug in RA [42], firstly due to its excellent long-term effectiveness in most patients, secondly due to its favorable long-term safety profile, and thirdly because it is the most commonly used DMARD and because of its acceptance as the most effective DMARD by the community of rheumatologists [42,44]. Several studies further suggested that combination therapy, with two or three drugs, may be more effective than single drug therapy [9,27,30,45–47]. In addition, combination therapy has been shown to be effective

and safe in early RA patients [9,27,46,48–55]. Even more studies suggest the benefit of starting DMARD combination therapy, in particular DMARDs in combination with glucocorticosteroids, instead of monotherapy [22,26,47,50,56,57].

Deciding which drugs to use in combination therapy is difficult because the mode of action of most DMARDs is still uncertain. MTX + hydroxychloroquine (HCQ) is by far the most commonly prescribed DMARD combination by rheumatologists in the US [58]. Several authors suggested that the combined use of HCQ and MTX can decrease the toxicity of MTX [59,60]. The protective effect of HCQ may occur through increasing the number and size of lysosomes as well as stabilizing the lysosomes [59]. In contrast to the working-mechanism of MTX, glucocorticoids (GCs) act very quickly. GCs have a long history of good efficacy and safety in the treatment of RA. According to the EULAR guidelines, GCs at low to moderately high doses can be added to synthetic DMARD monotherapy or combinations of synthetic DMARDs as bridging therapy, as GCs have shown to provide benefit as an initial short-term treatment. Conversely, long-term GC use is questioned because adverse events, such as GC induced osteoporosis and serious infections, are mainly associated with higher cumulative doses and therefore GCs are often prescribed for short periods of time only. GCs can be used orally, but also intramuscular or locally in the form of intra-articular injections. Addition of low-dose GCs, most often in combination with MTX, has been shown to significantly improve structural outcomes and to reduce symptom severity in patients with RA [61]. Chapter 4 compares the effectiveness of a step-up MTX monotherapy approach versus an initial DMARD combination approach in daily clinical practice.

Remission

The concept of disease remission can be interpreted in multiple ways. In some contexts it indicates (significantly) decreased disease severity, in other contexts it implies that the disease has disappeared entirely or at least that evidence of residual disease activity is absent. Some definitions indicate very low disease activity states while other definitions describe remission as the complete absence of disease, with no detectable symptoms, signs or disease markers. One of the remaining questions is whether remission is reached when a patient has no disease activity, but is still receiving medication, or if the patient must be off treatment to be considered to be in remission, i.e. drug free remission [62].

Within the concept of remission, we can define two clinical states. Firstly, remission can be defined as a state in which there is no disease activity at all and without any use of drugs, which seems compatible with curing of RA. This state requires the absence of clinical signs and

symptoms related to arthritis and absence of progression of radiographic damage during a specific time period, without the use of DMARDs. Only a small percentage of patients achieve this form of remission, which could be either the result of DMARD use or the result of a natural disease course. Secondly, the term remission is often used to describe a state of disease in which RA patients have limited or no signs of symptoms of disease activity while still using DMARDs. This state of remission refers more to a state that signifies that a patient is optimally being treated to present standards [63].

The latter definition of clinical remission has now become a realistic goal in RA. However, there is a wide variety of definitions of clinical remission, based on single measures, cut-off values on composite indices and Boolean criteria. The ACR remission criteria [64] and remission based on the CDAI and on the SDAI are generally considered to be strict. Remission based on DAS, DAS28 and single measures are less strict and classify a higher percentage of patients in remission. Obviously, the prevalence of remission in a population thus varies substantially with the definitions used, and this hinders the interpretation of research outcomes and comparison between studies. Therefore, there is a need for more consistency and stringency in remission definitions. The ACR/EULAR committee proposed two definitions of remission in clinical trials [65]. One is a Boolean-based definition, which is more categorical in structure than the traditional definition from Pinals et al. [64] and the other is based on a composite index of RA activity, the SDAI [36,66].

As a result of the availability of new medications and superior treatment strategies, remission has now become an achievable and realistic goal in daily clinical practice [31,67]. Furthermore, sustained remission, i.e. disease remission over longer periods of time, and also sustained drug-free remission is nowadays achievable, albeit in smaller proportions of patients [68,69]. An increasing number of patients in RCTs and pragmatic studies now achieve remission or low disease activity with good clinical outcomes [20,21,55].

Presently, however, the concept of cure in RA is not realistic, so the aim of current treatment is a relevant reduction in disease activity in the hope of achieving prolonged remission. Remission rates vary widely between studies, with reported rates varying from 10% to 78% [70]. As noted above, remission rates are difficult to compare because of the use of different remission criteria and different study designs. Several of the previously mentioned treat to target studies have reported on remission rates, albeit again using different definitions of remission and follow-up. The TICORA study, a single-blinded randomized controlled trial (RCT) randomly allocated patients to an intensive group or routine group. This study reported a remission rate of 65% (defined as DAS44 < 1.6) after 18 months of follow up [20]. The BeSt study, a multicenter RCT

allocated patients to 4 different treatment strategies; sequential DMARD monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with tapered high-dose prednisone (group 3) and an initial combination therapy with the tumor necrosis factor antagonist infliximab (group 4). The BeSt reported a DAS44 remission rate of 32% after 12 months [26]. The CAMERA trial, a multicenter open label strategy trial, randomly assigned patients to the intensive strategy group or the conventional strategy group. This study reported remission rates of 35% in the first 12 months (defining remission as no swollen joints and at least two out of three of the following criteria: number of tender joints ≤ 3 , ESR ≤ 20 mm/h and VAS general well-being ≤ 20 mm) [21]. The IMPROVED study, a multicenter clinical trial in recent onset RA and undifferentiated arthritis (UA) patients, found a DAS44 remission rate of 61% after 4 months [71]. The CareRA trial, a prospective 2-year investigator-initiated multicenter RCT, allocated high-risk patients into three different treatments. This trial reported a DAS28-CRP remission rate ranging from 68.1-73.6% within 4 months [29]. Data on remission rates in daily clinical practice cohorts, however, are scarce. Therefore, in this thesis we will describe and compare remission rates in two T2T cohorts in daily clinical practice (chapters 3 and 4).

Predictors of remission

The ultimate goal in treating RA is being able to predict the course of the disease in order to offer personalized treatment for each patient [72]. In the past, treatment of RA aimed at decreasing disease activity to reach a state of low disease activity. Currently, the perceived achievable goal is disease remission [73–75]. Early diagnosis and intensive combination treatment have made substantial decreases in disease activity, structural damage and long-term disability [25,31,44,50,76–78]. Data from several studies, however, still show that a proportion of patients in daily clinical practice fail to become free of signs and symptoms [79–84]. At the moment of diagnosis, it is still a challenge to predict whether an individual patient will respond well to a certain treatment. Therefore, it is important to identify predictors of reaching remission in the early stages of the disease, so that patients with poor prognostic factors can perhaps receive more aggressive individualized treatment. The literature currently provides a wide range of different predictors of achieving remission. A literature review of 18 studies examining the predictive value of baseline variables indicated a number of independent predictors of remission, including baseline clinical and laboratory characteristics and genetic markers [85]. Male sex [89–94] and higher age [88,91] were both shown to be independent predictors of remission. Patients with a positive rheumatoid factor (RF) status at baseline were less likely to achieve remission [79,86,88,92,93]. Likewise, anti-cyclic citrullinated peptide (anti-CCP) antibody status [82], higher

level of C reactive protein (CRP) [94] and presence of erosions at baseline [79] were also shown to be predictive for not achieving remission rapidly. A multiparameter prospective study, reported low disease activity score, lower Ritchie score, and lower baseline total radiographic score as prognostic factors for remission in early RA [79].

Although a wide range of predictors has been identified, robust and accurate prediction models for use in clinical practice are still lacking. Chapter 3 will additionally explore predictors of reaching remission in an initial DMARD combination therapy in daily clinical practice.

Radiographic damage, progression and predictors

RA is a very heterogeneous disease in which outcomes are difficult to predict. The course of radiographic progression differs between patients and although some patients do not develop joint damage at all, the majority of the patients do. According to previous systematic reviews, 39–73% of early RA patients develop one or more erosions in the first 5 years [4,5]. Radiographic progression can follow a linear or sigmoid curve (s-curve), but is generally more rapid during the first two years of the disease. Important to know is that most radiographic progression occurs during the first 5 years of the disease [95].

Over the years, several scoring methods for assessing joint damage as visible on radiographs have been developed. The most well-known are the Larsen- and Sharp methods and their subsequent modifications [96–99]. The main difference between these two methods is that Larsen applies a global grading of joint damage, while Sharp quantifies the number and size of erosions per joint and the amount of joint space narrowing (JSN) [100]. The Sharp / van der Heijde (SvdH) score assesses erosions and joint space narrowing separately in radiographs of the hands and feet, and has a range from 0 to 448. The SvdH method scores the presence of erosions in 32 joints of hands and wrists (graded from 0 to 5) and in 12 joints of the feet (graded from 0 to 10), and the presence of joint space narrowing in 30 joints of the hands and wrists (graded from 0-4) and in 12 joints of the feet (graded from 0 to 4) [101,102]. The total erosions score in the hands can range from 0 to 160 and in the feet the erosion score can range from 0-120. The maximal range for erosions is 280 units. The total joint space narrowing score of the hands can range from 0 to 120 and at the feet the narrowing score can range from 0 to 48. The maximal range for joint space narrowing is 168 units (Figure 1). According to Bruynesteyn et al., the SvdH score was the only system that was both sensitive (79%) and specific (84%) for detecting radiographic changes that justify a change in DMARD therapy according to a panel of experts [103].

Figure 1: Sites and surfaces for assessment of erosions and joint space narrowing of hands and feet. **A:** joints were scored for joint space narrowing with two vertical stripes. **B:** joints and surfaces of the joints were scored for erosions with black dots.

**Drawing by myself based on the article of van der Heijde[101]*

The clinical disease course of RA varies widely, ranging from mild to aggressive, whereby inflammation may cause severe disabilities for patients. Inflammatory disease activity is considered to be the driver of radiographic progression. Immediately after a diagnosis of RA is made, it is essential to determine whether the disease course will be mild, moderate, severe, or show no progression at all. The use of early and aggressive targeted treatment with DMARDs has already been shown to decrease disease activity and slow radiographic damage [20,26,50,51,104–107]. Literature suggests that disease progression occurs at any stage of the disease but the fastest rate occurs early on in the disease [108]. Specifically, the majority of damage experienced in RA occurs within the first 5 years of disease onset [109]. In about 10% of patients with RA, severe joint damage with important functional disability occurs within 2 years of disease onset [110]. These patients may require a more intensive treatment approach than those with less severe disease [111]. Consequently, there is a need for accurate predictors of radiographic progression. Prognostic markers for RA severity, especially in patients with rapidly progressing disease, will play an increasingly important role in the management of RA because timely initiation of

therapies that provide rapid and effective suppression of inflammation can halt structural damage [105,112,113].

Many retrospective and prospective studies have already examined the course and structural outcome of RA and have investigated the role of potential prognostic factors, including clinical signs of disease activity and systemic indices of inflammation [114–118]. However, the rate of radiographic progression and the prognostic factors of radiographic progression have varied widely between studies. Main prognostic factors for patients at risk for a poor prognosis appear to be female sex, RF positivity, higher ESR or CRP, high baseline joint damage, and anti-cyclic citrullinated peptide antibody (anti-CCP) positivity [116,117,119–121]. RF is one of the most powerful predictors of joint damage [115–117,122]. Although several predictors of radiographic progression have been described in the literature, unfortunately these results have been conflicting. Therefore, there is still a need for reliable predictors to select patients who might benefit from a more intensive treatment.

Additionally, several RCTs have shown that combination therapy with DMARDs and glucocorticoids or with bDMARDs is more effective in achieving good clinical outcomes and preventing joint damage than DMARD monotherapy in early RA patients [9,25,50,123]. Even in daily clinical practice, initial DMARD combination therapy with steroids (ICTS) is more effective than initial DMARD monotherapy (IMT) [124]. Additionally, those patients following an ICTS approach had less rapid radiographic progression after one year, despite severe baseline disease characteristics [125]. Chapter 5 compares the 1-year radiographic progression rates between initial step-up MTX monotherapy versus initial DMARD combination therapy and explores baseline predictors of progression.

Early and rapid reduction of disease activity substantially reduces radiographic damage [18,53]. However, even in patients with a moderate or low disease activity, radiographic progression may still occur. Moreover, despite intensive treatment, early joint damage still predicts further radiographic progression in the long-term [126]. While patterns of radiographic progression seems to be linear at group level, they may be highly variable within the individual RA patient over time [127,128]. The exact individual relationship between disease activity and the radiographic course in patients is still not clear. Therefore, chapter 7 will investigate the individual relationship between disease activity and radiographic progression in order to optimize treatment strategies.

PROMS and T2T

The patient perspective and patient-reported outcomes (PROMs) have become increasingly recognized as important in rheumatic diseases over the past years. PROMs have become important in routine follow-up, in observational studies and in clinical trials [129–131]. The use of PROMs is feasible in daily clinical care as they may be easily administered and can be answered by patients in a short time period. PROMs can provide important information to the treating rheumatologists. Rheumatologists can use PROMs to either evaluate the healthcare being delivered to groups of patients or for evaluating the effects of treatments in individual patients. Physicians utilizing PROMs can thus gain knowledge about their patients' health, function status, treatment preferences, satisfaction, symptoms and quality of life. PROMs may also facilitate understanding the development of health or functioning of patients at an individual level and in comparison with other patients (groups).

PROMs can additionally be used during consultations and in the monitoring health of patients. Also, PROMs can be used to evaluate and improve the quality of care and to measure and compare the performance of healthcare providers [132]. PROMs may thus provide information for various transparency purposes, such as choice and accountability information for patients, policy makers and healthcare insurers. Knowledge of a patient's wellbeing and insight into how this is influenced by treatment is an unquestionable need for daily clinical practice since the primary goal of a rheumatologist is to improve the patient's wellbeing, and not to merely control the disease.

Before starting a treatment, the patient's opinions and goals should be considered, since expectations and values might differ from their physician's [133,134]. PROMs may help patients to express their perception of the disease and their expectations and values on mental, social and physical functioning [135]. The simplest forms of PROMs are single questions, e.g. about pain, fatigue, morning stiffness and global disease activity, scored on either a VAS or numeric rating scale (NRS). These measures are widely applied in RA, either alone or as part of more extensive patient-reported questionnaires. Most PROMs however are comprehensive questionnaires, often containing 20 or more items for the patient to fill out, such as those for health-related quality of life or disability.

Measurement of both PROMs and (clinical) disease activity is of additional value in daily clinical practice in clinical decision-making, thereby providing patients the best available treatment approach [129,131]. As with any treatment, the ultimate goal is not merely to suppress disease activity but to restore patients' health and functioning to pre-disease levels or at least to minimize disease-related impairments [12,136]. It is increasingly recognized that to this end it is

relevant to assess treatment benefits using a comprehensive set of outcomes that includes disease outcomes relevant to the patient as well as markers of inflammatory activity and physical function. For instance, the Outcome Measures in Rheumatology (OMERACT) initiative recently endorsed an extended set of outcomes for the assessment of flares, which includes the patient-reported outcome domains of fatigue, stiffness, self-management and participation in addition to the 7 core outcome domains of pain, physical function, tender joints, swollen joints, acute phase response, patient global and physician global that have been endorsed independently by the American College of Rheumatology (ACR) and World Health Organization/International League Against Rheumatism [137]. Despite this recently increased attention for the patient's perspective in RA outcome assessment, not much is currently known about the relationship between favourable clinical outcomes achieved using 'T2T' and patient's subjective evaluations of overall health changes. Chapter 6 examines the extent to which discrepancies between patients' judgements of improvement and clinical improvements could be explained by changes in specific domains of health-related quality of life (HRQoL).

SF36

Health-related quality of life (HRQoL) is a multidimensional concept that incorporates physical, psychological and social aspects. For measuring the state of and changes in health, different questionnaires can be used. There are three main groups of instruments; generic, disease-specific and domain-specific. Generic instruments measure the quality of life in terms of all aspects related to health, regardless of the presence or absence of specific diseases. Disease-specific instruments measure the effects of a particular disease. Domain-specific instruments include only one particular domain of quality of life, for example physical function. Generic questionnaires, which measure health at a global level, are most widely applicable. Alternatively, disease-specific questionnaires have the problem of incomparability with other disease-specific questionnaires. There are several commonly used generic and validated questionnaires to measure HRQoL, like the SF-36, SF-12 and the EQ-6D.

The 36-item short-form (SF-36) was constructed to survey health status in the Medical Outcomes Study. The SF-36 was designed for use in clinical practice and research, health policy evaluations, and general population surveys. The SF-36 asks patients for their views about their health. This information can help visualize how patients feel and how well they are able to do their daily activities. The SF-36 is organized into eight health concepts/domains whose scores are obtained via summation and transformation of item values into a scale score between 0 and 100, where higher values represent better health status: 1) limitations in physical activities because of

health problems (Physical Function, PF, 10 items); 2) limitations in social activities because of physical or emotional problems (Social Function, SF, 2 items); 3) role limitations in usual role activities because of physical health problems (Physical Role, RP, 4 items); 4) bodily pain (BP, 2 items); 5) mental health (psychological distress and well-being, MH, 5 items); 6) role limitations in usual role activities because of emotional problems (Emotional Role, RE, 3 items); 7) vitality (energy and fatigue, VT, 4 items); and 8) general health perceptions (GHP, 5 items). Furthermore, domains can be merged into two components: the physical component score (PCS; including PF, RP, BP and GHP) and the mental component score (MCS; VT, SF, RE and MH) [138].

Health Assessment Questionnaire (HAQ-DI)

Physical function is a very important outcome domain in both RA research and daily clinical practice. A change in physical function may indicate a change in disease activity (e.g. poorer physical function can be caused by active disease), pain or structural changes. Measures of functional disability have been developed in order to score how well patients were able to perform their daily living activities. One of the most widely used questionnaires to measure physical function and disabilities in daily living in RA patients is the Health Assessment Questionnaire Disability Index (HAQ-DI). The HAQ-DI consists of 24 questions regarding eight distinct categories: dressing, arising, eating, walking, hygiene, reach, grip and usual activities, with each question scored from 0 (without any difficulty) to 3 (unable to do) [139]. The overall score of the HAQ-DI can range from 0-3, where a higher score represents worse physical function.

The thesis

Major breakthroughs have been made in the management of RA. However, there are still some challenges to be achieved in the treatment of RA. In this thesis we will further discuss several of these important challenges.

As mentioned before, T2T is widely accepted as the standard of care for patients with rheumatoid arthritis (RA). Our group has previously shown in a pragmatic study in real-life that a T2T strategy is more effective than traditional routine care in terms of reducing disease activity and even cost-effective in the long term [17,18,140,141]. However, several questions still remained unclear. What is the most optimal therapeutic strategy in RA patients? Should we prefer initial combination therapy over step-up monotherapy? This thesis will give more insight in these unanswered questions by a comparison of two T2T strategies in early RA patients: a step-up

approach starting with methotrexate (MTX) monotherapy (cohort I) versus an initial DMARD combination approach (cohort II). The results of the studies in this thesis will contribute to a wider implementation of existing T2T strategies. Participating patients can benefit from optimal treatment therapy through targeted treatment, with timely changes in medication in case of insufficient treatment, remission adjustments and side effects. Patients also gain insight into the progress of their own disease. It is thus expected that prolonged suboptimal treatment of RA can be prevented and that patients reach the ultimate treatment target as soon as possible: safe long-term remission.

The DREAM remission induction cohorts

All data used in this thesis were collected within two remission induction cohorts of the DREAM registry (www.dreamregistry.nl). The DREAM (**D**utch **RhE**umatoid **A**rrhritis **M**onitoring) registry is a multicenter registry that aims to evaluate the effectiveness, toxicity and use of medication in patients with RA in daily clinical practice. Both strategies were consistent with daily clinical practice and complied with current guidelines for the treatment of RA and regulations regarding the prescribing of biologicals. The first cohort (strategy I) started in 2006, and the second (strategy II) in 2012.

Consecutive patients with newly diagnosed RA were invited to participate. Patients in both strategies were treated according to a T2T strategy with protocolized treatment adjustments aiming at remission ($\text{DAS28} < 2.6$). Briefly, the main differences between both strategies were; the start and dosage of medication step-up monotherapy (strategy I) versus initial combination therapy with an optional intramuscular injection with triamcinolone (strategy II), and also the time moments of evaluation. In both strategies, all patients were adults aged ≥ 18 years with a clinical diagnosis of RA and a disease duration (defined as time from the first symptoms to the diagnosis of RA) ≤ 1 year, a $\text{DAS28} \geq 2.6$ and participating patients had not received previously DMARDs and/or prednisolone. Patients in strategy I were evaluated at weeks 0, 8, 12, 20, 36, 52 and every 3 months thereafter, in strategy II at months 1, 2, 4, 6, 9, 12, 15 and every 3 months thereafter.

In both strategies patients were treated according to a protocolized T2T strategy aiming at remission, defined as $\text{DAS28} < 2.6$. At each visit, disease activity was assessed using the DAS28. Therapy adjustments were protocolized and based on the DAS28 score, with intensification of treatment if the predefined targets had not been reached. If $\text{DAS28} < 2.6$ was reached for the first time, the treatment was continued and medication was not changed. If there

was sustained remission ($\text{DAS28} < 2.6$ for six consecutive months), the medication was gradually tapered and eventually discontinued. In the case of a disease flare ($\text{DAS28} \geq 2.6$), the last effective medication or medication dose was restarted and treatment could subsequently be intensified if needed. In individual patients with contraindications for specific medications, protocol deviations were allowed. Concomitant treatment with nonsteroidal anti-inflammatory drugs, prednisolone at a dosage of ≤ 10 mg/day, and intra-articular corticosteroid injections was permitted. Figure 2 and 3 represents the treatment protocols of both strategies.

Start

Figure 2. Treatment of the DREAM remission induction cohort, strategy I

MTX= methotrexate SSZ=sulfasalazine

**Anti-tumour necrosis factor α (anti-TNF α) therapy could be prescribed to patients with at least moderate disease activity (Disease Activity Score in 28 joints (DAS28) ≥ 3.2) and in whom treatment with at least two disease-modifying antirheumatic drugs had failed (including methotrexate (MTX) 25mg/week).*

***Anti-TNF α therapy could be continued only if the DAS28 had decreased by > 1.2 after 3 months.*

Figure 3. Treatment of the DREAM remission induction cohort, strategy II

*MTX= methotrexate ** HCQ = hydroxychloroquine ***SSZ = sulfasalazine

REFERENCES

1. Combe B. Progression in early rheumatoid arthritis. *Best Pract. Res. Clin. Rheumatol.* 2009;23:59–69.
2. Alamanos Y, Voulgari PV DA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. *Semin. Arthritis Rheum.* 2006;182–8.
3. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann. Rheum. Dis.* 2014;73:1316–22.
4. Scott DL, Pugner K, Kaarela K, Doyle D V, Woolf A, Holmes J, et al. The links between joint damage and disability in rheumatoid arthritis. *Rheumatology (Oxford).* 2000;39:122–32.
5. Scott DL, Smith C, Kingsley G. Joint damage and disability in rheumatoid arthritis: an updated systematic review. *Clin. Exp. Rheumatol.* 21:S20–7.
6. Quinn MA, Emery P. Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention. *Clin. Exp. Rheumatol.* 2003;21:S154–7.
7. Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. *Arthritis Rheum.* 2006;55:864–72.
8. Boers M. Understanding the window of opportunity concept in early rheumatoid arthritis. *Arthritis Rheum.* 2003;48:1771–4.
9. Möttönen T, Hannonen P, Leirisalo-Repo M, Nissilä M, Kautiainen H, Korpela M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet.* 1999;353:1568–73.
10. Mäkinen H, Kautiainen H, Hannonen P, Möttönen T, Leirisalo-Repo M, Laasonen L, et al. Sustained remission and reduced radiographic progression with combination disease modifying antirheumatic drugs in early rheumatoid arthritis. *J. Rheumatol.* 2007;34:316–21.
11. Atar D, Birkeland KI, Uhlig T. “Treat to target”: moving targets from hypertension, hyperlipidaemia and diabetes to rheumatoid arthritis. *Ann. Rheum. Dis.* 2010;69:629–30.
12. Smolen JS, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann. Rheum. Dis.* 2010;69:631–7.
13. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann. Rheum. Dis.* 2007;66:34–45.
14. Smolen JS, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann. Rheum. Dis.* 2010;69:631–7.
15. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann. Rheum. Dis.* 2014;73:492–509.
16. Schipper LG, Vermeer M, Kuper HH, Hoekstra MO, Haagsma CJ, Den Broeder AA, et al. A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. *Ann. Rheum. Dis.* 2012;71:845–50.

17. Vermeer M, Kuper HH, Hoekstra M, Haagsma CJ, Posthumus MD, Brus HLM, et al. Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. *Arthritis Rheum.* 2011;63:2865–72.
18. Vermeer M, Kuper HH, Moens HJB, Drossaers-Bakker KW, van der Bijl AE, van Riel PLCM, et al. Sustained beneficial effects of a protocolized treat-to-target strategy in very early rheumatoid arthritis: three-year results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort. *Arthritis Care Res. (Hoboken).* 2013;65:1219–26.
19. Puolakka K, Kautiainen H, Möttönen T, Hannonen P, Korpela M, Hakala M, et al. Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. *Arthritis Rheum.* 2005;52:36–41.
20. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet.* 2004;364:263–9.
21. Verstappen SMM, Jacobs JWG, van der Veen MJ, Heurkens AHM, Schenk Y, ter Borg EJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann. Rheum. Dis.* 2007;66:1443–9.
22. Bakker MF, Jacobs JWG, Welsing PMJ, Verstappen SMM, Tekstra J, Ton E, et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. *Ann. Intern. Med.* 2012;156:329–39.
23. Hetland ML, Hørslev-Petersen K. The CIMESTRA study: intra-articular glucocorticosteroids and synthetic DMARDs in a treat-to-target strategy in early rheumatoid arthritis. *Clin. Exp. Rheumatol.* 30:S44-9.
24. Hetland ML, Stengaard-Pedersen K, Junker P, Lottenburger T, Hansen I, Andersen LS, et al. Aggressive combination therapy with intra-articular glucocorticoid injections and conventional disease-modifying anti-rheumatic drugs in early rheumatoid arthritis: second-year clinical and radiographic results from the CIMESTRA study. *Ann. Rheum. Dis.* 2008;67:815–22.
25. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJSM, Hazes JMW, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann. Intern. Med.* 2007;146:406–15.
26. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJSM, Hazes JMW, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. *Arthritis Rheum.* 2008;58:S126-35.
27. de Jong PH, Hazes JM, Barendregt PJ, Huisman M, van Zeben D, van der Lubbe PA, et al. Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. *Ann. Rheum. Dis.* 2013;72:72–8.
28. de Jong PH, Hazes JM, Han HK, Huisman M, van Zeben D, van der Lubbe PA, et al. Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. *Ann. Rheum. Dis.* 2014;73:1331–9.
29. Verschueren P, De Cock D, Corluy L, Joos R, Langenaken C, Taelman V, et al. Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: the CareRA trial. *Ann. Rheum. Dis.* 2015;74:27–34.

30. Choy EHS, Smith CM, Farewell V, Walker D, Hassell A, Chau L, et al. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. *Ann. Rheum. Dis.* 2008;67:656–63.
31. Ma MHY, Scott IC, Kingsley GH, Scott DL. Remission in early rheumatoid arthritis. *J. Rheumatol.* 2010;37:1444–53.
32. Steunebrink LMM, Vonkeman HE, ten Klooster PM, Hoekstra M, van Riel PLCM, van de Laar MAFJ. Recently diagnosed rheumatoid arthritis patients benefit from a treat-to-target strategy: results from the DREAM registry. *Clin. Rheumatol.* 2016;35:609–15.
33. Steunebrink LMM, Versteeg GA, Vonkeman HE, Ten Klooster PM, Kuper HH, Zijlstra TR, et al. Initial combination therapy versus step-up therapy in treatment to the target of remission in daily clinical practice in early rheumatoid arthritis patients: results from the DREAM registry. *Arthritis Res. Ther.* 2015;18:60.
34. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum.* 1995;38:44–8.
35. Aletaha D, Nell VPK, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res. Ther.* 2005;7:R796-806.
36. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology (Oxford).* 2003;42:244–57.
37. van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann. Rheum. Dis.* 1990;49:916–20.
38. Ometto F, Botsios C, Raffener B, Sfriso P, Bernardi L, Todesco S, et al. Methods used to assess remission and low disease activity in rheumatoid arthritis. *Autoimmun. Rev.* 2010;9:161–4.
39. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum.* 1995;38:44–8.
40. Fransen J, van Riel PLCM. The Disease Activity Score and the EULAR response criteria. *Clin. Exp. Rheumatol.* 23:S93-9.
41. van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Cri. *Arthritis Rheum.* 1996;39:34–40.
42. Pincus T, Yazici Y, Sokka T, Aletaha D, Smolen JS. Methotrexate as the “anchor drug” for the treatment of early rheumatoid arthritis. *Clin. Exp. Rheumatol.* 2003;21:S179–185.
43. van der Heide A, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma-Frankfort C, van der Veen MJ, et al. The effectiveness of early treatment with “second-line” antirheumatic drugs. A randomized, controlled trial. *Ann. Intern. Med.* 1996;124:699–707.

44. Katchamart W, Trudeau J, Phumethum V, Bombardier C. Efficacy and toxicity of methotrexate (MTX) monotherapy versus MTX combination therapy with non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: a systematic review and meta-analysis. *Ann. Rheum. Dis.* 2009;68:1105–12.
45. de Jong PH, Hazes JM, Han HK, Huisman M, van Zeven D, van der Lubbe PA, et al. Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. *Ann. Rheum. Dis.* 2014;73:1331–9.
46. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, van Zeven D, Kerstens PJSM, Hazes JMW, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum.* 2005;52:3381–90.
47. O'Dell JR, Haire CE, Erikson N, Drymalski W, Palmer W, Eckhoff PJ, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N. Engl. J. Med.* 1996;334:1287–91.
48. van der Heijde D, Breedveld FC, Kavanaugh A, Keystone EC, Landewé R, Patra K, et al. Disease activity, physical function, and radiographic progression after longterm therapy with adalimumab plus methotrexate: 5-year results of PREMIER. *J. Rheumatol.* 2010;37:2237–46.
49. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann. Rheum. Dis.* 2017;annrheumdis-2016-210715.
50. Boers M, Verhoeven AC, Markuse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet.* 1997;350:309–18.
51. Landewé RBM, Boers M, Verhoeven AC, Westhovens R, van de Laar MAFJ, Markuse HM, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. *Arthritis Rheum.* 2002;46:347–56.
52. Rantalaiho V, Kautiainen H, Korpela M, Hannonen P, Kaipiainen-Seppänen O, Möttönen T, et al. Targeted treatment with a combination of traditional DMARDs produces excellent clinical and radiographic long-term outcomes in early rheumatoid arthritis regardless of initial infliximab. The 5-year follow-up results of a randomised clinical trial, the NEO-RACo trial. *Ann. Rheum. Dis.* 2014;73:1954–61.
53. Klarenbeek NB, Güler-Yüksel M, van der Kooij SM, Han KH, Roday HK, Kerstens PJSM, et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. *Ann. Rheum. Dis.* 2011;70:1039–46.
54. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous. *Arthritis Rheum.* 2006;54:26–37.
55. Markuse IM, Akdemir G, Dirven L, Goekoop-Ruiterman YPM, van Groenendaal JHLM, Han KH, et al. Long-Term Outcomes of Patients With Recent-Onset Rheumatoid Arthritis After 10 Years of Tight Controlled Treatment: A Randomized Trial. *Ann. Intern. Med.* 2016;164:523–31.

56. Svensson B, Boonen A, Albertsson K, van der Heijde D, Keller C, Hafström I. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. *Arthritis Rheum.* 2005;52:3360–70.
57. Wassenberg S, Rau R, Steinfeld P, Zeidler H. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2005;52:3371–80.
58. Mikuls TR, O'Dell J. The changing face of rheumatoid arthritis therapy: results of serial surveys. *Arthritis Rheum.* 2000;43:464–5.
59. Fries JF, Singh G, Lenert L, Furst DE. Aspirin, hydroxychloroquine, and hepatic enzyme abnormalities with methotrexate in rheumatoid arthritis. *Arthritis Rheum.* 1990;33:1611–9.
60. Carmichael SJ, Beal J, Day RO, Tett SE. Combination therapy with methotrexate and hydroxychloroquine for rheumatoid arthritis increases exposure to methotrexate. *J. Rheumatol.* 2002;29:2077–83.
61. Kavanaugh A, Wells AF. Benefits and risks of low-dose glucocorticoid treatment in the patient with rheumatoid arthritis. *Rheumatology (Oxford).* 2014;53:1742–51.
62. Smolen JS, Aletaha D. What should be our treatment goal in rheumatoid arthritis today? *Clin. Exp. Rheumatol.* 24:S-7-13.
63. van der Helm-van Mil AHM, Breedveld FC, Huizinga TWJ. Aspects of early arthritis. Definition of disease states in early arthritis: remission versus minimal disease activity. *Arthritis Res. Ther.* 2006;8:216.
64. Pinals RS, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum.* 1981;24:1308–15.
65. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LHD, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum.* 2011;63:573–86.
66. Aletaha D, Ward MM, Machold KP, Nell VPK, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. *Arthritis Rheum.* 2005;52:2625–36.
67. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann. Rheum. Dis.* 2007;66:34–45.
68. Nagy G, van Vollenhoven RF. Sustained biologic-free and drug-free remission in rheumatoid arthritis, where are we now? *Arthritis Res. Ther.* 2015;17:181.
69. van den Broek M, Huizinga TW, Dijkmans BA, Allaart CF. Drug-free remission: is it already possible? *Curr. Opin. Rheumatol.* 2011;23:266–72.
70. van der Kooij SM, Allaart CF, Dijkmans BA, Breedveld FC. Innovative treatment strategies for patients with rheumatoid arthritis. *Curr. Opin. Rheumatol.* 2008;20:287–94.
71. Wevers-de Boer K, Visser K, Heimans L, Roday HK, Molenaar E, Groenendaal JHLM, et al. Remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis (the IMPROVED study). *Ann. Rheum. Dis.* 2012;71:1472–7.
72. Scherer HU, Dörner T, Burmester GR. Patient-tailored therapy in rheumatoid arthritis: an editorial review. *Curr. Opin. Rheumatol.* 2010;22:237–45.

73. Schoels M, Knevel R, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas DT, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. *Ann. Rheum. Dis.* 2010;69:638–43.
74. Gremese E, Salaffi F, Bosello SL, Ciapetti A, Bobbio-Pallavicini F, Caporali R, et al. Very early rheumatoid arthritis as a predictor of remission: a multicentre real life prospective study. *Ann. Rheum. Dis.* 2013;72:858–62.
75. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann. Rheum. Dis.* 2016;75:3–15.
76. Donahue KE, Gartlehner G, Jonas DE, Lux LJ, Thieda P, Jonas BL, et al. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. *Ann. Intern. Med.* 2008;148:124–34.
77. Ma MHY, Kingsley GH, Scott DL. A systematic comparison of combination DMARD therapy and tumour necrosis inhibitor therapy with methotrexate in patients with early rheumatoid arthritis. *Rheumatology (Oxford)*. 2010;49:91–8.
78. Capell HA, Madhok R, Porter DR, Munro RAL, McInnes IB, Hunter JA, et al. Combination therapy with sulfasalazine and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalazine: results from the double-blind placebo-controlled MASCOT study. *Ann. Rheum. Dis.* 2007;66:235–41.
79. Gossec L, Dougados M, Goupille P, Cantagrel A, Sibilia J, Meyer O, et al. Prognostic factors for remission in early rheumatoid arthritis: a multiparameter prospective study. *Ann. Rheum. Dis.* 2004;63:675–80.
80. Scott DL, Symmons DP, Coulton BL, Popert AJ. Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet.* 1987;1:1108–11.
81. Pope RM. Rheumatoid arthritis: pathogenesis and early recognition. *Am. J. Med.* 1996;100:3S–9S.
82. van der Helm-van Mil AHM, Breedveld FC, Huizinga TWJ. Aspects of early arthritis. Definition of disease states in early arthritis: remission versus minimal disease activity. *Arthritis Res. Ther.* 2006;8:216.
83. Shaver TS, Anderson JD, Weidensaul DN, Shahouri SH, Shahouri SS, Busch RE, et al. The problem of rheumatoid arthritis disease activity and remission in clinical practice. *J. Rheumatol.* 2008;35:1015–22.
84. Jayakumar K, Norton S, Dixey J, James D, Gough A, Williams P, et al. Sustained clinical remission in rheumatoid arthritis: prevalence and prognostic factors in an inception cohort of patients treated with conventional DMARDS. *Rheumatology (Oxford)*. 2012;51:169–75.
85. Katchamart W, Johnson S, Lin H-JL, Phumethum V, Salliot C, Bombardier C. Predictors for remission in rheumatoid arthritis patients: A systematic review. *Arthritis Care Res. (Hoboken)*. 2010;62:1128–43.
86. Forslind K, Hafström I, Ahlmén M, Svensson B. Sex: a major predictor of remission in early rheumatoid arthritis? *Ann. Rheum. Dis.* 2007;66:46–52.
87. Hyrich KL, Watson KD, Silman AJ, Symmons DPM, British Society for Rheumatology Biologics Register. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology (Oxford)*. 2006;45:1558–65.

88. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, Falappone PC, Ferrante A, Malesci D, et al. Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. *J. Rheumatol.* 2007;34:1670–3.
89. Burmester GR, Ferraccioli G, Flipo R-M, Monteagudo-Sáez I, Unnebrink K, Kary S, et al. Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. *Arthritis Rheum.* 2008;59:32–41.
90. van der Heijde D, Klareskog L, Landewé R, Bruyn GAW, Cantagrel A, Durez P, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum.* 2007;56:3928–39.
91. Ma MHY, Ibrahim F, Walker D, Hassell A, Choy EH, Kiely PDW, et al. Remission in early rheumatoid arthritis: predicting treatment response. *J. Rheumatol.* 2012;39:470–5.
92. Verstappen SMM, van Albada-Kuipers GA, Bijlsma JWJ, Blaauw AAM, Schenk Y, Haanen HCM, et al. A good response to early DMARD treatment of patients with rheumatoid arthritis in the first year predicts remission during follow up. *Ann. Rheum. Dis.* 2005;64:38–43.
93. Pease CT, Bhakta BB, Devlin J, Emery P. Does the age of onset of rheumatoid arthritis influence phenotype?: a prospective study of outcome and prognostic factors. *Rheumatology (Oxford).* 1999;38:228–34.
94. Emery P, Gabay C, Kraan M, Gomez-Reino J. Evidence-based review of biologic markers as indicators of disease progression and remission in rheumatoid arthritis. *Rheumatol. Int.* 2007;27:793–806.
95. Courvoisier N, Dougados M, Cantagrel A, Goupille P, Meyer O, Sibilia J, et al. Prognostic factors of 10-year radiographic outcome in early rheumatoid arthritis: a prospective study. *Arthritis Res. Ther.* 2008;10:R106.
96. Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. *Acta Radiol. Diagn. (Stockh).* 1977;18:481–91.
97. Rau R, Herborn G. A modified version of Larsen's scoring method to assess radiologic changes in rheumatoid arthritis. *J. Rheumatol.* 1995;22:1976–82.
98. Scott DL, Houssien DA, Laasonen L. Proposed modification to Larsen's scoring methods for hand and wrist radiographs. *Br. J. Rheumatol.* 1995;34:56.
99. Sharp JT, Young DY, Bluhm GB, Brook A, Brower AC, Corbett M, et al. How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? *Arthritis Rheum.* 1985;28:1326–35.
100. Landewé RBM, Strand V, Conaghan PG, van der Heijde D. Damage and progression on radiographs in individual joints: data from pivotal randomized controlled trials. *J. Rheumatol.* 2011;38:2018–22.
101. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. *J. Rheumatol.* 2000;27:261–3.
102. Bruynesteyn K, Van Der Heijde D, Boers M, Verhoeven A, Boonen A, Van Der Linden S. Contribution of progression of erosive damage in previously eroded joints in early rheumatoid arthritis trials: COBRA trial as an example. *Arthritis Rheum.* 2002;47:532–6.
103. Bruynesteyn K, van der Heijde D, Boers M, Saudan A, Peloso P, Paulus H, et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. *Arthritis Rheum.* 2002;46:913–20.

104. van Jaarsveld CH, Jacobs JW, van der Veen MJ, Blaauw AA, Kruize AA, Hofman DM, et al. Aggressive treatment in early rheumatoid arthritis: a randomised controlled trial. On behalf of the Rheumatic Research Foundation Utrecht, The Netherlands. *Ann. Rheum. Dis.* 2000;59:468–77.
105. Stenger AA, Van Leeuwen MA, Houtman PM, Bruyn GA, Speerstra F, Barendsen BC, et al. Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. *Br. J. Rheumatol.* 1998;37:1157–63.
106. Emery P, Marzo H, Proudman S. Management of patients with newly diagnosed rheumatoid arthritis. *Rheumatology (Oxford).* 1999;38 Suppl 2:27–31.
107. Abu-Shakra M, Toker R, Flusser D, Flusser G, Friger M, Sukenik S, et al. Clinical and radiographic outcomes of rheumatoid arthritis patients not treated with disease-modifying drugs. *Arthritis Rheum.* 1998;41:1190–5.
108. van der Heijde DM. Joint erosions and patients with early rheumatoid arthritis. *Br. J. Rheumatol.* 1995;34 Suppl 2:74–8.
109. Morel J, Combe B. How to predict prognosis in early rheumatoid arthritis. *Best Pract. Res. Clin. Rheumatol.* 2005;19:137–46.
110. Masi AT. Articular patterns in the early course of rheumatoid arthritis. *Am. J. Med.* 1983;75:16–26.
111. Drossaers-Bakker KW, de Buck M, van Zeben D, Zwinderman AH, Breedveld FC, Hazes JM. Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. *Arthritis Rheum.* 1999;42:1854–60.
112. St Clair EW, van der Heijde DMFM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum.* 2004;50:3432–43.
113. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N. Engl. J. Med.* 2000;343:1586–93.
114. Möttönen TT. Prediction of erosiveness and rate of development of new erosions in early rheumatoid arthritis. *Ann. Rheum. Dis.* 1988;47:648–53.
115. van der Heide A, Remme CA, Hofman DM, Jacobs JW, Bijlsma JW. Prediction of progression of radiologic damage in newly diagnosed rheumatoid arthritis. *Arthritis Rheum.* 1995;38:1466–74.
116. Jansen LM, van der Horst-Bruinsma IE, van Schaardenburg D, Bezemer PD, Dijkmans BA. Predictors of radiographic joint damage in patients with early rheumatoid arthritis. *Ann. Rheum. Dis.* 2001;60:924–7.
117. Combe B, Dougados M, Goupille P, Cantagrel A, Eliaou JF, Sibilia J, et al. Prognostic factors for radiographic damage in early rheumatoid arthritis: a multiparameter prospective study. *Arthritis Rheum.* 2001;44:1736–43.
118. van der Heijde DM, van Riel PL, van Leeuwen MA, van 't Hof MA, van Rijswijk MH, van de Putte LB. Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis. A prospective follow-up study of 147 patients. *Br. J. Rheumatol.* 1992;31:519–25.
119. Syversen SW, Gaarder PI, Goll GL, Ødegård S, Haavardsholm EA, Mowinckel P, et al. High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: results from a 10-year longitudinal study. *Ann. Rheum. Dis.* 2008;67:212–7.

120. Carpenter L, Nikiphorou E, Sharpe R, Norton S, Rennie K, Bunn F, et al. Have radiographic progression rates in early rheumatoid arthritis changed? A systematic review and meta-analysis of long-term cohorts. *Rheumatology (Oxford)*. 2016;55:1053–65.
121. Combe B, Logeart I, Belkacemi MC, Dadoun S, Schaeverbeke T, Daurès JP, et al. Comparison of the long-term outcome for patients with rheumatoid arthritis with persistent moderate disease activity or disease remission during the first year after diagnosis: data from the ESPOIR cohort. *Ann. Rheum. Dis.* 2015;74:724–9.
122. Matthey DL, Hassell AB, Dawes PT, Cheung NT, Poulton K V, Thomson W, et al. Independent association of rheumatoid factor and the HLA-DRB1 shared epitope with radiographic outcome in rheumatoid arthritis. *Arthritis Rheum.* 2001;44:1529–33.
123. Calgüneri M, Pay S, Calışkaner Z, Apraş S, Kiraz S, Ertenli I, et al. Combination therapy versus monotherapy for the treatment of patients with rheumatoid arthritis. *Clin. Exp. Rheumatol.* 17:699–704.
124. Verschueren P, Esselens G, Westhovens R. Daily practice effectiveness of a step-down treatment in comparison with a tight step-up for early rheumatoid arthritis. *Rheumatology (Oxford)*. 2008;47:59–64.
125. Durnez A, Vanderschueren G, Lateur L, Westhovens R, Verschueren P. Effectiveness of initial treatment allocation based on expert opinion for prevention of rapid radiographic progression in daily practice of an early RA cohort. *Ann. Rheum. Dis.* 2011;70:634–7.
126. van den Broek M, Dirven L, de Vries-Bouwstra JK, Dehpoor AJ, Goekoop-Ruiterman YPM, Gerards AH, et al. Rapid radiological progression in the first year of early rheumatoid arthritis is predictive of disability and joint damage progression during 8 years of follow-up. *Ann. Rheum. Dis.* 2012;71:1530–3.
127. Fex E, Jonsson K, Johnson U, Eberhardt K. Development of radiographic damage during the first 5-6 yr of rheumatoid arthritis. A prospective follow-up study of a Swedish cohort. *Br. J. Rheumatol.* 1996;35:1106–15.
128. Plant MJ, Jones PW, Saklatvala J, Ollier WE, Dawes PT. Patterns of radiological progression in early rheumatoid arthritis: results of an 8 year prospective study. *J. Rheumatol.* 1998;25:417–26.
129. Greenhalgh J, Meadows K. The effectiveness of the use of patient-based measures of health in routine practice in improving the process and outcomes of patient care: a literature review. *J. Eval. Clin. Pract.* 1999;5:401–16.
130. Marshall S, Haywood K, Fitzpatrick R. Impact of patient-reported outcome measures on routine practice: a structured review. *J. Eval. Clin. Pract.* 2006;12:559–68.
131. Valderas JM, Kotzeva A, Espallargues M, Guyatt G, Ferrans CE, Halyard MY, et al. The impact of measuring patient-reported outcomes in clinical practice: a systematic review of the literature. *Qual. Life Res.* 2008;17:179–93.
132. Black N. Patient reported outcome measures could help transform healthcare. *BMJ.* 2013;346:f167.
133. Studenic P, Radner H, Smolen JS, Aletaha D. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. *Arthritis Rheum.* 2012;64:2814–23.
134. Berkanovic E, Hurwicz ML, Lachenbruch PA. Concordant and discrepant views of patients' physical functioning. *Arthritis Care Res.* 1995;8:94–101.
135. Sanderson T, Morris M, Calnan M, Richards P, Hewlett S. Patient perspective of measuring treatment efficacy: the rheumatoid arthritis patient priorities for pharmacologic interventions outcomes. *Arthritis Care Res. (Hoboken)*. 2010;62:647–56.

136. Kirwan J, Heiberg T, Hewlett S, Hughes R, Kvien T, Ahlmèn M, et al. Outcomes from the Patient Perspective Workshop at OMERACT 6. *J. Rheumatol.* 2003;30:868–72.
137. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum.* 1993;36:729–40.
138. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med. Care.* 1992;30:473–83.
139. Bruce B, Fries JF. The Health Assessment Questionnaire (HAQ). *Clin. Exp. Rheumatol.* 2005;23:S14–8.
140. Schipper LG, van Hulst LTC, Grol R, van Riel PLCM, Hulscher MEJL, Fransen J. Meta-analysis of tight control strategies in rheumatoid arthritis: protocolized treatment has additional value with respect to the clinical outcome. *Rheumatology (Oxford).* 2010;49:2154–64.
141. Vermeer M, Kievit W, Kuper HH, Braakman-Jansen LM, Bernelot Moens HJ, Zijlstra TR, et al. Treating to the target of remission in early rheumatoid arthritis is cost-effective: results of the DREAM registry. *BMC Musculoskelet. Disord.* 2013;14:350.

CHAPTER 2

Outline of the thesis

There may be no cure for rheumatoid arthritis (RA) yet, but already much can be done for RA patients to alleviate their symptoms and improve their health-related quality of life. The goal of treatment is for patients to regain an optimal state of health, through suppression of inflammation and pain relief, as well as by prevention of long-term consequences such as joint damage and disability, without incurring severe side effects and complications [1–5]. Once a diagnosis of RA has been established, it is important to select the most appropriate treatment for the patient. The most appropriate treatment depends on the degree of inflammation and the reaction of the body to the treatment [6]. In addition to that, the dosing and possibly the type of medication may be different depending on individual response and preferences.

There are still important questions to be answered about the optimal treatment in early RA. For example, are the current available T2T treatment strategies sufficient or are there other treatment strategies that must be explored? Should we focus more on further intensification of DMARD therapy or on more personalized treatment strategies? In this thesis I will give an overview of several studies investigating initial combination DMARD therapy versus step-up DMARD mono-therapy, remission rates, predictors of remission, determinants of patient-perceived health non-improvement, predictors of radiographic progression, and the relation between disease activity and radiographic progression. Together, these studies provide a comprehensive account of real-world outcomes of current early RA T2T treatment and possible directions for further treatment improvements.

Outline

Despite many promising results in the literature on the management of early RA in the T2T era, several questions regarding the optimal treatment strategy, treatment initiation, radiographic damage and predictors of remission and radiographic damage, remain unanswered. The overall aim of this thesis is to thoroughly evaluate T2T strategies in early RA patients in daily clinical practice.

The specific aims of this thesis are:

- To compare the effectiveness of an initial DMARD combination therapy versus a step-up DMARD monotherapy;
- To give an overview of predictors for clinical remission in early RA patients treated according to T2T;
- To compare radiographic progression rates between both T2T strategies and to identify predictors of progression;

- To present determinants of patient-perceived health non-improvement in 'T2T' treated patients with a good clinical response;
- To clarify the relationship between disease activity and radiographic progression in the 'T2T' era.

The thesis is divided into several chapters:

Although the management of RA has undergone major paradigm changes, there is still potential room for improvement, particularly with respect to optimization of tight-control treatment strategies in daily clinical practice. In the clinically used disease activity indices, the treatment target remission does not require complete absence of all clinical symptoms, resulting in residual disease activity. The disease activity indices differ in the level of residual disease activity that is accepted. It is still a subject of discussion how much residual disease activity can be accepted in a patient without increasing the risk for long-term consequences, such as disability and joint damage. Several prediction models for remission in RA have been developed using clinical trial data, but prediction models for remission in daily clinical practice are lacking. Also, the variety in definitions for remission used in clinical trials and in daily clinical practice, leads to different reported remission rates, making results difficult to interpret [7–10]. Therefore, we identified remission rates and predictors of reaching remission in daily clinical practice in Dutch RA patients following a new initial DMARD combination treat-to-target ('T2T' strategy) in **chapter 3**.

Even though biological disease modifying antirheumatic drugs (bDMARDs) are highly effective, methotrexate (MTX) is still the drug of first choice for early RA and hence it is important to optimally treat patients with MTX either alone or in combination with other biological or conventional synthetic (cs)DMARDs [11]. Currently, it is unclear what the optimal MTX starting dose for individual patients is. The current treatment strategies and use of initial combination therapy have resulted in significantly improved short- and long-term outcomes for RA patients [12–16]. However, still no consensus has been reached about what the most appropriate initial 'intensive' treatment regimen should be. Most important discussion herein is that of initial MTX monotherapy versus a combination of DMARDs. Therefore, we examined in **chapter 4** the effectiveness of two 'T2T' strategies in reducing disease activity in early RA patients: a step-up sequential DMARD monotherapy versus an initial DMARD combination therapy.

In **chapter 5** the radiographic outcomes of both treatment strategies were compared. Joint erosions and joint space narrowing, visualized by X-rays, have been used for decades for quantifying radiographic damage. Prevention of structural damage is an important goal in the treatment of RA and recent research has shown that early intensive treatment improves both the

short- and long-term outcomes of RA [17–21]. Radiographic progression can develop at any stage of the disease process, but at the highest rate early on in the disease course [22]. In fact, even if DMARDs are initiated ‘very early’ in the disease process, some patients may still develop erosions and progressive joint damage [17, 23, 24]. However, whether initial combination therapy and the subsequent shorter time to remission, as compared to initial step-up monotherapy, also results in better radiographic outcomes has not been studied well in real-life clinical practice. Therefore, **chapter 5** will compare radiographic progression rates between an initial DMARD combination therapy versus a step-up sequential DMARD monotherapy and explore predictors of radiographic progression in early RA patients.

As we already know, T2T leads to better clinical outcomes than alternative treatment approaches. However, measures of inflammatory disease activity may not always correspond with the perception of the health status of the patient [25]. Therefore, we investigated in **Chapter 6** the determinants of perceived health non-improvement in patients with good clinical response. This chapter examines the characteristics (or predictors) of patients with a disassociation between clinical and subjective health outcomes of T2T.

According to clinical trials, there is evidence that ongoing disease activity, as expressed by elevated CRP levels or composite disease activity score, leads to more rapid joint destruction [26]. Several studies have confirmed that time-integrated disease activity was strongly associated with radiographic progression in RA patients conventionally treated with synthetic DMARDs and/or non-steroidal anti-inflammatory drugs (NSAIDs) [27–32]. More recently, however, several studies showed a weaker association or even a disconnection between inflammation and joint destruction in RA patients treated with aggressive conventional synthetic DMARDs [33, 34] and in established RA patients treated with combined biological DMARDs [35, 36]. Taken together, these findings indicate that the exact relationship between disease activity and the radiographic course in RA patients is not so clear in current intensive treatment paradigms and that joint destruction might be more a more individually determined disease process in the current T2T era. Therefore, we investigated in **Chapter 7** the individual relationship between disease activity and radiographic progression in patients with early RA.

Last but not least, **Chapter 8** is the final chapter of this thesis and represents a summary and general discussion. It reflects the whole research project and returns to its initial aims, elaborating on the implications of the results, and discussing future research and clinical developments.

REFERENCES

1. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines: Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheum* 2002, 46:328–46.
2. Verhoeven AC, Boers M, Tugwell P: Combination therapy in rheumatoid arthritis: updated systematic review. *Br J Rheumatol* 1998, 37:612–9.
3. Möttönen T, Hannonen P, Leirisalo-Repo M, Nissilä M, Kautiainen H, Korpela M, Laasonen L, Julkunen H, Luukkainen R, Vuori K, Paimela L, Bläfield H, Hakala M, Ilva K, Yli-Kerttula U, Puolakka K, Järvinen P, Hakola M, Piirainen H, Ahonen J, Pälvimäki I, Forsberg S, Koota K, Friman C: Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* 1999, 353:1568–73.
4. Möttönen TT, Hannonen PJ, Boers M: Combination DMARD therapy including corticosteroids in early rheumatoid arthritis. *Clin Exp Rheumatol*, 17(6 Suppl 18):S59–65.
5. Drossaers-Bakker KW, de Buck M, van Zeben D, Zwinderman AH, Breedveld FC, Hazes JM: Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. *Arthritis Rheum* 1999, 42:1854–60.
6. Gaffo A, Saag KG, Curtis JR: Treatment of rheumatoid arthritis. *Am J Health Syst Pharm* 2006, 63:2451–65.
7. Landewé R, van der Heijde D, van der Linden S, Boers M: Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. *Ann Rheum Dis* 2006, 65:637–41.
8. Mäkinen H, Hannonen P, Sokka T: Definitions of remission for rheumatoid arthritis and review of selected clinical cohorts and randomised clinical trials for the rate of remission. *Clin Exp Rheumatol*, 24(6 Suppl 43):S-22-8.
9. Boers M, Brooks P, Strand C V, Tugwell P: The OMERACT filter for Outcome Measures in Rheumatology. *J Rheumatol* 1998, 25:198–9.
10. Sokka T, Hetland ML, Mäkinen H, Kautiainen H, Hørslev-Petersen K, Luukkainen RK, Combe B, Badsha H, Drosos AA, Devlin J, Ferraccioli G, Morelli A, Hoekstra M, Majdan M, Sadkiewicz S, Belmonte M, Holmqvist A-C, Choy E, Burmester GR, Tunc R, Dimić A, Nedović J, Stanković A, Bergman M, Toloza S, Pincus T, Questionnaires in Standard Monitoring of Patients With Rheumatoid Arthritis Group: Remission and rheumatoid arthritis: data on patients receiving usual care in twenty-four countries. *Arthritis Rheum* 2008, 58:2642–51.
11. Willkens RF: Resolve: methotrexate is the drug of choice after NSAIDs in rheumatoid arthritis. *Semin Arthritis Rheum* 1990, 20:76–80.
12. Smolen JS, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas D, Burmester G, Combe B, Cutolo M, de Wit M, Dougados M, Emery P, Gibofsky A, Gomez-Reino JJ, Haraoui B, Kalden J, Keystone EC, Kvien TK, McInnes I, Martin-Mola E, Montecucco C, Schoels M, van der Heijde D, van der Heijde D, T2T Expert Committee: Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010, 69:631–7.
13. Schipper LG, Vermeer M, Kuper HH, Hoekstra MO, Haagsma CJ, Den Broeder AA, van Riel P, Fransen J, van de Laar MAFJ: A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. *Ann Rheum Dis* 2012, 71:845–50.

14. Vermeer M, Kuper HH, Hoekstra M, Haagsma CJ, Posthumus MD, Brus HLM, van Riel PLCM, van de Laar MAFJ: Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. *Arthritis Rheum* 2011, 63:2865–72.
15. Markusse IM, Akdemir G, Dirven L, Goekoop-Ruiterman YPM, van Groenendaal JHLM, Han KH, Molenaar THE, Le Cessie S, Lems WF, van der Lubbe PAHM, Kerstens PJSM, Peeters AJ, Roday HK, de Sonnaville PBJ, Speyer I, Stijnen T, Ten Wolde S, Huizinga TWJ, Allaart CF: Long-Term Outcomes of Patients With Recent-Onset Rheumatoid Arthritis After 10 Years of Tight Controlled Treatment: A Randomized Trial. *Ann Intern Med* 2016, 164:523–31.
16. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJSM, Hazes JMW, Zwinderman AH, Roday HK, Han KH, Westedt ML, Gerards AH, van Groenendaal JHLM, Lems WF, van Krugten M V, Breedveld FC, Dijkmans BAC: Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. *Arthritis Rheum* 2008, 58(2 Suppl):S126–35.
17. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, Hazes JM: Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med* 2001, 111:446–51.
18. Quinn MA, Emery P: Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention. *Clin Exp Rheumatol* 2003, 21(5 Suppl 31):S154–7.
19. Nell VPK, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS: Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology (Oxford)* 2004, 43:906–14.
20. Steunebrink LMM, Vonkeman HE, ten Klooster PM, Hoekstra M, van Riel PLCM, van de Laar MAFJ: Recently diagnosed rheumatoid arthritis patients benefit from a treat-to-target strategy: results from the DREAM registry. *Clin Rheumatol* 2016, 35:609–615.
21. Steunebrink LMM, Versteeg GA, Vonkeman HE, ten Klooster PM, Kuper HH, Zijlstra TR, van Riel PLCM, van de Laar MAFJ: Initial combination therapy versus step-up therapy in treatment to the target of remission in daily clinical practice in early rheumatoid arthritis patients: Results from the DREAM registry. *Arthritis Res Ther* 2016, 18.
22. van der Heijde DM: Joint erosions and patients with early rheumatoid arthritis. *Br J Rheumatol* 1995, 34 Suppl 2:74–8.
23. van Aken J, Lard LR, le Cessie S, Hazes JMW, Breedveld FC, Huizinga TWJ: Radiological outcome after four years of early versus delayed treatment strategy in patients with recent onset rheumatoid arthritis. *Ann Rheum Dis* 2004, 63:274–9.
24. Maillefert JF, Combe B, Goupille P, Cantagrel A, Dougados M: Long term structural effects of combination therapy in patients with early rheumatoid arthritis: five year follow up of a prospective double blind controlled study. *Ann Rheum Dis* 2003, 62:764–6.
25. Vermeer M, Kuper HH, van der Bijl AE, Baan H, Posthumus MD, Brus HLM, van Riel PLCM, van de Laar MAFJ: The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. *Rheumatology (Oxford)* 2012, 51:1076–80.
26. van der Heijde D: Radiographic progression in rheumatoid arthritis: does it reflect outcome? Does it reflect treatment? *Ann Rheum Dis* 2001, 60 Suppl 3:iii47–50.

27. Leeuwen M van, Rijswijk M van: The acute-phase response in relation to radiographic progression in early rheumatoid arthritis: a prospective study during the first three years of the disease. *Br J Rheumatol* 1993, 32(suppl 3):9–13.
28. Kuper HH, van Leeuwen MA, van Riel PL, Prevoo ML, Houtman PM, Lolkema WF, van Rijswijk MH: Radiographic damage in large joints in early rheumatoid arthritis: relationship with radiographic damage in hands and feet, disease activity, and physical disability. *Br J Rheumatol* 1997, 36:855–60.
29. van Leeuwen MA, van Rijswijk MH, Sluiter WJ, van Riel PL, Kuper IH, van de Putte LB, Pepys MB, Limburg PC: Individual relationship between progression of radiological damage and the acute phase response in early rheumatoid arthritis. Towards development of a decision support system. *J Rheumatol* 1997, 24:20–7.
30. Plant MJ, Williams AL, O'Sullivan MM, Lewis PA, Coles EC, Jessop JD: Relationship between time-integrated C-reactive protein levels and radiologic progression in patients with rheumatoid arthritis. *Arthritis Rheum* 2000, 43:1473–7.
31. Knijff-Dutmer E, Drossaers-Bakker W, Verhoeven A, van der Sluijs Veer G, Boers M, van der Linden S, van de Laar M: Rheumatoid factor measured by fluoroimmunoassay: a responsive measure of rheumatoid arthritis disease activity that is associated with joint damage. *Ann Rheum Dis* 2002, 61:603–7.
32. Wick MC, Anderwald C, Weiss RJ, Imhof H, Kainberger F, Smolen JS: Radiological progression of joint damage in a longitudinal cohort of early DMARD-treated rheumatoid arthritis patients followed for 10 years. *Scand J Rheumatol* 2004, 33:162–6.
33. Wick MC, Lindblad S, Klareskog L, Van Vollenhoven RF: Relationship between inflammation and joint destruction in early rheumatoid arthritis: a mathematical description. *Ann Rheum Dis* 2004, 63:848–52.
34. Knevel R, van Nies JAB, le Cessie S, Huizinga TWJ, Brouwer E, van der Helm-van Mil AHM: Evaluation of the contribution of cumulative levels of inflammation to the variance in joint destruction in rheumatoid arthritis. *Ann Rheum Dis* 2013, 72:307–8.
35. Smolen JS, Han C, Bala M, Maini RN, Kalden JR, van der Heijde D, Breedveld FC, Furst DE, Lipsky PE, ATTRACT Study Group: Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum* 2005, 52:1020–30.
36. Landewé R, van der Heijde D, Klareskog L, van Vollenhoven R, Fatenejad S: Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate: results from the trial of etanercept and methotrexate with radiographic and patient outcomes. *Arthritis Rheum* 2006, 54:3119–25.

Recently diagnosed rheumatoid arthritis patients benefit from a treat-to-target strategy: results from the DREAM registry

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ABSTRACT

Despite considerable evidence on the efficacy and safety of early aggressive treat-to-target (T2T) strategies in early rheumatoid arthritis (RA), a proportion of patients still fail to reach remission. The goal of this study is to examine remission rates and predictors of remission in a real life T2T cohort of consecutive patients with a recent diagnosis of RA.

Baseline demographics, clinical, laboratory and patient-reported variables and 1-year follow-up disease activity data were used from patients with early RA included in the DREAM remission induction cohort II study. Survival analyses and simple and multivariable logistic regression analyses were used to examine remission rates and significant predictors of achieving remission. A total of 137 recently diagnosed consecutive RA patients were available for this study. During the first year after inclusion, DAS28 remission was achieved at least once in 77.2% of the patients and the median time to first remission was 17 weeks. None of the examined baseline variables were robustly associated with achieving remission within 1 year and in the multivariable analysis only lower ESR ($p=0.005$) remained significantly associated with achieving fast remission within 17 weeks. During the first year of their disease a high proportion of recently diagnosed RA patient achieved remission, with only a small percentage of patients needing bDMARD therapy. Combined with the absence of baseline predictors of remission, this suggests that clinicians in daily clinical practice may focus on DAS28 scores only, without needing to take other patients characteristics into account.

INTRODUCTION

Rheumatoid Arthritis (RA) is a clinical diagnosis (or phenotype), considered to be the result of unidentified causes or insufficiently known pathophysiological malfunctions. Many conventional synthetic Diseases-modifying anti-rheumatic drugs (csDMARDs) and biologicals (bDMARDs) are presently available and new treatment options and strategies have dramatically reduced the severity and impact of RA [1]. Early intensive combination therapies, aimed at achieving remission, have shown especially good clinical outcomes [2–4].

Early diagnosis and treatment of RA may constrain the progression of this disease. Since there is no cure for RA yet, the most important goal is to achieve stable remission as soon as possible [5–7]. Despite considerable evidence from clinical trials on the efficacy and safety of treatment strategies aiming at inducing remission, also known as treat-to-target (T2T), a relevant proportion of RA patients in daily clinical practice still fail to become free of signs and symptoms [8–13].

In recent years, the T2T approach has also been studied in observational studies such as the DREAM remission induction registry [3, 14], showing that remission is also an achievable goal in clinical practice. Ideally, this is achieved by a highly successful treatment strategy that is suitable for all RA patients in daily clinical care. If not all patients can be treated successfully, we may need personalized approaches and identification of those individual characteristics pointing to specific successful treatments [14, 15]. This personalized medicine approach has resulted in the search of predictors in genetic and other biomarkers [8, 16–18]. Unfortunately, until now major breakthroughs in predicting remission are lacking.

The DREAM remission induction cohort has demonstrated that T2T can be successfully implemented in a real life clinical setting. However, the question remains whether the T2T strategy fits all RA patients [13]. Therefore, the aim of this study is to examine remission rates and predictors of remission in a real life cohort of consecutive patients with a recent diagnosis of RA.

MATERIALS AND METHODS

Patients

This study used data from the ongoing DREAM (Dutch Rheumatoid Arthritis Monitoring) remission induction cohort II, an observational, multicenter cohort that was established in 2012 to evaluate the effects of a T2T strategy of initial combination therapy of methotrexate (MTX) and hydroxychloroquine (HCQ) aimed at quickly achieving a state of remission ($\text{DAS28} < 2.6$) in early RA patients. Adults ≥ 18 years with a clinical diagnosis of RA and a disease duration < 1

year were enrolled in our study. Consecutive patients from two hospitals in The Netherlands, Medisch Spectrum Twente in Enschede and Isala in Zwolle, were included as soon as they had been diagnosed with RA. The treatment strategy is in line with clinical practice and complies with the current guidelines for the treatment of RA. Exclusion criteria were the use of prednisolone ≥ 10 mg/day and/or previous or current treatment with DMARDs. The ethics committees of the participating hospitals determined, in accordance with the relevant law in the Netherlands, that no ethical approval was required because all data were collected in the course of regular daily clinical practice. Nonetheless, patients were fully informed and prior informed consent was obtained from each patient.

Treat-to-target protocol

Patients were evaluated at 0, 2, 4, and 6 months and every 3 months thereafter. Treatment advice consisted of an initial combination therapy of MTX 20 mg/week and HCQ 200 mg twice daily. As a bridging therapy, an optional intramuscular triamcinolone injection up to a maximum dosage of 120 mg could be given. After 1 month MTX dosage was increased to 25 mg/week, independent of disease activity. All patients who started MTX also received folic acid on the second day after MTX. After 2 months, in the case of persistent disease activity ($\text{DAS28} \geq 2.6$), MTX dosage was further increased to 30 mg/week and an extra optional intramuscular triamcinolone injection could be administered. After four months, in the case of moderate to high disease activity ($\text{DAS28} \geq 3.2$), a tumor necrosis factor (TNF) inhibitor (adalimumab, etanercept or infliximab) was added. In cases of low disease activity ($2.6 < \text{DAS28} < 3.2$), the attending rheumatologist could choose between adding sulphasalazine (SSZ) at 2000-3000 mg/day or an additional intramuscular triamcinolone injection.

Disease activity was assessed with the DAS28 during each subsequent visit. If remission (defined as $\text{DAS28} < 2.6$) had not been achieved, treatment was intensified. However, if the patient was in DAS28 remission, medication was not changed. In case of sustained remission (≥ 6 months), medication was progressively reduced and eventually discontinued according to a predetermined tapering schedule. In the case of disease flare ($\text{DAS28} \geq 2.6$), the most recent medication or medication dosage that was shown to be effective was restarted, and treatment could subsequently be intensified. In response to clinical indications, the attending rheumatologist was free to diverge from the medication schedule at any time.

Measures

At each assessment, data were collected on various core set measures, including measures of disease activity, health related quality of life, physical functioning, and laboratory measures. Disease activity was assessed by trained rheumatology nurses using the Disease Activity Score for 28 joints (DAS28), consisting of a 28 swollen and tender joint count, the erythrocyte sedimentation rate (ESR) and a 100 millimeter visual analog scale (VAS) on general health (where 0 = “very good” and 100 = “very bad”) [19]. The Health Assessment Questionnaire Disability Index (HAQ-DI) was used to assess physical function [20]. Furthermore, patients rated their pain on a 100 millimeter VAS (0 = “no pain” and 100 = “unbearable pain”) and completed the 36 items of the Short Form Health Survey (SF-36) in order to assess their current physical and mental health status [21].

Statistical analysis

Missing values for ESR (total 5%, baseline 0.7%) and for CRP (total 0.8%, baseline 0%) were imputed based on age, sex, swollen and tender joint counts, and ESR or CRP using single imputation by applying the expectation-maximization method. Descriptive statistics for normally distributed variables or categorical variables were reported as frequencies, percentages, means and standard deviations (mean $\pm$ SD). If variables were not normally distributed, the median with the corresponding interquartile range (IQR) was reported. Kaplan-Meier survival analysis was performed to examine DAS28 remission rates and to compute the time point at which 50% of the patients had achieved their first DAS28 remission (DAS28 < 2.6). Next, univariate logistic regression analyses were performed to examine associations between baseline variables and remission at the median survival time or within 1 year. Continuous predictors were evaluated for the suitability of the linearity assumption by plotting each variable against the logit of probability. Variables found to be related marginally ($p < 0.20$) to DAS28 remission at 17 weeks or 52 weeks in the univariate analysis were entered into multivariable logistic regression analysis as independent variables. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The final model was tested for goodness of fit using the Hosmer and Lemeshow test. The explained variance of the model was examined using Nagelkerke’s pseudo R^2 . All statistical calculations were performed using version 22 of the SPSS statistical package for Windows.

RESULTS

Baseline characteristics

Table 1 summarizes the baseline characteristics of the total patient group and stratified by patients achieving remission or not at 6 months. A total of 137 patients were included. Patients had active disease at baseline, as demonstrated by high DAS28 scores and pain scores. Patients were, on average, 59 years old and the majority was female. Characteristics were similar between those that did or did not achieve remission at 6 months.

Table 1. Baseline characteristics

Characteristic	Score range of measure	Total group (n=137)	Remission at 6 months (n=86)	No remission at 6 months (n= 51)
Female sex, n (%)	-	82 (59.9)	48 (55.8)	17 (33.3)
Age, mean $\pm$ SD years	-	58.9 $\pm$ 13.5	59.0 $\pm$ 12.8	58.9 $\pm$ 14.9
DAS28 - ESR, mean $\pm$ SD	0-10	4.9 $\pm$ 1.2	4.7 $\pm$ 1.2	5.2 $\pm$ 1.2
DAS28 - CRP, mean $\pm$ SD	0-10	4.5 $\pm$ 1.2	4.4 $\pm$ 1.2	4.7 $\pm$ 1.2
ESR (mm/h), median (IQR)	0-140	29.0 (15.0-46.0) (n=136)	24.5 (12.8-38.8)	35.0 (18.0-53.0) (n=50)
CRP (mg/l), median (IQR)	0-999	12.0 (4.0-26.5)	11.5 (4.0-27.0)	13.0 (5.0-26.0)
Anti-CCP positive, n (%)	-	83 (61.0) (n=136)	54 (62.8)	29 (56.9) (n=50)
RF positive, n (%)	-	80 (58.4)	48 (55.8)	32 (62.7)
Number of SJC, median (IQR)	0-28	5.0 (2.0-10.0)	5.5 (2.0-10.0)	4.0 (2.0-10.0)
Number of TJC, median (IQR)	0-28	4.0 (2.0-11.0)	3.5 (1.8-1.3)	5.0 (2.0-11.0)
HAQ-SDI, mean $\pm$ SD	0-3	0.9 $\pm$ 0.7 (n=90)	0.9 $\pm$ 0.6 (n=63)	0.9 $\pm$ 0.8 (n=27)
VAS well-being, mean $\pm$ SD	0-100	51.9 $\pm$ 26.3	50.5 $\pm$ 25.2	54.3 $\pm$ 28.2
VAS pain, mean $\pm$ SD	0-100	58.8 $\pm$ 22.3 (n=75)	60 $\pm$ 21.9 (n=46)	56.8 $\pm$ 23.1 (n=29)
SF36-PCS, mean $\pm$ SD	0-100	37.3 $\pm$ 9.2 (n=88)	37.6 $\pm$ 9.0 (n=62)	36.7 $\pm$ 9.9 (n=26)
SF36-MCS, mean $\pm$ SD	0-100	44.8 $\pm$ 11.9 (n=88)	44.9 $\pm$ 13.1 (n=62)	44.6 $\pm$ 8.3 (n=26)
BMI, kg/m ² , mean $\pm$ SD	-	26.1 $\pm$ 4.0 (n=128)	26.1 $\pm$ 3.7 (n=80)	26.0 $\pm$ 4.4 (n=48)

DAS28 Disease Activity Score in 28 joints, ESR erythrocyte sedimentation rate, CRP C-reactive protein, TJC tender joint count, SJC swollen joint count, HAQ-DI Health Assessment Questionnaire disability index (standard scoring), SF-36 Short-Form 36 health survey (version 2), PCS physical component summary, MCS mental component summary, BMI body mass index, RF rheumatoid factor, Anti-CCP anti-cyclic citrullinated peptide

Time to reach first remission

After 1 year of follow-up, remission (DAS28 < 2.6) was achieved at least once in 77.2% of the patients and the median time to first remission was 17.0 (95% CI: 13.0-20.0) weeks (Fig. 1). A total of 71 patients (51.8%) achieved remission within 17 weeks.

Figure 1: *Kaplan-Meier curve for time to reach first remission after a 1-year follow-up in early RA patients*

Univariate associations with remission within 17 and 52 weeks

Except for the baseline DAS28 score, none of the independent variables violated the assumption of linearity. Baseline DAS28 scores were dichotomized in high disease activity (> 5.1) versus low and moderate disease activity. None of the examined baseline variables were significantly associated with achieving remission within 1 year (Table 2) and only lower HAQ-DI scores were marginally predictive of 1-year remission. Therefore, no multivariable model was tested for remission within 52 weeks. Lower ESR ($p = 0.007$), male gender ($p = 0.057$), and fewer tender joints ($p = 0.175$) were significantly or marginally associated with achieving remission within 17 weeks. As these variables were not strongly intercorrelated (all correlations < 0.10), they were simultaneously entered into multivariable analysis.

Table 2. *Univariate predictors of remission within 17 weeks and 52 weeks*

Variable	Remission within 17 weeks			Remission within 52 weeks		
	OR	95% CI	p	OR	95% CI	p
High disease activity (DAS28 >5.1)	0.575	0.287 – 1.151	0.118	0.596	0.266 – 1.338	0.210
BMI	1.023	0.937 – 1.117	0.614	0.947	0.856 – 1.048	0.292
ESR	0.979	0.965 – 0.994	0.007	0.992	0.977 – 1.007	0.280
CRP	0.996	0.985 – 1.007	0.460	1.000	0.987 – 1.012	0.940
Anti-CCP positive	0.775	0.397 – 1.514	0.456	0.761	0.348 – 1.663	0.494
RF	1.110	0.788 – 1.564	0.549	1.071	0.710 – 1.616	0.744
Female sex	0.508	0.253 – 1.019	0.057	0.775	0.338 – 1.779	0.548
Age	0.993	0.969 – 1.018	0.587	0.988	0.959 – 1.019	0.456
HAQ-DI	0.820	0.444 – 1.514	0.526	0.671	0.300 – 1.500	0.331
PCS	1.025	0.978 – 1.074	0.309	1.014	0.954 – 1.077	0.663
MCS	1.009	0.973 – 1.046	0.621	1.013	0.967 – 1.062	0.577
VAS general wellbeing	0.994	0.981 – 1.007	0.332	0.993	0.977 – 1.009	0.374
SJC	0.978	0.922 – 1.037	0.454	1.029	0.955 – 1.108	0.452
TJC	0.963	0.912 – 1.017	0.175	0.969	0.912 – 1.030	0.312

DAS28 disease activity score in 28 joints, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *TJC* tender joint count, *SJC* swollen joint count, *HAQ-DI* Health Assessment Questionnaire disability index (standard scoring), *SF-36* Short-Form 36 health survey (version 2), *PCS* physical component summary, *MCS* mental component summary, *BMI* body mass index, *RF* rheumatoid factor, *Anti-CCP* anti-cyclic citrullinated peptide

Multivariate predictors of remission within 17 weeks

The resultant multivariable model (Table 3) showed an adequate fit to the data (Hosmer and Lemeshow test: $\chi^2 (8) = 10.43$ $p = 0.24$), but only lower baseline ESR remained significantly predictive ($p = 0.005$) of achieving remission within 17 weeks (Table 3). No other variables were found to be significantly associated with remission and the total explained variance was low (13%).

Table 3. *Multivariate predictors of remission within 17 weeks in early RA*

Variable	Patients in remission in ≤ 17 weeks		
	OR	95% CI	p
ESR	0.978	0.963 – 0.993	0.005
Female sex	0.519	0.251 – 1.074	0.077
TJC	0.959	0.905 – 1.017	0.163

Nagelkerke $R^2 = 0.129$, ESR erythrocyte sedimentation rate, TJC tender joint count

Medication at 12 months

At 12 months, 7.3% ($n = 10$) of the patients were off medication entirely. The majority of the patients (54%, $n = 74$) still used the initial combination medication of MTX + HCQ. In 9.5% ($n = 13$) of the patients MTX monotherapy was used, while 13.9% ($n = 19$) used another mono-csDMARD. MTX + bDMARD was used in 7.3% ($n = 10$) of the patients at 12 months. Only one patient (0.7%) was prescribed a bDMARD as mono therapy. The combination of two csDMARD and a bDMARD (MTX+HCQ+ADA) was used in 2.2% of the patients ($n = 3$) and SSZ+HCQ was used in 1.5% of the patients ($n = 2$). Five patients (3.6%) were lost to follow-up (Fig. 2).

At baseline, 74 patients (54%) received an intramuscular injection with triamcinolone. Furthermore, 30 patients (21.9%) received triamcinolone injections between baseline and 12 months. Of these, 28 patients received one injection, only 2 patients received 2 injections after baseline. Patients who received triamcinolone injections at baseline had significantly more swollen joints (8.0 (3.0 – 12.3) vs. 3.0 (2.0 – 6.0)), $p < 0.001$ and more tender joints (6.0 (2.0 – 12.0) vs. 4.0 (1.0 – 8.0)), $p = 0.039$ than patients who did not receive a triamcinolone injection. There were no significant differences in general health and ESR between those that received a baseline triamcinolone injection and those that did not.

Figure 2: *Medication percentages of patients with early RA at 12 months*

DISCUSSION

This study demonstrated that almost 80% of recently diagnosed RA patients rapidly achieved remission during the first year of their disease. Among a wide range of possible prognostic factors of achieving remission, no accurate predictors could be identified. This provides additional evidence that a T2T strategy aiming at remission is beneficial for recently diagnosed RA patients in clinical practice and should therefore be implemented widely.

The vast majority of the patients in the current study achieved the treatment target using csDMARDs only and only 10% of patients needed to be prescribed a bDMARD within 12 months. In contrast to most previous T2T protocols, the protocol additionally allowed for optional intramuscular triamcinolone injections at the discretion of the treating rheumatologist. Interestingly, patients who received an injection at baseline generally had more swollen and tender joints than those who did not. However, there was no association with ESR or patient-reported general health. Apparently, the rheumatologists seemed to base their decision of using triamcinolone injections mostly on the number of affected joints and not on other indicators of disease activity. Future randomized studies could examine whether the number of affected joints is indeed a relevant indicator for the effectiveness of additional triamcinolone injections.

Fundamental, translational and clinical studies should ultimately lead to improvement of clinical care. Subsequent implementation in healthcare is often the real challenge, clinicians have to demonstrate that innovations are effective and safe, and contribute to increased health of the patient. The major strength of this study is the use of real life data from consecutive patients, recently diagnosed with RA, who were being treated according to a state of art T2T remission

induction protocol. Limitations of the study are the relatively low number of patients ($n=137$) and the absence of potential genetic predictors and other biomarkers. Also, in our study the follow-up period was only one year. Although this period of follow-up is not representative for the long patient journey of RA, until now successful early treatment is the best predictor of the future. However, longer follow-up is needed to establish whether current clinical remission rates prove sustainable [22].

The current study examined the prognostic value of a wide range of commonly available demographic and disease-related variables. Among these, no predictors were identified for (not) reaching remission. While some markers appeared to be associated with early remission at 17 weeks, only ESR remained significantly predictive in multivariable analysis. The finding that low ESR at baseline was associated with achieving DAS28 remission at 17 weeks is not surprising, as ESR is one of the components of the DAS28. Moreover, this finding is in line with earlier studies by Forslind et al. [23], who found that patients with high baseline DAS28 were less likely to achieve remission in all models and at all time points. Low ESR also showed a non-significant trend in the study by Vazquez et al. [24] and Burmester et al. [25] also found a univariate association with lower CRP, an acute phase reactant similar to ESR.

The finding that none of the potential predictors were significantly associated with achieving remission, is in contrast with previous reports in early RA which have reported a variety of predictors ranging from sociodemographic characteristics, clinical and laboratory measures, to genetic markers. More specifically, female sex [23, 26, 27], older age [26, 28], RF positivity [17, 23, 29], and smoking [30] were previously found to be associated with fewer remission periods. The finding that none of these factors were predictive in the present study may be due to the very high proportion of patients achieving remission (almost 80%) in the current T2T strategy where other studies have reported remission percentages ranging from 10-65% [31].

In conclusion, the results of this study demonstrated that the current T2T strategy appears to be broadly applicable to all patients with recently diagnosed RA. Together with the absence of clear baseline predictors of remission, this suggests that clinicians in daily clinical practice may focus on DAS28 scores only, without needing to take other patients characteristics into account.

REFERENCES

1. Donahue KE, Gartlehner G, Jonas DE, Lux LJ, Thieda P, Jonas BL, Hansen RA, Morgan LC, Lohr KN: Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. *Ann Intern Med* 2008, 148:124–34.
2. Ma MHY, Kingsley GH, Scott DL: A systematic comparison of combination DMARD therapy and tumour necrosis inhibitor therapy with methotrexate in patients with early rheumatoid arthritis. *Rheumatology (Oxford)* 2010, 49:91–8.
3. Vermeer M, Kuper HH, Hoekstra M, Haagsma CJ, Posthumus MD, Brus HLM, van Riel PLCM, van de Laar MAFJ: Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. *Arthritis Rheum* 2011, 63:2865–72.
4. Vermeer M, Kuper HH, Moens HJB, Drossaers-Bakker KW, van der Bijl AE, van Riel PLCM, van de Laar MAFJ: Sustained beneficial effects of a protocolized treat-to-target strategy in very early rheumatoid arthritis: three-year results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort. *Arthritis Care Res (Hoboken)* 2013, 65:1219–26.
5. Gremese E, Salaffi F, Bosello SL, Ciapetti A, Bobbio-Pallavicini F, Caporali R, Ferraccioli G: Very early rheumatoid arthritis as a predictor of remission: a multicentre real life prospective study. *Ann Rheum Dis* 2013, 72:858–62.
6. Schoels M, Knevel R, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas DT, Burmester G, Combe B, Cutolo M, Dougados M, Emery P, van der Heijde D, Huizinga TWJ, Kalden J, Keystone EC, Kvien TK, Martin-Mola E, Montecucco C, de Wit M, Smolen JS: Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. *Ann Rheum Dis* 2010, 69:638–43.
7. Smolen JS, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas D, Burmester G, Combe B, Cutolo M, de Wit M, Dougados M, Emery P, Gibofsky A, Gomez-Reino JJ, Haraoui B, Kalden J, Keystone EC, Kvien TK, McInnes I, Martin-Mola E, Montecucco C, Schoels M, van der Heijde D, van der Heijde D: Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010, 69:631–7.
8. Gossec L, Dougados M, Goupille P, Cantagrel A, Sibilia J, Meyer O, Sany J, Daurès J-P, Combe B: Prognostic factors for remission in early rheumatoid arthritis: a multiparameter prospective study. *Ann Rheum Dis* 2004, 63:675–80.
9. Scott DL, Symmons DP, Coulton BL, Popert AJ: Long-term outcome of treating rheumatoid arthritis: results after 20 years. *Lancet* 1987, 1:1108–11.
10. Pope RM: Rheumatoid arthritis: pathogenesis and early recognition. *Am J Med* 1996, 100:3S–9S.
11. Shaver TS, Anderson JD, Weidensaul DN, Shahouri SH, Shahouri SS, Busch RE, Mikuls TR, Michaud K, Wolfe F: The problem of rheumatoid arthritis disease activity and remission in clinical practice. *J Rheumatol* 2008, 35:1015–22.
12. van der Helm-van Mil AHM, Breedveld FC, Huizinga TWJ: Aspects of early arthritis. Definition of disease states in early arthritis: remission versus minimal disease activity. *Arthritis Res Ther* 2006, 8:216.
13. Jayakumar K, Norton S, Dixey J, James D, Gough A, Williams P, Prouse P, Young A: Sustained clinical remission in rheumatoid arthritis: prevalence and prognostic factors in an inception cohort of patients treated with conventional DMARDS. *Rheumatology (Oxford)* 2012, 51:169–75.

14. Schipper LG, Vermeer M, Kuper HH, Hoekstra MO, Haagsma CJ, Den Broeder AA, van Riel P, Fransen J, van de Laar MAFJ: A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. *Ann Rheum Dis* 2012, 71:845–50.
15. Siemons L, Ten Klooster PM, Vonkeman HE, W Glas CA, van de Laar MAFJ: Distinct trajectories of disease activity over the first year in early rheumatoid arthritis patients following a treat-to-target strategy. *Arthritis Care Res (Hoboken)* 2013.
16. Eberhardt K, Fex E: Clinical course and remission rate in patients with early rheumatoid arthritis: relationship to outcome after 5 years. *Br J Rheumatol* 1998, 37:1324–9.
17. Verstappen SMM, van Albada-Kuipers GA, Bijlsma JWJ, Blaauw AAM, Schenk Y, Haanen HCM, Jacobs JWJ: A good response to early DMARD treatment of patients with rheumatoid arthritis in the first year predicts remission during follow up. *Ann Rheum Dis* 2005, 64:38–43.
18. Möttönen T, Hannonen P, Korpela M, Nissilä M, Kautiainen H, Ilonen J, Laasonen L, Kaipainen-Seppänen O, Franzen P, Helve T, Koski J, Gripenberg-Gahmberg M, Myllykangas-Luosujärvi R, Leirisalo-Repo M: Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. *Arthritis Rheum* 2002, 46:894–8.
19. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL: Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995, 38:44–8.
20. Bruce B, Fries JF: The Health Assessment Questionnaire (HAQ). *Clin Exp Rheumatol* 2005, 23(5 Suppl 39):S14–8.
21. Ware JE, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992, 30:473–83.
22. Kuriya B, Xiong J, Boire G, Haraoui B, Hitchon C, Pope J, Thorne JC, Tin D, Keystone EC, Bykerk V: Earlier Time to Remission Predicts Sustained Clinical Remission in Early Rheumatoid Arthritis - Results from the Canadian Early Arthritis Cohort (CATCH). *J Rheumatol* 2014, 41:2161–6.
23. Forslind K, Hafström I, Ahlmén M, Svensson B: Sex: a major predictor of remission in early rheumatoid arthritis? *Ann Rheum Dis* 2007, 66:46–52.
24. Vázquez I, Graell E, Gratacós J, Cañete JD, Viñas O, Ercilla MG, Gómez A, Hernández M V, Rodríguez-Cros JR, Larrosa M, Sanmartí R: Prognostic markers of clinical remission in early rheumatoid arthritis after two years of DMARDs in a clinical setting. *Clin Exp Rheumatol* , 25:231–8.
25. Burmester GR, Ferraccioli G, Flipo R-M, Monteagudo-Sáez I, Unnebrink K, Kary S, Kupper H: Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. *Arthritis Rheum* 2008, 59:32–41.
26. Wolfe F, Hawley DJ: Remission in rheumatoid arthritis. *J Rheumatol* 1985, 12:245–52.
27. Harrison BJ, Symmonds DP, Brennan P, Barrett EM, Silman AJ: Natural remission in inflammatory polyarthritis: issues of definition and prediction. *Br J Rheumatol* 1996, 35:1096–100.
28. Pease CT, Bhakta BB, Devlin J, Emery P: Does the age of onset of rheumatoid arthritis influence phenotype?: a prospective study of outcome and prognostic factors. *Rheumatology (Oxford)* 1999, 38:228–34.

29. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, Falappone PC, Ferrante A, Malesci D, Massara A, Nacci F, Secchi ME, Manganelli S, Salaffi F, Bambara ML, Bombardieri S, Cutolo M, Ferri C, Galeazzi M, Gerli R, Giacomelli R, Grassi W, Lapadula G, Cerinic MM, Montecucco C, Trotta F, Triolo G, Valentini G, Valesini G, Ferraccioli GF: Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. *J Rheumatol* 2007, 34:1670–3.
30. van der Woude D, Young A, Jayakumar K, Mertens BJ, Toes REM, van der Heijde D, Huizinga TWJ, van der Helm-van Mil AHM: Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large early arthritis cohorts. *Arthritis Rheum* 2009, 60:2262–71.
31. van der Kooij SM, Allaart CF, Dijkmans BA, Breedveld FC: Innovative treatment strategies for patients with rheumatoid arthritis. *Curr Opin Rheumatol* 2008, 20:287–94.

Initial combination therapy versus step-up therapy in treatment to the target of remission in daily clinical practice in early rheumatoid arthritis patients: results from the DREAM registry

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ABSTRACT

Background: Treat-to-target (T2T) is widely accepted as the standard of care for patients with rheumatoid arthritis (RA) and has been shown to be more effective than traditional routine care. The objective of this study was to compare the effectiveness of two T2T strategies in patients with early RA: a step-up approach starting with methotrexate (MTX) monotherapy (cohort I) versus an initial disease modifying antirheumatic drug combination approach (cohort II).

Methods: A total of 128 patients from cohort II were case-control-matched with 128 patients from cohort I on gender, age and baseline disease activity. Twelve-month follow-up data were available for 121 patients in both cohorts. The primary outcome was the proportion of patients having reached at least one 28-joint Disease Activity Score (DAS28) score < 2.6 (remission) during 12 months of follow-up. Secondary outcomes were time until remission was achieved and mean DAS28 scores at 6- and 12-months follow-up.

Results: After 12 months of follow-up, remission was reached at least once in 77.3% of the patients in cohort II versus 71.9% in cohort I ($P = 0.31$). Median time until first remission was 17 weeks in cohort II versus 27 weeks in cohort I ($P = 0.04$). A significant time by strategy interaction was found in mean DAS28 scores. Post-hoc analysis revealed a significant difference in mean DAS28 scores between both cohorts at 6 months ($P = 0.04$), but not at 12 months ($P = 0.36$).

Conclusions: The initial combination strategy resulted in a comparable remission rate after 1 year but a significantly shorter time until remission. At 6 months, mean DAS28 scores were lower in patients with initial combination treatment than in those with step-up therapy. At 12 months, no significant differences remained in mean DAS28 scores or the proportion of patients in remission.

BACKGROUND

Treat-to-target (T2T) is widely accepted as the standard of care for patients with rheumatoid arthritis (RA) and is now recommended in national and international guidelines [1, 2]. Under the controlled conditions of randomized clinical trials, T2T aiming at remission or low disease activity leads to good clinical outcomes [3–5]. Furthermore it has been shown that T2T is more effective than traditional routine care, especially when a protocol treatment strategy is used [6]. Recently, it was shown that T2T also leads to more rapid and higher 28-joint Disease Activity Score (DAS28) remission rates and larger improvements in functional ability and patient assessments than usual care in daily clinical practice [7]. Previous clinical trials have additionally compared the effectiveness of different disease-modifying antirheumatic drug (DMARD) strategies, including initial monotherapy, initial combination therapy or step-up combination therapy with and without the use of corticosteroids or biologicals [5, 8–13]. On the basis of these trials, initial combination therapy appears to be more effective than initial monotherapy [5, 12, 14], while the combination of methotrexate (MTX) monotherapy with high-dose step-down prednisone seems to have equally good results [11, 15]. However, the optimal treatment protocol is still not clear.

A challenge in the field of RA management remains the implementation of T2T strategies in daily clinical practice. Healthcare professionals may be reluctant to prescribe complex combination therapies, including high-dose corticosteroids, because of concerns about patient compliance and unfavorable side effects [16]. Moreover, time constraints and problems with organizational structures and processes can complicate successful implementation of T2T in daily clinical practice [17]. T2T starting with MTX monotherapy was successfully implemented in the first Dutch Rheumatoid Arthritis Monitoring (DREAM) registry remission induction cohort [18–20]. Despite very promising results, T2T did not have the same impact on all patients [21]. A relevant proportion of patients still did not reach clinical remission within 12 months of treatment [18]. DREAM registry remission induction cohort I was used in the first observational study to describe the results of implementing a T2T strategy in daily clinical practice. Subsequent studies using different T2T strategies are needed to establish which strategy gives the optimal result in daily clinical practice.

Consequently, a second inception cohort was started (cohort II), in which patients were treated with initial combination DMARD therapy, consisting of high-dose MTX and hydroxychloroquine (HCQ) with an optional intramuscular triamcinolone acetonide (TCA) injection at the discretion of the rheumatologist. The aim of the present study was to compare the clinical outcomes of both treatment strategies after 1 year of follow-up.

METHODS

Data selection and study design

In this study, we used data from the ongoing DREAM registry remission induction strategies I and II, two observational, multicenter cohorts established in 2006 and 2012, respectively. In both cohorts, all adults aged ≥ 18 years with a clinical diagnosis of RA and a disease duration (time from the diagnosis to the start of therapy) < 1 year were enrolled consecutively immediately after a clinical diagnosis of RA. For this study, data from two hospitals were used: Medisch Spectrum Twente in Enschede and Isala Klinieken in Zwolle, both in the Netherlands. Both treatment strategies were in line with clinical practice and complied with current guidelines for treatment of RA. Exclusion criteria for both cohorts were use of prednisolone ≥ 10 mg/day or previous or current treatment with DMARDs. The medical ethics committees of the Medisch Spectrum Twente, Enschede and Isala, Zwolle hospitals determined, in accordance with Dutch law, that no ethical approval was required, because all data were collected in the course of regular daily clinical practice. Nonetheless, patients were completely informed about the study, and informed consent was obtained from each patient.

At the time of the present analysis, 137 patients had a follow-up of at least 1 year in cohort II. For the aim of this quasi-experimental study, a total of 128 patients from cohort II could be individually matched with 128 patients from cohort I on sex, age (± 5 yrs.) and baseline disease activity (± 0.5 on the DAS28).

Treat-to-target protocol

T2T protocol in cohort I

Patients were evaluated at 0, 8, 12, 20, 24, 36, and 52 weeks and every 3 months thereafter. Per-protocol treatment advice was an initial monotherapy of 15 mg/week MTX, with folic acid taken on the second day after MTX. In case of insufficient response (DAS28 ≥ 2.6) at the first subsequent time point, the following per-protocol treatment steps were advised. After two months, the MTX dosage was increased to 25 mg/week; after 3 months, sulfasalazine (SSZ) 2000 mg/day was added. After 20 weeks, the SSZ dosage was increased to 3000 mg/day. In accordance with Dutch reimbursement regulations, anti-tumor necrosis factor (anti-TNF)- α treatment was prescribed at week 24 for patients whose DAS28 remained ≥ 3.2 . In these cases, SSZ was replaced with subcutaneous administration of 40 mg adalimumab every 2 weeks. At week 36, the frequency of adalimumab was increased to 40 mg/week for patients with DAS28 ≥ 2.6 . At week 52, adalimumab was exchanged for etanercept 50 mg/week for patients with DAS28 ≥ 3.2 . If at any time point the target of DAS28 < 2.6 was met, medication was held constant.

In case of sustained remission (≥ 6 months), medication was gradually reduced and eventually discontinued. In case of a disease flare ($\text{DAS28} \geq 2.6$), the last effective medication or medication dose was restarted and treatment could subsequently be intensified. In individual patients with contraindications to specific medication, deviations from the protocol were allowed. In patients with an allergy to sulfa drugs (sulfonamides), SSZ was replaced by oral HCQ at a dosage of 400 mg/day. Concomitant treatment with nonsteroidal anti-inflammatory drugs, prednisolone at a dosage of ≤ 10 mg/day and intraarticular corticosteroid injections was allowed at the discretion of the attending rheumatologist. On clinical indication, the attending rheumatologist was free to diverge from the medication schedule at any time. Further details of the study protocol are reported elsewhere [18].

T2T protocol in cohort II

Patients were evaluated at months 0, 2, 4, 6 and every 3 months thereafter. Treatment advice was an initial combination therapy of MTX 20 mg/week and HCQ 200 mg twice daily. As bridging therapy, an optional intramuscular triamcinolone injection to a maximum dosage of 120 mg could be given. After 1 month, the MTX dosage was increased to 25 mg/week, independent of disease activity. All patients who started MTX also received folic acid on the second day after MTX. After 2 months, in case of persistent disease activity ($\text{DAS28} \geq 2.6$), the MTX dosage was further increased to 30 mg/week and an extra optional intramuscular triamcinolone injection could be administered. After four months, in case of moderate to high disease activity ($\text{DAS28} \geq 3.2$), a TNF inhibitor (adalimumab, etanercept or infliximab) was added. In case of low disease activity ($2.6 < \text{DAS28} < 3.2$), the attending rheumatologist could choose between SSZ 2000-3000 mg/day or an intramuscular triamcinolone injection.

Similar to cohort I, disease activity was assessed using the DAS28 at each subsequent visit. If remission ($\text{DAS28} < 2.6$) had not been reached, treatment was intensified. If the patient was in DAS28 remission, medication was held constant. In case of sustained remission (≥ 6 months), medication was tapered and eventually discontinued according to a predetermined tapering schedule. In case of disease flare ($\text{DAS28} \geq 2.6$), the last effective medication or medication dosage was restarted and treatment could subsequently be intensified. On clinical indication, the attending rheumatologist was free to diverge from the medication schedule at any time. For patients with contraindications to specific medications, deviations from the protocol were also allowed.

Assessments

At each assessment, data were collected on various clinical and patient-reported outcome measures, including measures of disease activity, health-related quality of life, physical functioning, and laboratory measures. Disease activity was assessed by trained rheumatology nurses using the DAS28, consisting of swollen and tender joint counts in 28 joints, the erythrocyte sedimentation rate (ESR), and a 100-mm visual analog scale (VAS) on general health (0 = “very good” and 100 = “very bad”) [22]. The Health Assessment Questionnaire Disability Index (HAQ-DI) was used to assess physical function [23]. Furthermore, patients rated their pain on a 100-mm VAS (0 = “no pain” and 100 = “unbearable pain”) and completed the 36-item Short Form Health Survey (SF-36) for assessment of their current physical and mental health status [24].

Outcome measures

The primary outcome was the proportion of patients having reached at least one DAS28 < 2.6 (DAS28 remission) after 1 year of follow-up. Secondary outcomes were time until remission was achieved and changes in mean DAS28 scores at 6 months and 1 year.

Statistical analysis

All statistical calculations were performed using the statistical package IBM SPSS version 20.0 for Windows (IBM, Armonk, NY, USA). Missing values for ESR (1.8%) and well-being (0.3%) were imputed on the basis of swollen and tender joint counts and C-reactive protein (CRP) using single imputation with the expectation-maximization method in SPSS. Descriptive statistics for normally distributed variables or categorical variables were reported as frequencies, means, and standard deviations (SD). If variables were not normally distributed, the median with the corresponding interquartile range (IQR) was reported. To test for any baseline differences, we performed independent t tests for normally distributed variables, Mann-Whitney U tests for nonnormally distributed variables and χ^2 tests for categorical variables. Differences in the proportion of patients achieving remission were tested using χ^2 tests. To compare time until first moment of DAS28 remission, Kaplan-Meier survival analysis was used with log-rank testing for between-group differences. The course of DAS28 over time was compared between groups by specifying a linear mixed model with strategy and time as fixed factors. As the visit schedules were slightly different between both cohorts, only baseline, 6-month, and 12-month data were used for this analysis. An ante-dependence structure was used as a model for the covariance matrix because it gave the best fit to the data.

Post-hoc analysis of covariance (ANCOVA) was performed with baseline DAS28 score as a covariate. For all tests, $P < 0.05$ was considered to be significant.

RESULTS

Table 1 summarizes baseline patient characteristics of both cohorts. All patients had active disease with a mean DAS28 of 4.8 ± 1.1 in cohort II versus 4.5 ± 1.1 in cohort I. Twelve-month data were available for 121 patients (94.5%) in both cohorts. In cohort I, seven patients were lost to follow-up of whom one had received another diagnosis (systemic lupus erythematosus), four were lost to follow-up for unknown reasons, and two had no 12-month visit (but were still in the cohort). In cohort II, seven patients were lost to follow-up of whom one died, one achieved medication-free remission, one was misdiagnosed as having arthritis, two were lost to follow-up for unknown reasons, and two had no 12-month visit (but were still in the cohort).

Table 1 Baseline characteristics of patients in both cohorts

Characteristics	Cohort I ($n = 128$)	Cohort II ($n = 128$)	<i>P</i> -value
Female, sex n (%)	79 (61.7%)	79 (61.7%)	1.00
Age, mean $\pm$ SD years	59.1 ± 13.0	59.5 ± 12.8	0.81
DAS28 - ESR, mean $\pm$ SD	4.5 ± 1.1	4.8 ± 1.1	0.02
ESR (mm/h), median (IQR)	22.0 (14.0 – 41.0)	29.0 ^a (14.0 – 45.0)	0.20
CRP (mg/l), median (IQR)	10.0 ^b (5.0 – 22.0)	11.5 (4.3 – 24.8)	0.79
Anti-CCP-positive, n (%)	74 ^c (58.3%)	77 ^c (60.2%)	0.93
RF-positive, n (%)	62 (48.4%)	76 (59.4%)	0.11
SJC, <i>n</i> , median (IQR)	6.0 (3.0 – 9.0)	5.0 (2.0 – 10.0)	0.24
TJC, <i>n</i> , median (IQR)	3.0 (1.0 – 7.0)	4.0 (2.0 – 10.0)	0.03
HAQ-SDI, median (IQR)	1.19 ^d (0.88 – 1.63)	1.0 ^e (0.38 – 1.50)	<0.01
VAS well-being, median (IQR)	50.0 (28.3 – 65.0)	51.0 (35.0 – 70.0)	0.29
VAS pain, median (IQR)	50.0 ^f (39.8 – 64.0)	62.0 ^g (49.0 – 75.0)	<0.01
SF36-PCS, mean $\pm$ SD	38.1 ± 7.6^h	37.3 ± 9.2^i	0.51
SF36-MCS, mean $\pm$ SD	40.7 ± 7.4^j	44.9 ± 11.9^k	0.00
BMI, kg/m ² , mean $\pm$ SD	26.5 ± 4.8^l	26.0 ± 4.1^m	0.39

^a $n = 127$, ^b $n = 121$, ^c $n = 127$, ^d $n = 102$, ^e $n = 87$, ^f $n = 122$, ^g $n = 72$, ^h $n = 105$, ⁱ $n = 86$, ^j $n = 105$, ^k $n = 86$, ^l $n = 126$,

^m $n = 119$

DAS28-ESR Disease Activity Score in 28 joints using erythrocyte sedimentation rate, CRP C-reactive protein, TJC tender joint count, SJC swollen joint count, HAQ-SDI Health Assessment Questionnaire Disability Index (standard scoring), SF-36 36-item Short Form Health survey (version 2), PCS Physical Component Summary, MCS Mental Component Summary, BMI body mass index, RF rheumatoid factor, CCP cyclic citrullinated peptide, VAS visual analogue scale

Remission

First remission within 6 months was achieved in 63.3% (81 of 128) of the patients in cohort II versus 48.4% (62 of 128) in cohort I ($P = 0.02$). First remission within 12 months was achieved in 77.3% ($n = 99$ of 128) of the patients in cohort II versus 71.9% (92 of 128) in cohort I ($P = 0.31$). Median time until first remission was 17 weeks (95% confidence interval [CI] 13.2 – 20.8) in cohort II versus 27 weeks (95% CI 20.7– 33.3) in cohort I ($P = 0.04$) (Fig. 1).

The proportion of patients in remission in cohort II and I at the time of the 6-months assessments were 61.7% (74 of 120) and 45.9% (56 of 122) ($P = 0.01$), respectively. The proportion of patients in remission in cohorts II and I at the 12-months assessments were 63.6% (77 of 121) and 60.3% ($n = 73$ of 121) ($P = 0.60$).

The majority of the patients in both cohorts reached their first remission using the initial medication only. In cohort II, 84.8% achieved remission with MTX + HCQ, while in cohort I 63.0% achieved remission with MTX monotherapy.

Figure 1. Kaplan-Meier curves for time until first remission was reached. The solid line represents cohort II, and the dashed line represents cohort I

Course over time of the DAS28

Figure 2 represents the mean DAS28 over time in both cohorts. A significant time by strategy interaction was found ($P = 0.01$), indicating a different pattern of DAS28 change over time between both cohorts. At 6 months, the mean DAS28 in cohort II was below the cutoff for remission (DAS28 < 2.6), while the mean DAS28 in cohort I was still above remission (DAS28 > 2.6). At 12 months, mean DAS28 was < 2.6 in both cohorts. According to the post hoc ANCOVA, mean DAS28 scores were significantly lower in cohort II at 6 months (mean difference 0.30, 95 % CI 0.01 – 0.58, $P = 0.04$) but not at 12 months (mean difference 0.13, 95 % CI -0.14 – 0.40, $P = 0.36$).

Figure 2. Decrease in mean 28-joint Disease Activity score (DAS28) in treat to target cohort II versus cohort I in 1 year. The dashed line represents cohort II, and the solid line represents cohort I

Medication use

At baseline, 67 patients (53.3%) in cohort II received an intramuscular injection with triamcinolone versus 4 patients (3.1%) in cohort I ($P < 0.01$). Receiving an injection with triamcinolone in cohort II was associated with a higher odds ratio (OR 2.14, 95 % CI 1.03 – 4.46, $P = 0.04$) of achieving first remission within 6 months but no longer with achieving remission within 12 months (OR 1.77, 95 % CI 0.77 – 4.10, $P = 0.18$). The actual medication used at 12 months (Table 2) was significantly different between both cohorts ($P = 0.03$).

The vast majority of the patients in both cohorts received conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) only at 12 months. A small percentage of the patients in both cohorts were prescribed a biologic DMARD. In cohort II, there were slightly more patients for whom DMARD therapy was fully discontinued.

Table 2. *Medication at 12 months*

Medication	Cohort I (<i>n</i> = 128)	Cohort II (<i>n</i> = 128)
No DMARD	2 (1.6%)	10 (7.8%)
csDMARD only	116 (90.6%)	104 (81.3%)
bDMARD	5 (3.9%)	11 (8.6%)
Lost to follow up	5 (3.9%)	3 (2.3%)

DMARD disease-modifying antirheumatic drug, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *bDMARD* biologic disease-modifying antirheumatic drug

DISCUSSION

The results of this study suggest that the previously reported outcomes that were achieved by implementation of T2T with initial MTX monotherapy in daily clinical practice may be reproduced, and even improved upon, using an initial combination approach. In the present study, DAS28 remission was reached at least once in 77.3% of the patients in cohort II versus 71.9% in cohort I in 1 year of follow-up. Although after 1 year there was no significant difference in the number of patients who had reached remission, remission was reached significantly more rapidly, with a median time to first remission of 17 weeks in cohort II versus 27 weeks in cohort I. A significant difference between strategies in mean DAS28 scores was also found at 6 months, but no longer at 12 months. Therefore, T2T using initial combination therapy may not be superior in the number of patients achieving remission in the longer term but the strategy does lead to a significantly shorter time until first remission is achieved.

Researchers in various T2T studies in patients with recent-onset RA have reported remission rates varying from 10% to 78% [25]. However, it should be noted that these remission rates are difficult to compare, as the investigators in these studies used different criteria for remission and reported slightly different follow-up periods. The TICORA study had the highest proportion (65%) of patients in remission (defined as DAS44 < 1.6) after 18 months of follow-up so far [4]. In the BeST study, the overall proportion of patients in DAS44 remission at 1 year was 32%, with no differences between the four therapeutic groups [26]. The CAMERA group reported that 35% of the patients in the intensive group attained remission (defined as no swollen joints and at least two of three of the following criteria: number of tender joints ≤ 3, ESR ≤ 20 mm/h and VAS general well-being ≤ 20 mm) for a period of 3 months after 1 year of follow-up [3]. The IMPROVED study showed an early DAS44 remission rate of 61% [15].

The CareRA trial researchers, comparing three different intensive combination strategies with glucocorticoids, reported DAS28 (based on CRP) remission rates ranging from 68.1 to 73.6% within 16 weeks [27]. The tREACH trial investigators compared two triple-DMARD induction therapies with MTX monotherapy and reported that approximately 78% of the patients using triple-DMARD therapy had a DAS < 2.4 after three months, compared with 60% of the patients using MTX monotherapy [28].

The present study shows that both DREAM registry remission induction cohorts I and II resulted in comparably high proportions of patients achieving remission within 12 months. While the implementation of a protocol 'T2T' may in itself explain the high remission rates in both cohorts, apparently even better results may be attained regarding the time needed to achieve first remission by implementing initial combination protocols in daily clinical practice. This is in accordance with previous randomized clinical trials. Among the different therapeutic strategies, early combination therapy that included high-dose step-down DMARDs and low-dose steroids was shown to be most effective in the management of early RA [8, 26, 29–31]. Low dose prednisone added to conventional DMARD treatment in patients with early RA induced earlier and better disease activity control and provided greater probability for a more stable clinical remission over time [32]. A strict protocol, frequent monitoring, and the commitment and adherence of doctors and nurses may also contribute to optimal outcomes in daily clinical practice [6, 33].

Differences in disease activity and in time until remission are clinically important and are likely to also have significant social and economic impact. For instance, patients with persistently active disease are more likely to discontinue work [34]. The DREAM registry remission induction cohort I already showed the feasibility of sustained remission in daily clinical practice [19]. Cohort II also demonstrated impressive improvements in disease activity, comparable with or even better than that reported in previous studies of combination therapy for RA [5, 8, 11–13, 18]. In the present study, mean DAS28 scores were significantly lower in cohort II than those in cohort I at 6 months but not at 12 months. This is in line with clinical trials showing that initial combination therapy appears to result in more rapid improvements in disease activity, daily functioning, and quality of life than initial monotherapy [4, 11, 26, 35].

Optimal use of MTX in combination with other DMARDs early in the course of the disease leads to considerable improvement in disease activity [3, 4, 19]. Unfortunately, previous studies show some conflicting results regarding the efficacy of monotherapy versus combination therapy. Double- or triple-combination therapy appears to lead to better clinical outcomes than MTX monotherapy [13, 26, 35].

The TEAR trial concluded that combination treatment was more effective than MTX monotherapy before step-up therapy [14]. The CARDERA study, which was not an initial combination therapy, showed that intensive combination therapy with MTX, ciclosporin and glucocorticosteroids after failure of MTX monotherapy leads to sustained benefits in damage and disability outcomes [36]. However, a recent study done in Belgium (the CareRA trial) showed that in high-risk patients with RA, MTX in combination with a moderate step-down dose of glucocorticosteroids was as effective in inducing remission as DMARD combination therapies with moderate or high step-down glucocorticosteroid doses [27]. In contrast, the tREACH trial showed that a DMARD combination was better than MTX monotherapy, both in combination with low-dose glucocorticoids bridging [12]. In the United States, MTX + HCQ is by far the DMARD combination most commonly prescribed by rheumatologists [37]. It has been shown to be more potent than MTX used alone [38]. An explanation for this may be that HCQ increases the bioavailability of MTX and/or reduces the clearance of the drug [39].

In the present study, the vast majority of the patients in both cohorts achieved the treatment target using csDMARDs only, and a small number of the patients in both cohorts were using biologic DMARDs at 12 months. This highlights again the importance of the initial treatment choice for the majority of the patients.

It should be noted that the present study was a quasi-experimental study of two cohorts separated over time. The first cohort started in 2006 with MTX mono-therapy, and the second cohort started in 2012 with a DMARD combination therapy. Although we did not conduct a randomized trial, we still think that the design and results of the study allow us to compare the two cohorts. The cohorts consist of very similar populations of all consecutive newly diagnosed patients with RA treated in the same hospitals by the same rheumatologists. Patients in cohort II were additionally case-control-matched with patients in cohort I on gender, age and baseline disease activity. Although baseline disease activity, disability and pain were slightly but significantly worse in cohort II, the number of patients achieving remission within 6 months was even higher in this cohort. Moreover, post hoc analyses of mean DAS28 scores controlling for baseline disease activity produced very similar results.

Because in our study we used real-life observational data, the results are generalizable to daily clinical practice. Longer follow-up is needed to investigate the sustainability of remission in cohort II. However, previous studies have shown that a shorter time until remission is related to the sustainability of remission, supporting the importance of early intervention with effective therapy to achieve early remission [40].

Although the remission rates in this study were very high, there is still a small percentage of patients who do not achieve remission, thus creating a need to further identify predictors of remission [21].

CONCLUSIONS

Initial RA combination therapy with high-dose MTX, HCQ and optional intramuscular TCA was not superior in achieving the number of patients in remission after 1 year, but it did result in a shorter time until first remission versus a step-up approach using MTX and SSZ in the setting of T2T therapy in daily clinical practice.

REFERENCES

1. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, Emery P, Gaujoux-Viala C, Gossec L, Nam J, Ramiro S, Winthrop K, de Wit M, Aletaha D, Betteridge N, Bijlsma JWJ, Boers M, Buttgereit F, Combe B, Cutolo M, Damjanov N, Hazes JMW, Kouloumas M, Kvien TK, Mariette X, Pavelka K, van Riel PLCM, Rubbert-Roth A, Scholte-Voshaar M, Scott DL, et al.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014, 73:492–509.
2. Smolen JS, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas D, Burmester G, Combe B, Cutolo M, de Wit M, Dougados M, Emery P, Gibofsky A, Gomez-Reino JJ, Haraoui B, Kalden J, Keystone EC, Kvien TK, McInnes I, Martin-Mola E, Montecucco C, Schoels M, van der Heijde D, van der Heijde D: Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010, 69:631–7.
3. Verstappen SMM, Jacobs JWJ, van der Veen MJ, Heurkens AHM, Schenk Y, ter Borg EJ, Blaauw AAM, Bijlsma JWJ: Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis* 2007, 66:1443–9.
4. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, Kincaid W, Porter D: Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004, 364:263–9.
5. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJSM, Hazes JMW, Zwinderman AH, Roday HK, Han KH, Westedt ML, Gerards AH, van Groenendaal JHLM, Lems WF, van Krugten M V, Breedveld FC, Dijkmans BAC: Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005, 52:3381–90.
6. Schipper LG, van Hulst LTC, Grol R, van Riel PLCM, Hulscher MEJL, Fransen J: Meta-analysis of tight control strategies in rheumatoid arthritis: protocolized treatment has additional value with respect to the clinical outcome. *Rheumatology (Oxford)* 2010, 49:2154–64.
7. Schipper LG, Vermeer M, Kuper HH, Hoekstra MO, Haagsma CJ, Den Broeder AA, van Riel P, Fransen J, van de Laar MAFJ: A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. *Ann Rheum Dis* 2012, 71:845–50.
8. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, van Zeben D, Dijkmans BA, Peeters AJ, Jacobs P, van den Brink HR, Schouten HJ, van der Heijde DM, Boonen A, van der Linden S: Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997, 350:309–18.
9. Mäkinen H, Kautiainen H, Hannonen P, Möttönen T, Leirisalo-Repo M, Laasonen L, Korpela M, Bläfield H, Hakola M, Sokka T: Sustained remission and reduced radiographic progression with combination disease modifying antirheumatic drugs in early rheumatoid arthritis. *J Rheumatol* 2007, 34:316–21.
10. Heimans L, Wevers-de Boer KVC, Visser K, Goekoop RJ, van Oosterhout M, Harbers JB, Bijkerk C, Speyer I, de Buck MPDM, de Sonnaville PBJ, Grillet BAM, Huizinga TWJ, Allaart CF: A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study. *Ann Rheum Dis* 2014, 73:1356–61.

11. den Uyl D, ter Wee M, Boers M, Kerstens P, Voskuyl A, Nurmohamed M, Raterman H, van Schaardenburg D, van Dillen N, Dijkmans B, Lems W: A non-inferiority trial of an attenuated combination strategy ('COBRA-light') compared to the original COBRA strategy: clinical results after 26 weeks. *Ann Rheum Dis* 2014, 73:1071–8.
12. de Jong PH, Hazes JM, Han HK, Huisman M, van Zeben D, van der Lubbe PA, Gerards AH, van Schaeybroeck B, de Sonnaville PB, van Krugten M V, Luime JJ, Weel AE: Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. *Ann Rheum Dis* 2014, 73:1331–9.
13. O'Dell JR, Leff R, Paulsen G, Haire C, Mallek J, Eckhoff PJ, Fernandez A, Blakely K, Wees S, Stoner J, Hadley S, Felt J, Palmer W, Waytz P, Churchill M, Klassen L, Moore G: Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002, 46:1164–70.
14. Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, Bridges SL, Zhang J, McVie T, Howard G, van der Heijde D, Cofield SS: A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the treatment of Early Aggressive Rheumatoid Arthritis Trial. *Arthritis Rheum* 2012, 64:2824–35.
15. Wevers-de Boer K, Visser K, Heimans L, Roday HK, Molenaar E, Groenendaal JHLM, Peeters AJ, Westedt M-L, Collée G, de Sonnaville PBJ, Grillet BAM, Huizinga TWJ, Allaart CF: Remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis (the IMPROVED study). *Ann Rheum Dis* 2012, 71:1472–7.
16. van Tuyl LHD, Plass AMC, Lems WF, Voskuyl AE, Dijkmans BAC, Boers M: Why are Dutch rheumatologists reluctant to use the COBRA treatment strategy in early rheumatoid arthritis? *Ann Rheum Dis* 2007, 66:974–6.
17. Meyfroidt S, van Hulst L, De Cock D, Van der Elst K, Joly J, Westhovens R, Hulscher M, Verschueren P: Factors influencing the prescription of intensive combination treatment strategies for early rheumatoid arthritis. *Scand J Rheumatol* 2014, 43:265–72.
18. Vermeer M, Kuper HH, Hoekstra M, Haagsma CJ, Posthumus MD, Brus HLM, van Riel PLCM, van de Laar MAFJ: Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. *Arthritis Rheum* 2011, 63:2865–72.
19. Vermeer M, Kuper HH, Moens HJB, Drossaers-Bakker KW, van der Bijl AE, van Riel PLCM, van de Laar MAFJ: Sustained beneficial effects of a protocolized treat-to-target strategy in very early rheumatoid arthritis: three-year results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort. *Arthritis Care Res (Hoboken)* 2013, 65:1219–26.
20. Vermeer M, Kievit W, Kuper HH, Braakman-Jansen LM, Bernelot Moens HJ, Zijlstra TR, den Broeder AA, van Riel PL, Fransen J, van de Laar MA: Treating to the target of remission in early rheumatoid arthritis is cost-effective: results of the DREAM registry. *BMC Musculoskelet Disord* 2013, 14:350.
21. Siemons L, Ten Klooster PM, Vonkeman HE, W Glas CA, van de Laar MAFJ: Distinct trajectories of disease activity over the first year in early rheumatoid arthritis patients following a treat-to-target strategy. *Arthritis Care Res (Hoboken)* 2013.

22. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL: Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995, 38:44–8.
23. Bruce B, Fries JF: The Health Assessment Questionnaire (HAQ). *Clin Exp Rheumatol* 2005, 23(5 Suppl 39):S14–8.
24. Ware JE, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992, 30:473–83.
25. van der Kooij SM, Allaart CF, Dijkmans BA, Breedveld FC: Innovative treatment strategies for patients with rheumatoid arthritis. *Curr Opin Rheumatol* 2008, 20:287–94.
26. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJSM, Hazes JMW, Zwinderman AH, Roday HK, Han KH, Westedt ML, Gerards AH, van Groenendaal JHLM, Lems WF, van Krugten M V, Breedveld FC, Dijkmans BAC: Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. *Arthritis Rheum* 2008, 58(2 Suppl):S126–35.
27. Verschueren P, De Cock D, Corluy L, Joos R, Langenaken C, Taelman V, Raeman F, Ravelingien I, Vandevyvere K, Lenaerts J, Geens E, Geusens P, Vanhoof J, Durnez A, Remans J, Vander Cruyssen B, Van Essche E, Sileghem A, De Brabanter G, Joly J, Meyfroidt S, Van der Elst K, Westhovens R: Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: the CareRA trial. *Ann Rheum Dis* 2015, 74:27–34.
28. de Jong PH, Hazes JM, Barendregt PJ, Huisman M, van Zeben D, van der Lubbe PA, Gerards AH, de Jager MH, de Sonnaville PB, Grillet BA, Luime JJ, Weel AE: Induction therapy with a combination of DMARDs is better than methotrexate monotherapy: first results of the tREACH trial. *Ann Rheum Dis* 2013, 72:72–8.
29. Wassenberg S, Rau R, Steinfeld P, Zeidler H: Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005, 52:3371–80.
30. Kirwan JR: The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. *N Engl J Med* 1995, 333:142–6.
31. Svensson B, Boonen A, Albertsson K, van der Heijde D, Keller C, Hafström I: Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. *Arthritis Rheum* 2005, 52:3360–70.
32. Todoerti M, Scirè CA, Boffini N, Bugatti S, Montecucco C, Caporali R: Early disease control by low-dose prednisone comedication may affect the quality of remission in patients with early rheumatoid arthritis. *Ann N Y Acad Sci* 2010, 1193:139–45.
33. Vermeer M, Kuper HH, Bernelot Moens HJ, Hoekstra M, Posthumus MD, van Riel PL, van de Laar MA: Adherence to a treat-to-target strategy in early rheumatoid arthritis: results of the DREAM remission induction cohort. *Arthritis Res Ther* 2012, 14:R254.

34. Puolakka K, Kautiainen H, Möttönen T, Hannonen P, Korpela M, Julkunen H, Luukkainen R, Vuori K, Paimela L, Blåfield H, Hakala M, Leirisalo-Repo M: Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: a five-year randomized followup trial. *Arthritis Rheum* 2004, 50:55–62.
35. Möttönen T, Hannonen P, Leirisalo-Repo M, Nissilä M, Kautiainen H, Korpela M, Laasonen L, Julkunen H, Luukkainen R, Vuori K, Paimela L, Blåfield H, Hakala M, Ilva K, Yli-Kerttula U, Puolakka K, Järvinen P, Hakola M, Piirainen H, Ahonen J, Pälvimäki I, Forsberg S, Koota K, Friman C: Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* 1999, 353:1568–73.
36. Choy EHS, Smith CM, Farewell V, Walker D, Hassell A, Chau L, Scott DL: Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. *Ann Rheum Dis* 2008, 67:656–63.
37. Mikuls TR, O'Dell J: The changing face of rheumatoid arthritis therapy: results of serial surveys. *Arthritis Rheum* 2000, 43:464–5.
38. Trnavský K, Gatterová J, Lindusková M, Pelisková Z: Combination therapy with hydroxychloroquine and methotrexate in rheumatoid arthritis. *Z Rheumatol* 1993, 52:292–6.
39. Carmichael SJ, Beal J, Day RO, Tett SE: Combination therapy with methotrexate and hydroxychloroquine for rheumatoid arthritis increases exposure to methotrexate. *J Rheumatol* 2002, 29:2077–83.
40. Schipper LG, Fransen J, den Broeder AA, Van Riel PLCM: Time to achieve remission determines time to be in remission. *Arthritis Res Ther* 2010, 12:R97.

CHAPTER 5

Radiographic progression in early rheumatoid arthritis patients following initial combination versus step-up treat-to-target therapy in daily clinical practice: results from the DREAM registry

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ABSTRACT

Background: Early and intensive targeted treatment with disease modifying anti-rheumatic drugs (DMARDs) has been shown to lead to substantial reductions in disease activity and radiographic damage in patients with early rheumatoid arthritis (RA). The aim of this quasi-experimental study was to compare the first-year radiographic progression rates between a treat-to-target (T2T) strategy with initial combination therapy (strategy II, started in 2012) versus an initial step-up monotherapy (strategy I, started in 2006).

Methods: A total of 128 patients from strategy II was individually matched with 128 patients from strategy I on sex, age (± 5 yrs.) and baseline disease activity (± 0.5 on the DAS28). Differences in radiographic progression (Sharp/van der Heijde) scores (SHS) and the number of patients experiencing a minimal clinically important difference (MCID; ≥ 5 SHS points) between both strategies were tested with Mann Whitney U and chi-square tests. Next, linear and logistic regression analyses were performed to examine which baseline variables were associated with radiographic progression scores and the probability of experiencing an MCID within 1 year.

Results: Patients with initial combination therapy had slightly higher baseline disease activity scores and pain scores, but better mental health scores. Patients with initial monotherapy had significantly more, and more frequently clinically relevant, radiographic progression after 1 year. Experiencing a MCID was independently associated with fewer tender joints ($P = 0.050$) and higher erythrocyte sedimentation rate ($P = 0.015$) at baseline.

Conclusion: Treating early RA patients with initial combination therapy results in better radiographic outcomes than initial monotherapy in daily clinical practice.

BACKGROUND

Rheumatoid arthritis (RA) is characterized by joint inflammation leading to joint destruction and related to a decrease in functional capacity, work disability, and reduced quality of life [1]. Prevention of structural damage is an important goal in the treatment of RA. In the last years, research has shown that early intensive treatment improves both the short- and long-term outcomes of RA [2–6]. The benefits of early use of (combinations of) disease modifying anti-rheumatic drugs (DMARDs) and biological agents [7–12], in combination with protocolled treatment aimed at a predefined goal (treat-to-target (T2T)) [13–15], has led to a change in traditional treatment paradigms. More specifically, early and intensive targeted treatment with DMARDs has been shown to lead to substantial reductions in disease activity [5, 6] and radiologic damage in patients with early RA [8, 13, 16–21].

However, in some early RA patients joint damage progresses even during DMARD use. In fact, even if DMARDs are initiated ‘very early’ in the disease, some patients may still develop erosions and progressive joint damage [2, 4, 22, 23]. Previous research has shown that in 7–17% of patients with RA in prolonged clinical remission, progression of joint damage still occurs [24, 25]. Van der Kooij et al. (2009) showed that 10–33% of patients in drug-free remission still showed progressive joint damage over a period of 4 years follow-up [26]. Whether the complete absence of arthritis activity prevents further joint damage in all patients, is still a matter of debate.

Previously, we demonstrated that implementation of a step-up T2T strategy in RA in daily clinical practice led to limited radiographic damage during a follow-up of 3 years [27, 28]. We also showed that while a T2T strategy with initial combination therapy was not superior to a T2T strategy with step-up therapy in the proportion of patients in remission at 12 months follow-up (77% versus 72%, respectively), the strategy with initial combination therapy did result in a significantly shorter time until remission. At 6 months, mean disease activity scores were lower in patients with initial combination therapy than in those with step-up therapy [6]. This is in line with clinical trials showing that initial combination therapy results in more rapid improvements in disease activity, daily functioning and quality of life than initial monotherapy [9, 13, 29, 30]. However, whether initial combination therapy and the subsequent shorter time to remission, as compared to initial step-up monotherapy, also results in better radiological outcomes has not been well studied in real-life clinical practice. Therefore, the aim of the present study was to compare the first-year radiological progression rates between a T2T strategy with initial combination therapy versus a T2T strategy with initial step-up monotherapy within the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry.

METHODS

Data selection and study design

This study used data from the ongoing DREAM 'T2T' remission induction strategies I (initial step-up monotherapy) and II (initial combination therapy), two observational, multicenter strategies which were established in 2006 and 2012, respectively [5, 6, 27]. In both strategies, adults ≥ 18 years with a clinical diagnosis of RA and a disease duration (time from the diagnosis to the start of therapy) < 1 year were enrolled consecutively immediately after a clinical diagnosis of RA. For this study, data were used from two participating hospitals; Medisch Spectrum Twente in Enschede and Isala in Zwolle, both in The Netherlands. Patients included from 2006 to 2012 were used for strategy I, and patients included from 2012 to 2013 were used for strategy II. Both treatment strategies were in line with clinical practice and comply with current guidelines for treatment of RA. Exclusion criteria for both strategies were use of prednisolone ≥ 10 mg/day or previous or current treatment with disease-modifying antirheumatic drugs (DMARDs). The Medical Ethics Committees of the Medisch Spectrum Twente, Enschede and Isala, Zwolle hospitals determined, in accordance with Dutch Law on medical-scientific research with humans, that no ethical approval was required because all data were collected in the course of regular daily clinical practice. Nonetheless, patients were completely informed and informed consent was obtained from each patient.

At the time of the current analysis, 137 patients had a follow-up of at least 1 year in strategy II. For the aim of this quasi-experimental study, a total of 128 patients from strategy II could be individually matched with 128 patients from strategy I on sex, age (± 5 yrs.) and baseline disease activity (± 0.5 on the DAS28).

Treat to target protocol

Patients in both strategies were treated according to a 'T2T' strategy with protocolized treatment adjustments aiming at remission (DAS28 < 2.6), details of which have previously been published [5, 6, 27]. Briefly, the main differences between both strategies were; time moments of evaluation, and the medication that was started immediately after diagnosis (mono/step-up therapy versus combination therapy). In strategy I, patients were evaluated at 0, 8, 12, 20, 24, 36, and 52 weeks and every 3 months thereafter. In strategy II, patients were evaluated at months 0, 2, 4, 6 and every 3 months thereafter.

In strategy I, treatment protocol was an initial monotherapy of 15 mg/week methotrexate (MTX), with folic acid taken at the second day after MTX. In case of insufficient response (DAS28 ≥ 2.6) at the subsequent time-points, the following per protocol treatment steps were

advised: after two months, MTX dosage was increased to 25 mg/week; after 3 months sulfasalazine (SSZ) 2000 mg/day was added; in week 20 SSZ dosages was increased to 3000 mg/day. Tumor necrosis factor inhibitor (TNFi) was prescribed at week 24 for patients with persistent moderate disease activity (DAS28 remained ≥ 3.2). If remission is achieved with DMARDs and/or TNFi, while maintaining remission for at least 6 months, medications were tapered and if possible discontinued starting with the TNFi and subsequently with the DMARDs.

In strategy II, treatment protocol was an initial combination therapy of MTX 20 mg/week and hydroxychloroquine (HCQ) 200 mg twice daily. As bridging therapy, an optional intramuscular triamcinolone injection to a maximum dosage of 120 mg could be given. After 1 month, MTX dosage was increased to 25 mg/week, independent of disease activity. After 2 months, in case of persistent disease activity (DAS28 ≥ 2.6), MTX dosage was further increased to 30 mg/week and an extra optional intramuscular triamcinolone injection could be administered. TNFi was prescribed at 4 months for patients with persistent moderate disease activity (DAS28 ≥ 3.2). If sustained remission for at least 6 months remission was achieved with DMARDs and/or TNFi, medications were tapered and if possible discontinued starting with the TNFi and subsequently with the DMARDs.

Assessments

At each assessment, data were collected on various clinical and patient-reported outcome measures, including measures of disease activity, health related quality of life, physical functioning, and laboratory measures. Disease activity was assessed by trained rheumatology nurses using the Disease Activity Score for 28 joints (DAS28), consisting of a 28 swollen and tender joint count, the erythrocyte sedimentation rate (ESR) and a 100 millimeter visual analog scale (VAS) on general health ("Considering all the ways your arthritis affects you, how are you doing now?", where 0 = "very good" and 100 = "very bad") [31]. The Health Assessment Questionnaire Disability Index (HAQ-DI) was used to assess physical function [32]. Furthermore, patients rated their pain in the past week on a 100 mm VAS (0 = "no pain" and 100 = "unbearable pain") and completed the Short Form Health Survey with 36 items (SF-36) in order to assess their current physical and mental health status [33]. Radiographs of hands and feet were obtained at baseline and annually thereafter. Radiographs were evaluated by two trained readers together, according to the modified Sharp/van der Heijde score (SHS) method [34], and a consensus score was obtained. Readers were not blinded to treatment strategy or assessment time point of the radiographs. A patient was classified as having erosive disease if the Sharp/van der

Heijde erosion score was ≥ 1 . Clinically relevant radiographic progression (minimal clinically important difference; MCID) was defined as an increase of ≥ 5 in the total SHS score [34].

Statistical analysis

Descriptive statistics for categorical and continuous variables were reported as frequencies, percentages, means and standard deviations (SD). If continuous variables were not normally distributed, the median with the corresponding interquartile range (IQR) was reported. To test for any baseline differences between both strategies, we performed independent t-tests for normally distributed variables, Mann-Whitney U tests for non-normally distributed variables and chi-square tests for categorical variables. As only two time points were examined (baseline and 12 months), radiographic progression was calculated for observed values only. Differences between both strategies in one-year radiographic progression and the proportion of patients experiencing an increase of ≥ 5 SHS points (MCID) were tested using Mann Whitney U test and chi-square test. Group differences in progression between strategies were additionally visualized with a cumulative probability plot [35]. Next, univariate and multivariate linear and logistic regression analyses were performed to examine which other baseline variables were associated with radiographic progression and experiencing MCID within 1 year and to test for possible interactions with treatment strategy. Continuous variables were mean centered to allow for meaningful interpretation of main effects in addition to the interaction. The linearity assumption of continuous variables in the linear regression analyses was checked with scatterplots. Variables significantly ($P < 0.05$) associated with progression or with a significant interaction term in univariate analysis were entered as a covariate into a multivariate linear and logistic regression analysis model. To avoid multicollinearity, Pearson correlations were calculated between the independent variables to check for multicollinearity problems ($r > 0.5$). The explained variance of the final linear and logistic models was examined using (Nagelkerke's pseudo) R^2 . The final logistic model was additionally tested for goodness of fit using the Hosmer and Lemeshow test. All statistical calculations were performed using version 22 of the SPSS statistical package for Windows.

RESULTS

Patient characteristics

A total of 256 patients was enrolled in the study, 128 patients for each T2T strategy. Baseline characteristic of patients in both strategies were generally similar (Table 1). Patients had active disease, with a mean DAS28 of 4.8 in the T2T strategy with initial combination therapy

(strategy II) versus a mean DAS28 of 4.5 in the 'T2T' strategy with initial monotherapy (strategy I). Most patients were female and the majority was anti-CCP positive. Patients starting with initial combination therapy had slightly higher baseline disease activity scores and pain scores, but better mental health scores. Patients receiving an injection of triamcinolone had higher baseline DAS28 scores than those that did not receive an injection in both strategy I (5.6 ± 1.5 versus 4.5 ± 1.1 ; $P = 0.038$) and strategy II (5.1 ± 1.1 versus 4.6 ± 0.9 ; $P = 0.011$). Approximately 18% of the patients received MTX at baseline subcutaneously, whereas 82% of the patients received MTX orally. At 12 months the majority of the patients in both strategies received conventional synthetic DMARDs (csDMARDs) only. In strategy I, almost 4% of the patients were prescribed a biological DMARD (bDMARD), versus almost 9% in strategy II. In strategy II there were slightly more patients in whom DMARD use was fully discontinued (8% versus 2%). Median dose of triamcinolone administered to patients at baseline in strategy I was 80 mg. 75% (3/4) of the patients received 80 mg triamcinolone and 25% (1/4) of the patients received 120 mg triamcinolone. The median dose of triamcinolone administered to patients at baseline in strategy II was 120 mg. 93% (62/67) of the patients received 120 mg triamcinolone and 7% (5/67) of the patients received 80 mg triamcinolone at baseline.

Within the first year, there were significantly more patients with registered complications in strategy II ($n = 45$ [35%]) than in strategy I ($n = 15$ [12%]; $p < 0.01$). In total, there were 27 complications registered in strategy I compared to 83 complications in strategy II. Complication in strategy I consisted of: malaise = 14; gastrointestinal = 2; lab abnormality = 4; skin/hair disorder/allergy = 3; infection = 2; cardiovascular event = 1; other = 1. Complication in strategy II consisted of: malaise = 38; gastrointestinal = 7; lab abnormality = 8; skin/hair disorder/allergy = 12; eye complaints = 8; pulmonary abnormality = 1; infection = 1; cardiovascular event = 2; other = 6.

Table 1. Patient characteristics

Characteristics	Strategy I (n=128)	Strategy II (n=128)	P
Female, sex n (%)	79 (61.7%)	79 (61.7%)	1.000
Age, mean $\pm$ SD years	59.1 $\pm$ 13.0	59.5 $\pm$ 12.8	0.809
DAS28 - ESR, mean $\pm$ SD	4.5 $\pm$ 1.1	4.8 $\pm$ 1.1	0.026
ESR (mm/h), median (IQR)	22.0 (14.0 – 41.0)	29.0 ^a (14.0 – 45.0)	0.195
CRP (mg/l), median (IQR)	10.0 ^b (5.0 – 22.0)	11.5 (4.3 – 24.8)	0.786
Anti-CCP positive, n (%)	74 ^c (58.3%)	77 ^c (60.2%)	0.701
RF positive, n (%)	62 (48.4%)	76 (59.4%)	0.114
Number of SJC, median (IQR)	6.0 (3.0 – 9.0)	5.0 (2.0 – 10.0)	0.235
Number of TJC, median (IQR)	3.0 (1.0 – 7.0)	4.0 (2.0 – 10.0)	0.025
HAQ-SDI, median (IQR)	1.2 ^d (0.9 – 1.6)	1.0 ^e (0.4 – 1.5)	0.003
VAS well-being, median (IQR)	50.0 (28.3 – 65.0)	51.0 (35.0 – 70.0)	0.290
VAS pain, median (IQR)	50.0 ^f (39.8 – 64.0)	62.0 ^g (49.0 – 75.0)	0.001
SF36-PCS, mean $\pm$ SD	38.1 $\pm$ 7.6 ^h	37.3 $\pm$ 9.2 ⁱ	0.512
SF36-MCS, mean $\pm$ SD	40.7 $\pm$ 7.4 ^j	44.9 $\pm$ 11.9 ^k	0.003
BMI, kg/m ² , mean $\pm$ SD	26.5 $\pm$ 4.8 ^l	26.0 $\pm$ 4.1 ^m	0.388
Baseline SHS-score, median (IQR)	3.0 (1.0 – 7.0) ⁿ	2.0 (1.0 – 5.8) ^o	0.119
Erosion, median (IQR)	0.0 (0.0 – 1.0) ⁿ	0.0 (0.0–1.0) ^o	0.012
Joint space narrowing, median (IQR)	2.0 (0.0 – 5.0) ⁿ	1.0 (0.0 – 1.0) ^o	0.586
Injection triamcinolone, n%	4 (3.1%)	67 (52.3%)	0.000

^a (n = 127), ^b (n = 121), ^c (n = 127), ^d (n = 102), ^e (n = 87), ^f (n = 122), ^g (n = 72), ^h (n = 105), ⁱ (n = 86),

^j (n = 105), ^k (n = 86), ^l (n = 126), ^m (n = 119), ⁿ (n = 126), ^o (n = 124)

DAS28 Disease Activity Score in 28 joints, ESR erythrocyte sedimentation rate, CRP C-reactive protein, TJC tender joint count, SJC swollen joint count, HAQ-SDI Health Assessment Questionnaire disability index (standard scoring), SF-36 Short-Form 36 health survey (version 2), PCS physical component summary, MCS mental component summary, BMI body mass index, RF rheumatoid factor, Anti-CCP anti-cyclic citrullinated peptide

Radiographic progression

Baseline radiographs were available for 250 patients (124 patients in strategy II and 126 patients in strategy I). One-year follow-up radiographs were available for 222 patients (104 patients in strategy II and 118 patients in strategy I). Baseline and follow-up SHS scores are presented separately for both treatment strategies in Fig. 1.

At baseline, median SHS scores were not significantly different ($P = 0.119$) between both strategies. Median baseline erosion scores tended to be slightly higher in strategy I ($P = 0.012$) with 43% (54/126) of the patients versus 30% (37/124) of the patients in strategy II having at least one erosion, while joint space narrowing (JSN) scores were not different between strategies with 71% (90/126) of the patients in strategy I versus 68% (84/124) of the patients in strategy II showing JSN.

At one-year follow-up, the median SHS score was significantly higher in patient treated with initial monotherapy ($P = 0.001$). The median SHS score increased from 3.0 (IQR 1.0 - 7.0) at baseline to 5.5 (IQR 3.0 – 12.0) in strategy I and from 2.0 (IQR 1.0 – 5.75) to 3.0 (IQR 1.0 – 9.0) in strategy II. One-year erosion scores were significantly different ($P < 0.001$) between both strategies, while JSN scores were not ($P = 0.117$). In strategy I, median erosion scores increased from 0.0 (IQR 0.0 – 1.0) to 2.0 (IQR 0.0 – 4.0) and median JSN scores increased from 2.0 (IQR 0.0 – 5.0) to 3.0 (IQR 1.0 - 7.0). In strategy II, median erosion scores increased from 0.0 (IQR 0.0 – 1.0) to 1.0 (0.0 – 2.0), while JSN scores increased from 1.0 (IQR 0.0 – 4.75) to 2.0 (IQR 1.0 – 6.0).

Median progression was significantly higher in strategy I (2.0; IQR 1.0 – 4.0) than in strategy II (1.0; IQR 0.0 – 3.0; $P < 0.001$). This difference was similar for both anti-CCP negative (2.0 [IQR 1.0 – 3.0] vs. 1.0 [IQR 0.0 – 2.0]; $P = 0.023$) and anti-CCP positive patients (3.0 [IQR 1.0 – 5.0] vs. 1.0 [QR 0.0 – 3.0]; $P < 0.001$). The difference in individual radiographic progression scores between both strategies was also visible in the cumulative probability plot (Fig. 2). Most notably, the proportion of patients with no radiographic progression at all was substantially higher in strategy II (initial combination therapy) (43%) than in strategy I (initial monotherapy) (14%).

Also, significantly more patients treated with initial monotherapy had clinically relevant progression (≥ 5 SHS points) after one year (26/118 [20%]) than patients treated with initial combination therapy (10/104 [8%]; $P = 0.012$).

Figure 1. Radiographic damage in both strategies. The data are presented as the mean $\pm$ standard error of mean. JSN = joint space narrowing; E = Erosion; SHS = Sharp/van der Heijde score

Figure 2. Cumulative probability of radiographic progression between both strategies

Univariate associations with progression

Fewer tender joints ($P = 0.033$), higher ESR ($P = 0.033$), higher age ($P = 0.042$), and no triamcinolone injection ($P = 0.007$) were significantly associated with more radiographic progression within the first year in the total sample (Table 2). There were no significant interactions with strategy in the linear regression analyses. With respect to clinically relevant radiographic progression, fewer tender joints ($P = 0.016$), higher ESR ($P = 0.038$), positive anti-CCP ($P = 0.040$) and lower BMI ($P = 0.039$) were significantly associated with experiencing a MCID. Moreover, there was a significant strategy interaction with swollen joint count scores and SF-36 PCS scores. Swollen joint count scores were not associated with experiencing a MCID in strategy II (OR = 0.90; CI 95% 0.77 – 1.07; $P = 0.227$) but were positively associated in strategy I (OR = 1.10; CI 95% 1.00 – 1.22; $P = 0.050$). SF-36 PCS scores were not associated with reaching a MCID in strategy I (OR = 0.98 CI 95% 0.92 – 1.04 $P = 0.503$) but were positively associated with reaching a MCID in strategy II (OR = 1.11; CI 95% 1.00 – 1.22; $P = 0.040$).

Table 2. Univariate analyses of progression and minimal clinically important difference (MCID ≥ 5)

Variable	Progression			Minimal clinical important difference (MCID ≥ 5)		
	B	95% CI	P	OR	95% CI	P
Strategy (monotherapy)	1.79	0.75 - 2.82	0.001	2.66	1.21 - 5.82	0.015
TJC28	-0.11	-0.20 - -0.01	0.033	0.89	0.81 - 0.98	0.016
SJC28	0.01	-0.10 - 0.13	0.805	1.03	0.96 - 1.10	0.471
ESR	0.03	0.00 - 0.05	0.033	1.02	1.00 - 1.03	0.038
CRP	0.02	-0.00 - 0.04	0.084	1.01	1.00 - 1.02	0.071
Wellbeing	-0.01	-0.04 - 0.01	0.196	0.99	0.98 - 1.01	0.319
PCS	0.01	-0.07 - 0.09	0.803	1.02	0.97 - 1.07	0.467
MCS	-0.03	-0.09 - 0.04	0.408	1.01	0.97 - 1.05	0.653
RF	0.09	-0.45 - 0.62	0.755	0.78	0.54 - 1.14	0.202
Anti-CCP positive	0.86	-0.23 - 1.95	0.123	2.41	1.04 - 5.57	0.040
Age	0.04	0.00 - 0.08	0.042	1.02	0.99 - 1.05	0.251
Gender	0.28	-0.82 - 1.38	0.621	0.75	0.36 - 1.56	0.443
DAS28_ESR	-0.02	-0.51 - 0.47	0.948	0.94	0.67 - 1.31	0.708
Remission 52 weeks	-0.83	-2.07 - 0.41	0.188	0.64	0.29 - 1.42	0.272
Remission 6 months	-0.73	-1.79 - 0.34	0.179	0.54	0.26 - 1.11	0.094
Remission 3 months	-0.90	-1.99 - 0.19	0.104	0.71	0.33 - 1.54	0.388
HAQ-SDI	0.62	-0.46 - 1.69	0.260	1.00	0.54 - 1.85	0.994
BMI	-0.05	-0.17 - 0.07	0.417	0.91	0.83 - 1.00	0.039
Injection triamcinolone	-1.63	-2.81 - -0.46	0.007	0.39	0.15 - 1.07	0.067

TJC tender joint count, SJC swollen joint count, ESR erythrocyte sedimentation rate, CRP C-reactive protein, PCS physical component summary, MCS Mental component summary, DAS28 Disease Activity in 28 joints, RF rheumatoid factor, Anti-CCP anti-cyclic citrullinated peptide, HAQ-SDI Health Assessment Questionnaire disability index (standard scoring), BMI body mass index

Multivariate analyses

Strategy I with initial monotherapy remained significantly associated with more radiographic progression and experiencing a MCID after controlling for covariates and strategy interactions in multivariate analyses (Table 3 and 4). None of the covariates remained significantly associated with continuous radiographic progression scores (Table 3). For clinically relevant progression, fewer tender joints ($P = 0.050$) and higher ESR ($P = 0.015$) remained significantly associated with experiencing a MCID (Table 4).

Table 3. *Multivariable linear regression analysis for progression*

Variable	B	95% CI	P
Strategy (Initial monotherapy)	1.32	0.06 – 2.57	0.039
TJC	-0.08	-0.17 – 0.02	0.130
ESR	0.02	-0.00 – 0.05	0.074
Age	0.04	-0.01 – 0.08	0.089
Injection triamcinolone	-0.76	-2.19 – 0.68	0.298

R-square progression = 0.079; N = 121

All continuous variables were mean-centered to avoid multicollinearity

TJC tender joint count, ESR erythrocyte sedimentation rate

Table 4. *Multivariable logistic regression analysis for clinically relevant progression ($\geq$ MCID of 5)*

Variable	OR	95% CI	p
Strategy (Initial monotherapy)	3.84	1.16 – 12.73	0.028
TJC	0.89	0.78 – 1.00	0.050
SJC	1.07	0.92 – 1.23	0.393
SJC * Strategy	1.17	0.90 – 1.51	0.236
ESR	1.03	1.01 – 1.05	0.015
Anti-CCP positive	1.91	0.66 – 5.48	0.229
SF-36 PCS	1.04	0.98 – 1.12	0.202
SF-36 PCS * Strategy	0.87	0.76 – 0.99	0.034
BMI	0.91	0.81 – 1.02	0.114

Nagelkerke R-square MCID = 0.266; N = 159

All continuous variables were mean-centered to avoid multicollinearity

TJC tender joint count, SJC swollen joint count, ESR erythrocyte sedimentation rate, Anti-CCP anti-cyclic citrullinated peptide

DISCUSSION

The aim of this study was to compare one-year radiographic outcomes of two treat-to-target strategies, with initial mono- versus combination therapy, in early RA patients in daily clinical practice. These two early RA strategies in the DREAM registry confirm that, overall, treat-to-target strategies result in limited short-term radiographic progression. We observed an even more favorable outcome among patients with early RA who were treated with initial combination therapy (strategy II), as compared to patients who were treated with initial monotherapy (strategy I). A substantially larger number of patients within strategy II showed no radiographic progression at all and only a small portion of patients showed clinically relevant progression.

Fewer painful joints and a higher erythrocyte sedimentation rate (ESR) at baseline turned out to be predictive of clinically relevant progression, independent of treatment strategy. Although high ESR is an established risk factor for progression [36–38], it was surprising that patients with fewer tender joints ended up with more structural progression. Although the exact reason for this finding is unknown, it could suggest that patients with a higher pain threshold may receive less than optimal treatment (e.g., less frequent glucocorticoid administrations or other treatment intensifications). Consequently, this finding deserves further study. Better physical health at baseline was predictive of clinically relevant progression in the strategy with initial combination therapy only. Treatment strategy remained the strongest independent predictor for the occurrence of radiographic progression after controlling for other potential predictors.

Previously, we demonstrated that patients treated according with initial combination therapy showed a more rapid improvement in disease activity than patients treated with step-up monotherapy [6]. Early and intensive treatment of RA is advocated, in order to prevent structural joint damage in the early phase of the disease and thereby prevent loss of function resulting from joint destruction and active arthritis [39]. Treatment with traditional DMARDs alone or in combination [9, 20] with glucocorticoids [40] has been shown to retard the progression of joint damage. In our study, the increase of median SHS score (progression) after one year of follow-up was significantly lower in patients who had been treated with initial combination therapy compared to patients who had been treated with initial step-up monotherapy. Our results are comparable to those of the FIN-RACO trial which showed that the short-term and long-term increase in median Larsen score was significantly lower in patients who were treated with combination DMARDs compared to patients receiving DMARD monotherapy during the first 2 years [41, 42]. Also, the COBRA study, although this study was not aiming at remission, compared step-down combination therapy with prednisolone, methotrexate, and sulfasalazine

(SSZ) to SSZ monotherapy and showed that after 1 year the rate of progression of joint damage was lower in the combination therapy group and less persistent over 4-5 years of follow-up [20].

Similar results were demonstrated in the BeST study [21], where radiological results showed that patients who had been treated with initial combination therapy including prednisone had less progression of radiographic joint damage than patients treated with sequential monotherapy. The BeST study also showed that the number of patients without any progression of radiographic joint damage was higher in the combination therapy group. In contrast to these studies, the tREACH trial found no difference in radiographic progression between initial triple DMARD therapy and intramuscular glucocorticosteroids versus initial triple DMARD therapy and oral glucocorticosteroids versus initial MTX monotherapy and oral glucocorticosteroids [43]. In the tREACH trial, all treatment groups used glucocorticoids, which might result in early control of the inflammatory disease, which in turn might lead to less short-term progression of damage. Our study in daily clinical practice confirmed that in early RA, starting with a combination therapy of multiple DMARDs has several positive outcomes. In general, it is assumed that rapid aggressive treatment may slow long-term progression [20]. From this perspective we might surmise that starting early RA treatment with a single DMARD would be a missed opportunity in a considerable number of patients.

The identification of possible prognostic factors of radiographic progression is relevant for tailoring treatment and for supporting the current treatment strategy. The strength and reliability of known prognostic factors may vary according to the outcome measure of interest. A systematic review by Carpenter (2016) indicated that RF, anti-CCP, along with increased markers of inflammation (ESR or CRP) were strongly associated with radiographic progression [44]. The ESPOIR study identified anti-CCP and baseline ESR as predictors of structural outcome [45]. Van der Heijde (1992) mentioned high disease activity measured as high ESR, CRP or DAS and a positive RF were all significantly associated with radiographic damage after 2 years of follow-up [46]. Our study cannot confirm all of these associations; but fewer tender joints and higher ESR were independently associated with radiographic progression in the total sample.

Glucocorticoids were part of strategy II, as bridging therapy, and were allowed in strategy I to reach remission. Glucocorticoids have previously been shown to retard radiographic progression [40, 47]. In the total sample, use of glucocorticoids at baseline was univariately associated with less radiographic progression. Looking at the initial combination strategy group only, however, there was no significant difference in radiographic progression between those patients who did or did not receive a baseline glucocorticoid injection (data not shown). Moreover, the association between corticosteroid use and radiographic progression did not

remain significant in the multivariate model that included strategy group. Consequently, the current study, albeit not specifically designed to answer this question, could not confirm that glucocorticoids retard short-term radiographic progression. It is possible that this association is confounded by indication, as patients who received an injection of triamcinolone had higher baseline DAS28 scores in both strategies.

The major strength of this study is the use of real life data from consecutive patients, recently diagnosed with RA, who were being treated according to a state-of-the-art T2T remission induction protocol. Results from this study demonstrated similar or even better radiographic outcomes than several T2T RCTs. Since RCTs generally have more strict inclusion criteria and more controlled protocols, it is important that treatment outcomes are also examined in real-life settings. This study is one of the first to directly compare the radiographic outcomes of different T2T strategies in early RA patients in daily clinical practice. Another strength of the study is that the Sharp/van der Heijde method was used instead of the Larsen method for scoring radiographic progression. The Sharp van der Heijde index may be considered as the best tool for evaluating patients with early RA because of its sensitivity in detecting signs of early disease and the possibility of expressing anatomical damage progression quantitatively [48]. Although this study was not powered a-priori for the current comparison of radiographic outcomes, a post-hoc power analysis indicated that with the sample size of 128 patients per strategy we had > 80% power to detect a small to moderate difference ($d = 0.39$) in progression between both strategies using a 2-sided Mann-Whitney u test with an alpha of 0.05.

The major limitation of this study is that it is a quasi-experimental study of two strategies separated over time. The first strategy started in 2006 with an initial step-up mono-therapy, the second strategy in 2012 started with an initial combination therapy. Also, both strategies differed not only with respect to initial DMARD therapy (step-up vs. combination), but also with respect to the use of glucocorticoids and MTX starting dose. Another limitation is the follow-up period of 1 year. Finally, an important limitation is that radiographs in both strategies were not scored in a randomized and blinded fashion, as is usually done in true clinical trials.

Although it is not a randomized trial, we still think that the design and results of the study allow us to compare between the two strategies. Both strategy cohorts consisted of very similar populations of all consecutive newly diagnosed RA patients, treated in the same hospitals by the same rheumatologists. Although early radiographic progression is strongly indicative of future radiographic progression, longer follow-up is needed to investigate whether initial combination therapy also shows long-term beneficial effects on radiographic progression. Long-term follow-up of the COBRA and FIN-RACO trials suggested a difference in progression of joint damage

after 1-2 years between combination and monotherapy [49, 50], while the BeSt study did not after 1-5 years [51]. In the long-term follow-up of strategy I within the DREAM registry, patients with early joint damage demonstrated more continued radiographic progression [52]. Because patients in strategy II showed less early radiographic progression, initial combination therapy might also prevent the destruction of joints on the long-term.

CONCLUSION

Patients treated with initial monotherapy had significantly more first-year radiographic progression than patients treated with initial combination therapy in daily clinical practice.

REFERENCES

1. Sokka T: Long-term outcomes of rheumatoid arthritis. *Curr Opin Rheumatol* 2009, 21:284–90.
2. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, Hazes JM: Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med* 2001, 111:446–51.
3. Quinn MA, Emery P: Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention. *Clin Exp Rheumatol* 2003, 21(5 Suppl 31):S154–7.
4. Nell VPK, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS: Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology (Oxford)* 2004, 43:906–14.
5. Steunebrink LMM, Vonkeman HE, ten Klooster PM, Hoekstra M, van Riel PLCM, van de Laar MAFJ: Recently diagnosed rheumatoid arthritis patients benefit from a treat-to-target strategy: results from the DREAM registry. *Clin Rheumatol* 2016, 35:609–615.
6. Steunebrink LMM, Versteeg GA, Vonkeman HE, Ten Klooster PM, Kuper HH, Zijlstra TR, van Riel PLCM, van de Laar MAFJ: Initial combination therapy versus step-up therapy in treatment to the target of remission in daily clinical practice in early rheumatoid arthritis patients: results from the DREAM registry. *Arthritis Res Ther* 2015, 18:60.
7. Finckh A, Liang MH, van Herckenrode CM, de Pablo P: Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. *Arthritis Rheum* 2006, 55:864–72.
8. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, van Zeben D, Dijkmans BA, Peeters AJ, Jacobs P, van den Brink HR, Schouten HJ, van der Heijde DM, Boonen A, van der Linden S: Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997, 350:309–18.
9. Möttönen T, Hannonen P, Leirisalo-Repo M, Nissilä M, Kautiainen H, Korpela M, Laasonen L, Julkunen H, Luukkainen R, Vuori K, Paimela L, Bläfield H, Hakala M, Ilva K, Yli-Kerttula U, Puolakka K, Järvinen P, Hakola M, Piirainen H, Ahonen J, Pälvimäki I, Forsberg S, Koota K, Friman C: Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* 1999, 353:1568–73.
10. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, Genovese MC, Wasko MC, Moreland LW, Weaver AL, Markenson J, Finck BK: A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000, 343:1586–93.
11. St Clair EW, van der Heijde DMFM, Smolen JS, Maini RN, Bathon JM, Emery P, Keystone E, Schiff M, Kalden JR, Wang B, Dewoody K, Weiss R, Baker D: Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004, 50:3432–43.
12. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, Sharp J, Perez JL, Spencer-Green GT: The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previo. *Arthritis Rheum* 2006, 54:26–37.

13. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, Kincaid W, Porter D: Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004, 364:263–9.
14. Verstappen SMM, Jacobs JWJ, van der Veen MJ, Heurkens AHM, Schenk Y, ter Borg EJ, Blaauw AAM, Bijlsma JWJ: Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis* 2007, 66:1443–9.
15. Smolen JS, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas D, Burmester G, Combe B, Cutolo M, de Wit M, Dougados M, Emery P, Gibofsky A, Gomez-Reino JJ, Haraoui B, Kalden J, Keystone EC, Kvien TK, McInnes I, Martin-Mola E, Montecucco C, Schoels M, van der Heijde D, van der Heijde D: Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010, 69:631–7.
16. van Jaarsveld CH, Jacobs JW, van der Veen MJ, Blaauw AA, Kruize AA, Hofman DM, Brus HL, van Albada-Kuipers GA, Heurkens AH, ter Borg EJ, Haanen HC, van Booma-Frankfort C, Schenk Y, Bijlsma JW: Aggressive treatment in early rheumatoid arthritis: a randomised controlled trial. On behalf of the Rheumatic Research Foundation Utrecht, The Netherlands. *Ann Rheum Dis* 2000, 59:468–77.
17. Stenger AA, Van Leeuwen MA, Houtman PM, Bruyn GA, Speerstra F, Barendsen BC, Velthuisen E, van Rijswijk MH: Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. *Br J Rheumatol* 1998, 37:1157–63.
18. Emery P, Marzo H, Proudman S: Management of patients with newly diagnosed rheumatoid arthritis. *Rheumatology (Oxford)* 1999, 38 Suppl 2:27–31.
19. Abu-Shakra M, Toker R, Flusser D, Flusser G, Friger M, Sukenik S, Buskila D: Clinical and radiographic outcomes of rheumatoid arthritis patients not treated with disease-modifying drugs. *Arthritis Rheum* 1998, 41:1190–5.
20. Landewé RBM, Boers M, Verhoeven AC, Westhovens R, van de Laar MAFJ, Markuse HM, van Denderen JC, Westedt ML, Peeters AJ, Dijkmans BAC, Jacobs P, Boonen A, van der Heijde DMFM, van der Linden S: COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. *Arthritis Rheum* 2002, 46:347–56.
21. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJSM, Hazes JMW, Zwinderman AH, Roday HK, Han KH, Westedt ML, Gerards AH, van Groenendaal JHLM, Lems WF, van Krugten M V, Breedveld FC, Dijkmans BAC: Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. *Arthritis Rheum* 2008, 58(2 Suppl):S126–35.
22. van Aken J, Lard LR, le Cessie S, Hazes JMW, Breedveld FC, Huizinga TWJ: Radiological outcome after four years of early versus delayed treatment strategy in patients with recent onset rheumatoid arthritis. *Ann Rheum Dis* 2004, 63:274–9.
23. Maillefert JF, Combe B, Goupille P, Cantagrel A, Dougados M: Long term structural effects of combination therapy in patients with early rheumatoid arthritis: five year follow up of a prospective double blind controlled study. *Ann Rheum Dis* 2003, 62:764–6.
24. Cohen G, Gossec L, Dougados M, Cantagrel A, Goupille P, Daures JP, Rincheval N, Combe B: Radiological damage in patients with rheumatoid arthritis on sustained remission. *Ann Rheum Dis* 2007, 66:358–63.
25. Molenaar ETH, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M, Dijkmans BAC: Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. *Arthritis Rheum* 2004, 50:36–42.

26. van der Kooij SM, Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Güler-Yüksel M, Zwinderman AH, Kerstens PJSM, van der Lubbe PAHM, de Beus WM, Grillet BAM, Roday HK, Huizinga TWJ, Breedveld FC, Dijkmans BAC, Allaart CF: Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. *Ann Rheum Dis* 2009, 68:914–21.
27. Vermeer M, Kuper HH, Hoekstra M, Haagsma CJ, Posthumus MD, Brus HLM, van Riel PLCM, van de Laar MAFJ: Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. *Arthritis Rheum* 2011, 63:2865–72.
28. Vermeer M, Kuper HH, Moens HJB, Drossaers-Bakker KW, van der Bijl AE, van Riel PLCM, van de Laar MAFJ: Sustained beneficial effects of a protocolized treat-to-target strategy in very early rheumatoid arthritis: three-year results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort. *Arthritis Care Res (Hoboken)* 2013, 65:1219–26.
29. den Uyl D, ter Wee M, Boers M, Kerstens P, Voskuyl A, Nurmohamed M, Raterman H, van Schaardenburg D, van Dillen N, Dijkmans B, Lems W: A non-inferiority trial of an attenuated combination strategy ('COBRA-light') compared to the original COBRA strategy: clinical results after 26 weeks. *Ann Rheum Dis* 2014, 73:1071–8.
30. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJSM, Hazes JMW, Zwinderman AH, Roday HK, Han KH, Westedt ML, Gerards AH, van Groenendaal JHLM, Lems WF, van Krugten M V, Breedveld FC, Dijkmans BAC: Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2005, 52:3381–90.
31. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL: Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995, 38:44–8.
32. Bruce B, Fries JF: The Health Assessment Questionnaire (HAQ). *Clin Exp Rheumatol* 2005, 23(5 Suppl 39):S14–8.
33. Ware JE, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992, 30:473–83.
34. van der Heijde D: How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 1999, 26:743–5.
35. Landewé R, van der Heijde D: Radiographic progression depicted by probability plots: presenting data with optimal use of individual values. *Arthritis Rheum* 2004, 50:699–706.
36. Jansen LM, van der Horst-Bruinsma IE, van Schaardenburg D, Bezemer PD, Dijkmans BA: Predictors of radiographic joint damage in patients with early rheumatoid arthritis. *Ann Rheum Dis* 2001, 60:924–7.
37. Smolen JS, Van Der Heijde DMFM, St Clair EW, Emery P, Bathon JM, Keystone E, Maini RN, Kalden JR, Schiff M, Baker D, Han C, Han J, Bala M, Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) Study Group: Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. *Arthritis Rheum* 2006, 54:702–10.

38. Syversen SW, Gaarder PI, Goll GL, Ødegård S, Haavardsholm EA, Mowinckel P, van der Heijde D, Landewé R, Kvien TK: High anti-cyclic citrullinated peptide levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: results from a 10-year longitudinal study. *Ann Rheum Dis* 2008, 67:212–7.
39. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, Emery P, Gaujoux-Viala C, Gossec L, Nam J, Ramiro S, Winthrop K, de Wit M, Aletaha D, Betteridge N, Bijlsma JWJ, Boers M, Buttgeriet F, Combe B, Cutolo M, Damjanov N, Hazes JMW, Kouloumas M, Kvien TK, Mariette X, Pavelka K, van Riel PLCM, Rubbert-Roth A, Scholte-Voshaar M, Scott DL, et al.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014, 73:492–509.
40. Kirwan JR, Bijlsma JWJ, Boers M, Shea BJ: Effects of glucocorticoids on radiological progression in rheumatoid arthritis. *Cochrane database Syst Rev* 2007:CD006356.
41. Korpela M, Laasonen L, Hannonen P, Kautiainen H, Leirisalo-Repo M, Hakala M, Paimela L, Blåfield H, Puolakka K, Möttönen T: Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. *Arthritis Rheum* 2004, 50:2072–81.
42. Mäkinen H, Kautiainen H, Hannonen P, Möttönen T, Leirisalo-Repo M, Laasonen L, Korpela M, Blåfield H, Hakola M, Sokka T: Sustained remission and reduced radiographic progression with combination disease modifying antirheumatic drugs in early rheumatoid arthritis. *J Rheumatol* 2007, 34:316–21.
43. de Jong PH, Hazes JM, Han HK, Huisman M, van Zeben D, van der Lubbe PA, Gerards AH, van Schaeybroeck B, de Sonnaville PB, van Krugten M V, Luime JJ, Weel AE: Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. *Ann Rheum Dis* 2014, 73:1331–9.
44. Carpenter L, Nikiphorou E, Sharpe R, Norton S, Rennie K, Bunn F, Scott DL, Dixey J, Young A: Have radiographic progression rates in early rheumatoid arthritis changed? A systematic review and meta-analysis of long-term cohorts. *Rheumatology (Oxford)* 2016, 55:1053–1065.
45. Combe B, Logeart I, Belkacemi MC, Dadoun S, Schaefferbeke T, Daurès JP, Dougados M: Comparison of the long-term outcome for patients with rheumatoid arthritis with persistent moderate disease activity or disease remission during the first year after diagnosis: data from the ESPOIR cohort. *Ann Rheum Dis* 2015, 74:724–9.
46. van der Heijde DM, van Riel PL, van Leeuwen MA, van 't Hof MA, van Rijswijk MH, van de Putte LB: Prognostic factors for radiographic damage and physical disability in early rheumatoid arthritis. A prospective follow-up study of 147 patients. *Br J Rheumatol* 1992, 31:519–25.
47. Kavanaugh A, Wells AF: Benefits and risks of low-dose glucocorticoid treatment in the patient with rheumatoid arthritis. *Rheumatology (Oxford)* 2014, 53:1742–51.
48. Giovagnoni A, Valeri G, Burrone E, Amici F: Rheumatoid arthritis: follow-up and response to treatment. *Eur J Radiol* 1998, 27 Suppl 1:S25–30.
49. van Tuyl LHD, Boers M, Lems WF, Landewé RB, Han H, van der Linden S, van de Laar M, Westhovens R, van Denderen JC, Westedt M-L, Peeters AJ, Jacobs P, Huizinga TWJ, van de Brink H, Dijkmans BAC, Voskuyl AE: Survival, comorbidities and joint damage 11 years after the COBRA combination therapy trial in early rheumatoid arthritis. *Ann Rheum Dis* 2010, 69:807–12.

50. Rantalaiho V, Korpela M, Laasonen L, Kautiainen H, Järvenpää S, Hannonen P, Leirisalo-Repo M, Blåfield H, Puolakka K, Karjalainen A, Möttönen T, FIN-RACo Trial Group: Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial. *Arthritis Res Ther* 2010, 12:R122.
51. Klarenbeek NB, Güler-Yüksel M, van der Kooij SM, Han KH, Roday HK, Kerstens PJSM, Seys PEH, Huizinga TWJ, Dijkmans BAC, Allaart CF: The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. *Ann Rheum Dis* 2011, 70:1039–46.
52. Versteeg LGA, Steunebrink LMM, Kuper IH, Vonkeman HE, ten Klooster PM, van der Bijl AE, van de LM: Early Radiological Progression in Rheumatoid Arthritis Leads to More Long-Term Joint Damage in Daily Clinical Practice; Six Year Radiological Outcomes of a Strict Treat-to-Target Cohort in the Netherlands [abstract]. *Arthritis Rheumatol* 2016, 68(suppl 10).

Determinants of perceived health nonimprovement in early rheumatoid arthritis patients with favourable treatment outcomes

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ABSTRACT

Objective: To explore the association between achieving favorable clinical outcomes and patients' perceived change in overall health status after 12 months of treat-to-target in patients with early rheumatoid arthritis (RA) and to identify determinants of subjective nonimprovement.

Methods: Baseline and 12-month data of patients included in the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study with at least a moderate (by European League Against Rheumatism criteria) after 1 year were selected for analysis. Logistic regression analysis was used to identify factors associated with nonimproved perceived overall health status at 12 months.

Results: At 12 months, 75 of 210 patients (35%) did not consider their health to have improved despite having achieved favorable clinical outcomes. Relative change from baseline in pain (Wald = 20.20, $P < 0.01$) and fatigue (Wald = 5.58, $P = 0.02$) was independently associated with nonimproved perceived overall health status. The results were similar when only patients with ≤ 1 swollen joint were analyzed. An improvement of 55% in pain measured on a visual analog scale was found to discriminate reasonably well between patients who considered their health to have improved versus patients who did not, with an area under the receiver operating characteristic curve of 0.70 (95% CI: 0.61-0.78).

Conclusion: These results demonstrate that clinical improvements do not equate with improved subjective health for all patients. The association of nonimprovement with changes in pain and fatigue suggest that it might be worthwhile to monitor and address pain and fatigue in addition to and independently of disease activity in early RA.

SIGNIFICANCE & INNOVATIONS

- More than one-third of the patients included in our treat-to-target cohort who achieved at least a moderate response (by European League Against Rheumatism criteria) after 12 months perceived their overall health not to have improved at all over the same period;
- Perceived nonimprovement was associated with less improvement from baseline in visual analog scale pain and fatigue measures;
- Improvement in clinical signs and symptoms alone may not be enough to achieve favorable outcomes for all patients with early rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory disease of the connective tissues of the body, particularly the synovial joints. Persistent inflammation may lead to damage of the joint capsule and the articular cartilage. Based on the insight that early, aggressive suppression of inflammation can prevent or minimize joint damage and associated disability, current treatment guidelines advocate a treat-to-target (TTT) approach as the optimal treatment strategy (1,2). Within this treatment paradigm, medication adjustments are made until predefined disease activity targets (usually remission or low disease activity) are reached. Although accumulating evidence suggests that the TTT approach leads to better clinical outcomes than alternative treatment approaches, previous studies have demonstrated that measures of inflammatory disease activity do not always correspond with the perception of health status by patients. For example, it has been observed in several studies that the patient global assessment of disease activity may be elevated in patients without biomedical signs of the disease[3, 4]. Consequently, little is known about the extent to which favorable clinical outcomes associated with TTT translate into improved subjective health status. In the present study, we explored the discordance between achieving favorable clinical outcomes after 1 year of TTT and patients' self-reported overall health improvements over that period. We also examined the extent to which discrepancies between patients' judgments of improvement and clinical judgements of improvement could be explained by changes in specific domains of health-related quality of life (HRQoL). We used receiver operating characteristic (ROC) curves to identify the percentage improvement in these domains that best differentiated patients who considered their health to have improved from those who did not.

MATERIALS AND METHODS

Data selection and study design

Data were used from early RA patients participating in the Dutch Rheumatoid Arthritis Monitoring remission induction cohort. The remission induction cohort consists of patients with a clinical diagnosis of RA and symptom duration of <1 year following a TTT strategy aimed at achieving fast remission. Baseline and 12-month follow-up data were available for 259 patients. For the present study, baseline and 1-year follow-up data of 210 patients (81%) who achieved a moderate to good European League Against Rheumatism (EULAR) response were selected for analysis[5]. The medical ethics committees of the participating hospitals determined, in accordance with Dutch law, that no ethical approval was required for this study because all data were collected in the course of regular daily clinical practice. Nonetheless, patients were completely informed, and informed consent was obtained from each patient.

Assessments

At baseline, individual components of the American College of Rheumatology 1987 classification criteria, including morning stiffness, presence of erosions, and symmetric disease manifestation, were obtained (6). At each visit, data were collected on various clinical and patient-reported outcome measures, including measures of disease activity, HRQoL, physical functioning, pain, fatigue, joint stiffness, and laboratory measures. Disease activity was assessed by trained rheumatology nurses using the Disease Activity Score in 28 joints (DAS28), consisting of a 28 swollen joint count (SJC), 28 tender joint count (TJC), the erythrocyte sedimentation rate (ESR) and a 100-millimeter visual analog scale (VAS) on general health (where 0 = very good and 100 = very bad)[7]. In the analysis, DAS28-3 was computed for the SJC, TJC, and ESR. HRQoL was assessed at each visit using the 36-item Short Form Health Survey (SF-36). The Health Assessment Questionnaire Disability Index (HAQ-DI) was used to assess physical function[8]. Pain and fatigue were each measured using a 100-millimeter VAS. Radiographs of the hands and feet were obtained at baseline and at 12-months. Radiographs were evaluated by 2 observers, according to the modified Sharp/van der Heijde (SHS) scoring method[9], and a consensus score was obtained. A patient was classified as having erosive disease (by SHS) if the erosion score was ≥ 1 [9]. Clinically significant radiographic progression was defined as 5 units[10]. Complete baseline and 12-month radiographs were available for 251 patients. The level of achieved therapeutic response after 12-months was classified using the EULAR response criteria [11]. Subjective change in health after 1 year of TTT was assessed with the SF-36 5-point health transition question (“Compared to 1 year ago, how would you rate your health in general now?”). Scores were dichotomized (improved versus not improved) for analysis, since patients rarely selected the response options representing deteriorated health.

Statistical analysis

Baseline characteristics of the patients with a satisfactory clinical response after 1 year of TTT were summarized using the mean $\pm$ SD for continuous data and numbers (percentages) for nominal data and were compared between patients who perceived their health to have improved after 1 year of TTT (improvers) versus patients who perceived their health not to have improved (nonimprovers) using Welch’s *t*-tests and chi-square tests, respectively, or distribution free equivalent as appropriate. Binary logistic regression analysis was performed to identify factors associated with nonimprovement in subjective overall health status. First, univariate odds ratios (ORs) and 95% confidence intervals (95% CIs) were obtained for potential predictors of nonimprovement. We considered radiographic progression from baseline to 12 months and 12-

month relative change scores (change scores /baseline scores x 100) in SF-36 subscale scores, except the general health subscale, as potential explanatory variables. Nagelkerke's R^2 was used as a measure of effect size. Guidelines provided by Cohen were followed to classify effects as small (≥ 0.01 and < 0.09), moderate (≥ 0.09 and < 0.20) or large (≥ 0.20)[12]. Next, a multivariate logistic regression model with 12-month subjective health change status as the dependent variable was fitted using stepwise backward elimination of independent variables that showed a marginal significant relationship with nonimprovement in the univariate analysis ($P < 0.10$) based on likelihood ratio tests. The variance inflation factor was used to check for collinearity between the independent variables. The assumption of linearity in the logit for all of the continuous variables was examined using Box-Tidwell transformation tests. The area under the ROC curve was obtained to evaluate the discriminatory power of variables that were independently associated with nonimprovement in the multivariable logistic regression model. An area under the ROC curve > 0.70 was considered to indicate adequate accuracy in classifying patients as nonimproved versus improved[13]. Optimal cutoff points were derived using the Youden index (i.e. maximum value of sensitivity and specificity).

Missing values for individual variables ranged from 2% (for radiographic progression) to 38.5 % (for VAS fatigue), with a mean percentage missing of 16.1% (see Supplementary Table 1). Multiple imputation by chained equations was performed to replace missing baseline or 12-month patient reported outcomes scores. In accordance with recommendations by Sterne et al[14], the imputation model included the dependent variable, subjective improvement after 1 year (yes/no), all independent variables except SHS score, as well as the following auxiliary variables, HAQ-DI, individual DAS28 components, and the C-reactive protein level. No imputations were made for SHS scores because of mostly nonsignificant correlations with other available variables. Fifty data sets with imputed plausible values were obtained, with 100 iterations between data sets. Rubin's rules were employed to obtain pooled parameter estimates and their associated 95% CIs. Pooled analyses are reported throughout. Sensitivity analyses using only the complete cases were performed for the univariate and multivariable regression analyses, as well as the ROC curves. In all cases, the parameter estimates obtained for the complete cases were nearly identical to the estimates obtained using the multiple imputed data (see Supplementary Tables 1, 2, 3). For the backward elimination procedure, weighted regression (1/m no. of imputed datasets) was performed on stacked datasets as suggested by Wood et al [15].

RESULTS

The baseline characteristics of all patients with a satisfactory clinical response after 1 year of TTT are shown in Table 1. The sample was typical for early RA, with moderate to high disease activity according to the DAS28, moderate disability according to the HAQ-DI, and a minority of patients with erosive disease at baseline. Despite having achieved a moderate or good EULAR response to TTT treatment, 75 patients (36%) did not consider their health to have improved over the course of the last 12 months (nonimprovers). The baseline characteristics were similar between improvers and nonimprovers, except for a trend toward a larger percentage of nonimprovers with morning stiffness.

Table 1. *Baseline characteristics**

Variable	Improvers (N= 135)	Non-improvers (N= 75)	P
Female, no (%)	95 (59)	39 (67.2)	0.17
Morning stiffness, no. (%)	64 (49.2)	30 (62.5)	0.08
Arthritis wrists and hands, no. (%)	131 (97.8)	45 (93.8)	0.15
Symmetrical arthritis, no. (%)	111 (82.8)	36 (75.0)	0.16
Erosive disease, no (%)	15 (12.2)	5 (11.1)	0.54
Age, years	60.11 ± 13.02	56.55 ± 14.20	0.08
VAS Fatigue	45.46 ± 26.59	47.85 ± 26.61	0.56
VAS Pain	54.25 ± 22.37	51.20 ± 20.63	0.54
HAQ-DI	1.10 ± 0.56	1.13 ± 0.6	0.71
Short Form 36			
Physical functioning	56.30 ± 23.76	58.68 ± 22.93	0.51
Physical role limitations	44.02 ± 22.88	39.45 ± 23.01	0.19
Bodily pain	41.76 ± 18.58	39.58 ± 17.58	0.43
Vitality	51.1 ± 19.04	47.2 ± 20.35	0.19
Social function	67.33 ± 22.54	64.5 ± 25.18	0.43
Emotional role limitations	62.93 ± 26.01	59.84 ± 29.78	0.45
Mental health	66.88 ± 17.17	68.23 ± 21.17	0.63
DAS28 ESR	4.89 ± 1.07	4.64 ± 1.01	0.13
Radiographic progression, median (IQR)	2 (0-4)	0 (1-3)	0.19

* Values are the mean ± SD unless otherwise indicated. VAS = visual analog scale; HAQ DI = Health Assessment Questionnaire disability index (standard scoring); DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; IQR = interquartile range

Univariate associations with 12-month subjective health changes

The 12-month change in scores of all potential determinants of patient-reported nonimproved overall health and their univariate relationship with subjective health improvement is shown in Table 2. The median radiographic progression was 2 units of the total SHS score in the overall sample and was not significantly associated with nonimprovement. Overall, 14.8% of patients had an SHS progression score > 5. This percentage was similar for nonimprovers and improvers

($\chi^2 = 1.36$; $P = 0.24$). Although patient-reported health status improved over 12 months for each of the SF-36 subscales, the mean relative change scores differed markedly across the various domains. The smallest improvements were observed for mental health (mean $\pm$ SE 20.62 $\pm$ 2.32%) and the largest improvements were observed for pain assessed by VAS (mean $\pm$ SE 58.23 $\pm$ 2.58%). Considerable improvement in fatigue was also observed in the overall sample (mean $\pm$ SE 51.99 $\pm$ 3.46%) over 12 months (Table 2). In the univariate analysis, 4 variables were significantly associated with subjective overall health improvement. Of these variables, relative change in pain assessed by VAS discriminated best between improvers and nonimprovers, with an effect size of moderate magnitude (Nagelkerke's $R^2 = 0.14$). Patients who considered their health to have improved over the preceding 12 months also exhibited significantly larger percentage improvements in pain and physical function, as assessed by SF-36 as well as VAS fatigue. However, the ability of these variables to discriminate between groups was small according to the effect size statistics (Nagelkerke's $R^2 < 0.09$). Finally, radiographic progression from baseline to 12 months and 12-month relative change scores in physical role functioning were marginally significant. The pooled parameter estimates for the univariate models and their significance levels were nearly identical to estimates obtained from the complete case analysis (see Supplementary Tables 1, 2, and 3).

Table 2. Associations of 12-month percentage improvement in SF-36 scale scores and observed 12-month radiographic progression with 12-month subjective health improvement*

Variable	Total sample, change	Improvers, change	Nonimprovers, change	OR (95% CI)	P	R ²
Radiographic progression, median (IQR)	2 (0-3)	2 (0-4)	0 (1-3)	0.94 (0.83-1.06)	0.08	0.02
VAS fatigue	51.99 ± 3.46	59.39 ± 4.48	41.52 ± 6.52	0.98 (0.97-1.00)	0.03	0.07
VAS pain	58.23 ± 2.58	68.70 ± 7.44	44.75 ± 3.83	0.98 (0.97-0.99)	<0.01	0.14
SF-36 bodily pain,	53.09 ± 3.06	60.89 ± 3.26	40.29 ± 6.61	0.98 (0.97-0.99)	<0.02	0.08
SF-36 physical functioning	33.33 ± 2.98	39.51 ± 5.70	24.74 ± 3.87	0.99 (0.98-1.00)	0.04	0.05
Sf-36 role physical	42.68 ± 3.18	47.97 ± 4.09	33.83 ± 5.41	0.99 (0.98-1.00)	0.09	0.04
SF-36 vitality	32.32 ± 2.96	34.42 ± 6.85	30.05 ± 4.10	0.99 (0.98-1.01)	0.56	0.00
SF-36 social functioning	28.91 ± 2.78	33.77 ± 4.31	23.72 ± 5.99	0.99 (0.98-1.00)	0.15	0.03
SF-36 role emotional	30.04 ± 2.99	32.11 ± 5.76	22.43 ± 3.21	0.99 (0.98-1.00)	0.22	0.03
SF-36 mental health	20.62 ± 2.32	22.57 ± 4.55	16.63 ± 4.20	0.99 (0.98-1.00)	0.29	0.02

* Values are the mean ± SE unless otherwise indicated. SF-36 = 36-item Short Form health survey (version 2); OR = odds ratio; 95% CI = 95% confidence interval; VAS = visual analogue scale

Multivariable predictors of 12-month subjective health changes

Since pain was assessed using both VAS pain and the SF-36 bodily pain scale in this study, the strongest univariate predictor, relative change in VAS pain, was entered in the multivariate model (see Supplementary Table 4). After the backward elimination procedure, only VAS pain remained as significant predictor of nonimprovement (OR 0.98, Wald = 20.20; $P < 0.01$). Subsequently, we explored a model in which the SF-36 bodily pain scale was entered instead of the VAS pain (see Supplementary Table 5). Here, pain (OR 0.98, Wald = 10.08; $P < 0.01$) and fatigue remained significant predictors of improvement (OR 0.99, Wald = 5.58; $P = 0.02$). Finally, we explored a model that included only patients with ≤ 1 swollen joint. This constituted 86% of the overall sample. In these models, we again found that VAS pain (OR 0.98, Wald = 15.60; $P < 0.01$) was the only measure that remained significant, while both bodily pain (OR 0.98, Wald = 11.87; $P < 0.01$) and fatigue (OR 0.99, Wald = 4.53; $P < 0.03$) again remained in the model without VAS Pain. Overall, change in pain was the strongest independent predictor of patient-reported overall health changes, irrespective of whether the SF-36 bodily pain scale or VAS pain was used and even when the analysis was limited to patients with no more than 1 swollen joint. If SF-36 bodily

pain was entered into the model instead of VAS pain, fatigue also showed an independent relationship with perceptions of overall health improvement.

Finally we examined the ability of the relative change from baseline in pain and fatigue scores to discriminate between improvers and nonimprovers using ROC curve analysis. Only the 12-month relative change in VAS pain had acceptable power in differentiating between patients who did versus those who did not consider their health to have improved over that period (Table 3). The optimal cutoff point for a relative change from baseline was 55% for pain and 45% for fatigue. Using this cutoff, the proportion of patients correctly classified was 70% (95% CI 69-71). VAS fatigue performed slightly less well, with an overall accuracy of 60% (95% CI 59-61) at the optimal cutoff point of 45%.

Table 3. Area under the receiver operating characteristic curve (AUC) and optimal cutoff points for relative changes in VAS pain and VAS fatigue to predict perceived health improvement*

Variable	AUC (95%CI)	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)
% change in VAS Pain	0.70 (0.61-0.78)	55.00	0.61 (0.58-0.64)	0.72 (0.71-0.73)
% change in VAS Fatigue	0.62 (0.54-0.70)	45.00	0.61 (0.58-0.64)	0.63 (0.61-0.65)

*VAS = visual analogue scale; 95% CI = 95% confidence interval

DISCUSSION

This study explored subjective health changes in patients with favorable clinical outcomes after 1 year of treatment according to a TTT protocol that corresponds to currently recommended best practices. As described in previous publications, the majority of patients in this cohort achieved predefined response criteria[16]. Moreover, only a minority of these patients showed clinically relevant radiographic progression at 1-year followup. Despite their good clinical response, more than one-third of the included patients perceived their health as not improved at all after 12 months of treatment. The relative change from baseline in pain scores and, to a lesser extent, in fatigue were found to be independent determinants of perceived health improvement.

The data further demonstrated that achieving 55% improvement in VAS pain scores was the threshold that best discriminated patients who felt their health had improved from patients who did not. Improvement of 55% on the VAS has previously been found to best characterize the point at which patients consider their pain improvement to be satisfactory, with excellent discriminatory properties[17]. Our results show that 55% improvement on VAS pain can also be used as a reasonable test of whether or not patients with a moderate or good EULAR response consider their overall health to have improved, with an observed accuracy of 70%. The discriminatory properties of fatigue were less pronounced, and a combined score that included

both fatigue and pain did not perform distinctly better than pain alone and was therefore not presented.

It is well established that relief from pain and fatigue are important treatment goals for patients with RA[18–21]. It is also known that pain and fatigue may persist in controlled disease[22, 23]. In this study we were able to extend previous findings by demonstrating that the magnitude of improvement in pain and fatigue help explain why patients who respond to treatment may not always perceive their health to be improved. Similarly, previous cross-sectional studies have demonstrated that patients tend to be more pessimistic about their status than physicians or clinical assessments and that patient-reported outcomes such as fatigue and pain are important determinants of patient global assessment[24, 25]. Moreover, previous reports have shown that the patient's global assessment of disease activity tends to yield discordant results compared with other clinical or physician-derived measures of inflammatory disease activity in various definitions of remission or low disease activity[3, 4]. We were able to demonstrate using longitudinal data that changes in pain and fatigue over the first year of treatment independently contribute to patients' perception of improvement in overall health status in the subpopulation with a favorable response to treatment. This finding suggest that pain and fatigue are subjective aspects of disease deserving of attention, even when patients are treated in accordance with current optimal treatment strategies and access to optimal (biologic) disease-modifying treatment.

Since the DAS28 and derived response criteria have been criticized for a lack of specificity when applied to individual patients (1,26), one concern with the interpretation of our results could be that some of the included patients still could have had significant levels of disease activity, despite meeting the response criteria. However, the same results were obtained when only patients with a maximum of 1 swollen joint at the 12-months visit were considered in the analysis. It therefore seems more likely that factors other than inflammatory activity contribute to pain and fatigue in patients who do not consider their health to have improved, despite responding to treatment. For example that abnormal pain processing (e.g. pain catastrophizing or pain hypersensitivity) may contribute to pain in a subpopulation of patients with RA[27]. Moreover, several studies have suggested that the cause of fatigue in RA is likely multifactorial[28]. Such findings suggest that it may be worthwhile to monitor patients' pain and fatigue outcomes, in addition to disease activity. In patients with persistent pain or fatigue, despite well-controlled disease, complementary pain treatment strategies as well as interventions specifically addressing fatigue might be beneficial. For this purpose, the use of unidimensional outcome measures of pain and fatigue such as the VAS do not allow for a comprehensive characterization of the issues actually experienced by patients. Several instruments have thus far

been proposed that can be used to provide a more comprehensive overview of different aspects of fatigue[29, 30], which might be useful in clinical practice as well as in research. Thus far, no RA-specific, multidimensional measures are available for pain. Although such measures exist in other fields, their measurement properties in RA are not well understood (31). Future studies should be directed at introducing new, multidimensional pain outcome measures in RA.

A strong point of this study is that data were obtained in an observational cohort study of consecutive, newly diagnosed RA patients. During the study, strict adherence to the treatment protocol was achieved (32). Because few of the eligibility criteria were maintained, the results presented here are likely to be representative of the general population of newly diagnosed RA patients that are treated in accordance with current treatment recommendations and with access to optimal currently available treatments. However, it should be kept in mind that different results might have been obtained in different settings, particularly in low-resource settings where not all patients might have access to expensive biologic medication or where health care systems preclude optimal adherence to current treatment guidelines and where overall outcomes may be less favorable. Another strong point of the study was the use of advanced statistical methods to account for missing values. Multiple imputation is a theoretically sound approach to handling missing values that has been shown to yield unbiased parameter estimates, even in cases where the percentage of missing data is large (50%) and sample size modest ($n=50$)[33].

A potential limitation is that retrospective judgments of subjective health changes according to the SF-36 health transition question were collapsed for analysis, as we felt uncomfortable with the potential impact influential outliers might have had on the parameter estimates of, for example, an ordinal regression model, particularly in view of the skewed distribution of scores over the 5 response options, with very few patients reporting to have experienced severe loss of health status. A limitation of this approach is that the ordered nature of the dependent variable and the information that this response format provides about the degree to which patients perceived their health to have improved was ignored in this study.

In conclusion, these results demonstrate that the absence of self-perceived health status improvement is quite common in early RA patients with favorable clinical outcomes after 1 year of rigorous TTT. The magnitude of improvement in pain and fatigue were shown to discriminate between improvers and non-improvers. These findings suggest that it might be worthwhile to monitor and address pain and fatigue in addition to, and independently of, disease activity in early rheumatoid arthritis.

REFERENCES

1. Smolen JS, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas D, Burmester G, Combe B, Cutolo M, de Wit M, Dougados M, Emery P, Gibofsky A, Gomez-Reino JJ, Haraoui B, Kalden J, Keystone EC, Kvien TK, McInnes I, Martin-Mola E, Montecucco C, Schoels M, van der Heijde D, van der Heijde D: Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010, 69:631–7.
2. Singh J, Saag K, Bridges S, Akl E: 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Rheumatol* 2016.
3. Vermeer M, Kuper HH, van der Bijl AE, Baan H, Posthumus MD, Brus HLM, van Riel PLCM, van de Laar MAFJ: The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. *Rheumatology (Oxford)* 2012, 51:1076–80.
4. Studenic P, Smolen JS, Aletaha D: Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. *Ann Rheum Dis* 2012, 71:1702–5.
5. Fransen J, van Riel PLCM: The Disease Activity Score and the EULAR response criteria. *Clin Exp Rheumatol* 2005, 23(Suppl. 39):S93–S99.
6. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988, 31:315–24.
7. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL: Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995, 38:44–8.
8. Bruce B, Fries JF: The Health Assessment Questionnaire (HAQ). *Clin Exp Rheumatol* 2005, 23(5 Suppl 39):S14–8.
9. van der Heijde D: How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 1999, 26:743–5.
10. Bruynesteyn K, van der Heijde D, Boers M, Lassere M, Boonen A, Edmonds J, Houben H, Paulus H, Peloso P, Saudan A, van der Linden S: Minimal clinically important difference in radiological progression of joint damage over 1 year in rheumatoid arthritis: preliminary results of a validation study with clinical experts. *J Rheumatol* 2001.
11. van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL: Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Cri. *Arthritis Rheum* 1996, 39:34–40.
12. Cohen J: A power primer. *Psychol Bull* 1992, 112:155–9.
13. Grzybowski M, Younger JG: Statistical methodology: III. Receiver operating characteristic (ROC) curves. *Acad Emerg Med* 1997, 4:818–826.
14. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR: Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009, 338(jun 29 1):b2393–b2393.
15. Wood AM, White IR, Royston P: How should variable selection be performed with multiply imputed data? *Stat Med* 2008, 27:3227–46.

16. Steunebrink LMM, Versteeg GA, Vonkeman HE, Ten Klooster PM, Kuper HH, Zijlstra TR, van Riel PLCM, van de Laar MAFJ: Initial combination therapy versus step-up therapy in treatment to the target of remission in daily clinical practice in early rheumatoid arthritis patients: results from the DREAM registry. *Arthritis Res Ther* 2015, 18:60.
17. Ten Klooster PM, Drossaers-Bakker KW, Taal E, Van De Laar MAFJ: Patient-perceived satisfactory improvement (PPSI): Interpreting meaningful change in pain from the patient's perspective. *Pain* 2006, 121:151–157.
18. Studenic P, Radner H, Smolen JS, Aletaha D: Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. *Arthritis Rheum* 2012, 64:2814–2823.
19. ten Klooster PM, Veehof MM, Taal E, van Riel PLCM, van de Laar MAFJ: Changes in priorities for improvement in patients with rheumatoid arthritis during 1 year of anti-tumour necrosis factor treatment. *Ann Rheum Dis* 2007, 66:1485–90.
20. Sanderson T, Morris M, Calnan M, Richards P, Hewlett S: Patient perspective of measuring treatment efficacy: the rheumatoid arthritis patient priorities for pharmacologic interventions outcomes. *Arthritis Care Res (Hoboken)* 2010, 62:647–56.
21. Heiberg T, Finset A, Uhlig T, Kvien TK: Seven year changes in health status and priorities for improvement of health in patients with rheumatoid arthritis. *Ann Rheum Dis* 2005, 64:191–5.
22. Altawil R, Saevarsdottir S, Wedrén S, Alfredsson L, Klareskog L, Lampa J: Remaining pain is common in early rheumatoid arthritis patients treated with methotrexate. *Arthritis Care Res (Hoboken)* 2016.
23. Repping-Wuts H, Fransen J, Van Achterberg T, Bleijenberg G, Van Riel P: Persistent severe fatigue in patients with rheumatoid arthritis. *J Clin Nurs* 2007, 16:377–383.
24. Barton JL, Imboden J, Graf J, Glidden D, Yelin EH, Schillinger D: Patient-physician discordance in assessments of global disease severity in rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2010, 62:857–64.
25. Khan NA, Spencer HJ, Abda E, Aggarwal A, Alten R, Ancuta C, Andersone D, Bergman M, Craig-Muller J, Detert J, Georgescu L, Gossec L, Hamoud H, Jacobs JWG, Laurindo IMM, Majdan M, Naranjo A, Pandya S, Pohl C, Schett G, Selim ZI, Toloza S, Yamanaka H, Sokka T: Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. *Arthritis Care Res (Hoboken)* 2012, 64:206–14.
26. Jacobs JWG, Ten Cate DF, van Laar JM: Monitoring of rheumatoid arthritis disease activity in individual patients: still a hurdle when implementing the treat-to-target principle in daily clinical practice. *Rheumatology (Oxford)* 2015, 54:959–61.
27. Lee YC, Nassikas NJ, Clauw DJ: The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. *Arthritis Res Ther* 2011, 13:211.
28. Nikolaus S, Bode C, Taal E, van de Laar MAFJ: Fatigue and factors related to fatigue in rheumatoid arthritis: a systematic review. *Arthritis Care Res (Hoboken)* 2013, 65:1128–46.
29. Nicklin J, Cramp F, Kirwan J, Greenwood R, Urban M, Hewlett S: Measuring fatigue in rheumatoid arthritis: a cross-sectional study to evaluate the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional questionnaire, visual analog scales, and numerical rating scales. *Arthritis Care Res (Hoboken)* 2010, 62:1559–68.

30. Nikolaus S, Bode C, Taal E, Vonkeman HE, Glas CAW, van de Laar MAFJ, Wolfe F, Hawley D, Wilson K, Belza B, Henke C, Yelin E, Eppstein W, Gillis C, Belza TB, Hewlett S, Cockshott Z, Byron M, Kitchen K, Tipler S, Pope D, Repping-Wuts H, Uitterhoeve R, Riel P van, Achterberg T van, Nikolaus S, Bode C, Taal E, Laar M van de, Hewlett S, et al.: Construct Validation of a Multidimensional Computerized Adaptive Test for Fatigue in Rheumatoid Arthritis. *PLoS One* 2015, 10:e0145008.
31. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, et al.: Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005, 113:9–19.
32. Vermeer M, Kuper HH, Bernelot Moens HJ, Hoekstra M, Posthumus MD, van Riel PL, van de Laar MA: Adherence to a treat-to-target strategy in early rheumatoid arthritis: results of the DREAM remission induction cohort. *Arthritis Res Ther* 2012, 14:R254.
33. Mishra S, Khare D: On comparative performance of multiple imputation methods for moderate to large proportions of missing data in clinical trials: a simulation study. *J Med Stat Informatics* 2014, 2:9.

SUPPLEMENTAL TABLES

Supplemental Table 1. *Sensitivity analysis 1, comparison of univariate odds ratios based on complete cases only versus multiple imputed*

Variable	OR CC	OR MI (95% CI)	Missing baseline	Missing T12
Radiographic progression, Median (IQR)	0.94	0.94 (0.83 - 1.06)	2%	2%
VAS fatigue, Mean, (SE)	0.98	0.98 (0.97 - 1.00)	38.3%	33.6%
VAS pain, Mean (SE)	0.98	0.98 (0.97 - 0.99)	6.3%	17.2%
SF-36 Bodily Pain, Mean (SE)	0.98	0.98 (0.97 - 0.99)	14.1%	32.4%
SF-36 Physical Functioning, Mean (SE)	0.99	0.99 (0.98 - 1.00)	14.1%	32.4%
SF-36 Role Physical, Mean (SE)	0.99	0.99 (0.98 - 1.00)	14.1%	32.4%
SF-36 Vitality, Mean (SE)	0.99	0.99 (0.98 - 1.01)	14.1%	32.4%
SF-36 Social Function, Mean (SE)	0.98	0.99 (0.98 - 1.00)	14.1%	32.4%
SF-36 Role Emotional, Mean (SE)	0.99	0.99 (0.98 - 1.00)	14.1%	32.4%
SF-36 Mental Health, Mean (SE)	0.98	0.99 (0.98 - 1.00)	14.1%	32.4%

SF-36 = Short-Form 36 health survey (version 2); VAS = Visual Analogue Scale; CC = complete cases; MI = multiple imputation

Supplemental Table 2. *Sensitivity analysis 2, comparison of multivariable odds ratios based on complete cases only versus multiple imputed*

	Model 1		Model 2	
	CC	MI	CC	MI
VAS Pain	0.98	0.98		
SF-36 Bodily Pain			0.98	0.98
VAS Fatigue			0.99	1.00

CC = complete cases; MI= multiple imputation

Supplemental Table 3. *Sensitivity analysis 3, comparison of area under the receiving operator curve based on complete cases only versus multiple imputed*

Variable	AUC CC	AUC MI (95%CI)
Percentage Change in VAS Pain	0.74 (0.64-0.82)	0.70 (0.61-0.78)
Percentage Change in VAS Fatigue	0.64 (0.49-0.78)	0.62 (0.54-0.70)

AUC = Area under the receiving operator curve; CC = complete cases; MI= multiple imputation

Supplemental Table 4. Backward Elimination with VAS pain

	Variable	Model Log Likelihood	Change in -2 Log Likelihood	Sig. of the Change
<i>Step 1</i>	SF-36 Role Physical	-56.263	.476	.490
	SF-36 Physical Functioning	-56.741	1.432	.231
	VAS Fatigue	-56.584	1.118	.290
	Radiographic Progression	-57.291	2.531	.112
	VAS Pain	-61.278	10.506	.001
<i>Step 2</i>	SF-36 Physical Functioning	-57.422	2.318	.128
	VAS Fatigue	-56.844	1.162	.281
	Radiographic Progression	-57.480	2.435	.119
	VAS Pain	-61.802	11.079	.001
<i>Step 3</i>	SF-36 Physical Functioning	-57.968	2.248	.134
	Radiographic Progression	-58.312	2.937	.087
	VAS Pain	-63.788	13.888	.000
<i>Step 4</i>	Radiographic Progression	-59.378	2.820	.093
	VAS Pain	-65.533	15.129	.000
<i>Step 5</i>	VAS Pain	-66.638	14.520	.000

SF-36 = Short-Form 36 health survey (version 2); VAS = Visual Analogue Scale

Supplemental Table 5. *Backward Elimination with SF-36 Bodily Pain scale*

	Variable	Model Log Likelihood	Change in -2 Log Likelihood	Sig. of the Change
<i>Step 1</i>	Radiographic Progression	-56.192	1.420	.233
	SF-36 Role Physical	-55.582	.201	.654
	SF-36 Physical Functioning	-55.720	.477	.490
	VAS Fatigue	-57.238	3.513	.061
	SF-36 Bodily Pain	-57.153	3.342	.068
<i>Step 2</i>	Radiographic Progression	-56.279	1.394	.238
	SF-36 Physical Functioning	-55.903	.641	.423
	VAS Fatigue	-57.388	3.611	.057
	SF-36 Bodily Pain	-57.596	4.028	.045
<i>Step 3</i>	Radiographic Progression	-56.581	1.356	.244
	VAS Fatigue	-57.638	3.471	.062
	SF-36 Bodily Pain	-59.403	7.001	.008
<i>Step 4</i>	VAS Fatigue	-58.507	3.854	.050
	SF-36 Bodily Pain	-60.183	7.204	.007

SF-36 = Short-Form 36 health survey (version 2); VAS = Visual Analogue Scale; BP_CAT; bodily pain

CHAPTER 7

Individual relationship between disease activity and radiographic progression in patients with early rheumatoid arthritis in the treat-to-target era

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic inflammatory joint disease with a variable course and outcome which often leads to radiographic joint damage. Earlier studies showed a strong association between time-integrated, or cumulative, disease activity and radiographic progression in conventionally treated patients. This study examined the longitudinal relationship between disease activity and radiographic progression in patients with early rheumatoid arthritis treated according to intensive treat-to-target (T2T) therapy in daily clinical practice.

Methods: Three-year follow-up data were used from 229 RA patients receiving step-up T2T included in the DREAM remission induction cohort. 28-joint disease activity scores (DAS28-ESR) were assessed at least every three months. X-rays of the hand and feet were assessed at baseline and after 0.5, 1, 2 and 3 years of treatment and scored using the modified Sharp/van der Heijde (SHS) method. Pearson correlations between time-integrated disease activity measures (AUC with trapezoid rule) and radiographic progression (from previous time point) at each of the follow-up time points were computed to estimate between-person associations. Individual trajectories of time-integrated disease activity scores at each of the 4 time intervals were plotted against cumulative radiographic progression scores to additionally examine within-person associations.

Results: At the group level, no or very weak positive correlations between time-integrated disease activity and radiographic progression were observed at the subsequent time moments. A wide inter-individual variation between disease activity and radiographic progression was also apparent from the individual trajectory plots. However, the individual slopes of the individual lines in each time interval confirmed a relatively constant association between disease activity and radiographic progression within patients. Within individual patients, time-integrated disease activity and radiographic progression were significantly and moderately correlated at the different time points. 12 – 30% of the patients in time-integrated DAS28 remission, still showed relevant radiographic damage (SHS ≥ 3).

Conclusion: Time-integrated disease activity and radiographic progression were only weakly associated at the group level in the first 3 years of treatment. In contrast, within individual patients a fairly linear relationship between disease activity and radiographic progression seemed to exist over time.

BACKGROUND

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease with a variable course and outcome which leads to disability through destruction of joints [1]. Studies have shown a strong association between time-integrated, or cumulative disease activity and radiographic progression in patients treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARD) [2–7].

Nowadays, treat-to-target (T2T) strategies, which focus on early and rapid reduction of disease activity, substantially reduce radiographic damage [8, 9]. However, despite this intensive treatment, early joint damage still predicts long-term radiographic progression [10]. This suggests that factors other than disease activity may affect radiographic progression in some of the patients. This disconnection between inflammation and progression of structural damage has already been described in RA patients treated with early aggressive csDMARD therapy [11] and in established RA patients treated with biological (combination) therapy [12, 13]. This is further supported by a recent study by Knevel et al. who examined the proportion of variance in radiographic progression explained by cumulative measures of disease activity separately for three increasingly aggressive csDMARD strategies. This study showed that the explained variance of CRP and swollen joint counts gradually decreased from 25% and 24% respectively in patients initially treated with no or delayed mild DMARD therapy, to 17% and 4% in patients initially treated with mild csDMARD therapy, and to 9% and 0% in patients with early aggressive DMARD treatment [14].

There is large variation across countries in reimbursement criteria for initiation of biological disease-modifying antirheumatic drug (bDMARD) therapy [15, 16]. These criteria are mainly based on the level of disease activity. In several countries bDMARDs can only be prescribed in patients with moderate or high disease activity. Current international guidelines recommend basing treatment decisions on disease activity, whereby radiographic damage should be taken into account. The advice is therefore to initiate bDMARDs after three to six months of treatment with csDMARDs, when the defined target (remission or absence of disease activity) is not met and when unfavorable prognostic factors, such as early joint damage, are present [17, 18]. However, it is possible that even in patients with moderate or low disease activity, radiographic progression may occur.

Patterns of radiographic progression may be highly variable within individual RA patients [19, 20]. The exact individual relationship between disease activity and radiographic progression in the current era of early and intensive T2T is not clear. However, this information is important for optimizing treatment strategies. Therefore, the aim of this study was to investigate the inter-

individual and intra-individual relationship between disease activity and radiographic progression in patients with early rheumatoid arthritis following a strict 'T2T' protocol in daily clinical practice.

PATIENTS AND METHODS

Data selection and study design

The Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort is a multicenter observational cohort study of early RA patients treated to target ('T2T') in daily clinical practice in The Netherlands [21]. Patient enrollment in the cohort started in 2006 and follow-up data collection is ongoing. Patients with a clinical diagnosis of RA (made at the discretion of the attending experienced rheumatologist) were included if they were > 18 years of age, had a symptom duration (defined as the time from the first reported symptom to the diagnosis of RA) < 1 year, had a Disease Activity Score in 28 joints (DAS28) ≥ 2.6 and had not previously received DMARDs and/or prednisolone. For the present study, patients enrolled before 2010 at the Medisch Spectrum Twente hospital and the Isala Zwolle hospital with at least two available radiographic assessments, were selected for analysis. The study was approved by the Medical Ethics Committees of both hospitals, and patients were fully informed and informed consent was obtained from all patients.

Treatment

Details on the treatment protocol have previously been published [9, 21]. Briefly, patients were treated according to a 'T2T' strategy aiming at remission (DAS28 < 2.6) and evaluated at 0, 8, 12, 20, 24, 36, and 52 weeks and every 3 months thereafter. Patients started with initial monotherapy of 15mg/week methotrexate (MTX) with folic acid taken at the second day after MTX. In case of insufficient response (DAS28 ≥ 2.6) at the evaluation time-points, the following per protocol treatment steps were advised: at week 8, MTX dosage was increased to 25 mg/week; at week 12 sulfasalazine (SSZ) 2000 mg/day was added; at week 20 SSZ dose was increased to 3000mg/day. Tumor necrosis factor inhibitor (TNFi) was prescribed at week 24 for patients with persistent moderate disease activity (DAS28 remained ≥ 3.2). In case of sustained remission (DAS28 < 2.6 for ≥ 6 months), medication was gradually reduced and eventually discontinued. In case of a disease flare (DAS28 ≥ 2.6), the last effective medication or medication dose was restarted and treatment could be subsequently intensified. In patients with contraindications to specific medication, deviations from the protocol were allowed. Concomitant treatment with nonsteroidal anti-inflammatory drugs, prednisolone at a dosage of ≤ 10 mg/day and/or intra-articular corticosteroid injections was allowed at the discretion of the attending rheumatologist.

On clinical indication the attending rheumatologist was free to diverge from the medication schedule at any time.

Assessments

Serial measurements of disease activity and radiographic damage were performed according to a predefined follow-up scheme. Disease activity measures were collected at baseline and at every follow-up visit (week 8, 12, 20, 24, 36, and 52, and every 3 months thereafter) and consisted of the 28-tender joint count (TJC28), 28-swollen joint count (SJC28), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, and a patient rating for general health on a 100-mm visual analog scale (VAS-GH). TJC28, SJC28, ESR and VAS-GH were used to calculate the composite DAS28 score [22]. Total DAS28 scores range from 0 to approximately 10. The level of disease activity can be interpreted as low (≤ 3.2), moderate (3.2 to ≤ 5.1), or high (> 5.1). A score < 2.6 corresponds to remission [23].

Radiographs of the hand and feet were taken at baseline, 6 months, 12 months, and yearly thereafter and were scored by 2 readers using the modified Sharp/van der Heijde scoring (SHS) system [24]. Relevant progression was defined as an increase of at least 3 units on the SHS for each time interval, based on the calculated smallest detectable change (SDC) of 2.25 over the 5 repeated assessments using the ANOVA-based method described by Bruynesteyn et al. [25].

Analysis

Time-integrated disease activity, as measured with the DAS28, was calculated by the area under the curve (AUC) method using trapezoidal integration [26]. In this method, the AUC between observations is the product of the time difference between the two measurements (in weeks) and the average of the two disease activity measurements. AUCs were calculated separately for each of the 4 time intervals of radiographic progression. In case of missing data on the disease activity parameter at a given time point, the area between the most recent non-missing time point and the next non-missing time-point within a time interval was calculated. Time-integrated disease activity scores per time interval were standardized by time (in weeks), yielding AUC values in the metric of the original measurement. Radiographic progression in each of the 4 time intervals was calculated by subtracting baseline SHS score values from the respective scores at each time point.

Pearson correlations between time-integrated disease activity measures and progression (from previous time point) at each of the follow-up time points were estimated. These correlations represent the inter-individual (between-person) association between disease activity and outcome at the different time-intervals.

Next, individual trajectories of time-integrated disease activity scores at each of the 4 time intervals were plotted against cumulative radiographic progression scores. These plots visualize the intra-individual relationship between time-integrated disease activity and radiographic progression over time. For each patient the slopes of this relation for each time period were calculated by dividing progression of SHS (from previous time point) by time-integrated disease activity in the same time interval. Pearson correlation coefficients between slopes at the different time periods were determined to test the significance of the intra-individual (within-person) associations between disease activity and outcome over time.

For each of the 4 follow-up time points, the proportion of patients showing relevant radiographic progression ($\geq$ smallest detectable change (SDC) of 3 on the SHS) in the preceding time interval was calculated and compared between patients with different predefined categories of disease activity as measured with the DAS28 using crosstabulations.

RESULTS

Patients and 1-year outcomes

From January 2006 to December 2009, a total of 229 patients were included in the study. The baseline characteristics of the patients are presented in Table 1. Most patients were female and the mean age was 57.5 years. Patients had an active disease with a mean DAS28 score of 4.9. The majority of the patients were anti-CCP and RF positive.

While mean time-integrated DAS28 scores decreased significantly from 3.6 to 2.2 between 6 and 12 months of treatment, and remained low (< 2.3) thereafter, radiographic damage kept increasing almost linearly (Figure 1).

Table 1. *Baseline characteristics of the patients (N=229)*

Characteristics	
Female, n (%)	145 (63,3)
Age, mean $\pm$ SD years	57.5 $\pm$ 15.0
BMI, mean ($\pm$ SD) kg/m ²	26.4 $\pm$ 4.6 ^a
Symptom duration, median (IQR) weeks	13.0 (8.0 - 26.0) ^b
RF positive, n (%)	140/228 (61.4)
Anti-CCP positive, n/total (%)	130/221 (58.8)
Fulfillment of ACR 1987 criteria, n/total (%)	178/225 (79.0)
Erosive disease, n/total (%)	34/226 (15.0)
DAS28, mean ($\pm$ SD)	4.9 $\pm$ 1.1
Number of tender joints (28 assessed), median (IQR)	5 (2 - 10)
Number of swollen joints (28 assessed), median (IQR)	8 (4 - 12)
ESR, median (IQR) mm/hour	28.0 (16.0 - 42.0)
CRP, median (IQR) mg/liter	12.0 (5.0 - 29.3)
VAS general health, median (IQR) 0-100 VAS	50 (30.0 - 66.5)
VAS pain, median (IQR) 0-100 VAS	50 (37.0 - 69.5)
VAS fatigue, median (IQR) 0-100 VAS	50 (24.3 - 71.5) ^c
HAQ-DI, median (IQR)	1.1 (0.6 - 1.5) ^d
SF-36 PCS, median (IQR)	35.4 (30.0 - 41.5) ^e
SF-36 MCS, median (IQR)	47.9 (39.0 - 56.4) ^f

BMI = body mass index; IQR = interquartile range; RF = rheumatoid factor; Anti-CCP = anti-cyclic citrullinated peptide; ACR= American College of Rheumatology; DAS28 = disease activity score based on 28 joint count; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; VAS = visual analogue scale; HAQ = Health Assessment Questionnaire; SF36 = Short-Form 36 health survey; PCS = physical component summary; MCS = mental component summary

a = 220; b = 228; c = 124; d = 191; e = 199; f = 199

Inter-individual relation between disease activity and outcome

At group level, there was no significant correlation between time-integrated disease activity and radiographic progression at the 6-month and 2-year follow-up and only a very weak positive association at the 1-year and 3-year follow-up (Table 2).

A wide inter-individual variation between disease activity and radiologic progression was also apparent from the individual trajectory plots (Figure 2). A substantial number of patients with low or moderate disease activity showed relevant radiographic progression, while many others showed no or very little progression at higher disease activity levels.

Intra-individual relation between disease activity and outcome

In contrast to the absence of inter-individual correlation, however, for many individual patients a different but fairly proportional relationship seemed to exist. Moreover, the slopes of the individual lines in each time interval were significantly and substantially correlated over time (Figure 2), suggesting a relatively constant association between disease activity and radiographic progression within individual patients. Individual slopes of the relationship between disease

activity and progression were significantly and moderately correlated for all time moments. Especially the slopes of the individual patients in the first 6 months were strongly related with the slopes in the later time periods. (Table 3).

Figure 1. Mean standardized time-integrated DAS28 disease activity scores (from previous time point) versus mean cumulative SHS progression scores (from baseline). Error bars are 95% confidence intervals.

*A total of 191 (16.7%) radiographs were missing from baseline to 3 year follow-up (baseline 3.5%; 6 months 15.3%; 1 year 15.7%; 2 year 25.3%; 4 year 23.6%).

Table 2: Between-person Pearson correlations between standardized time-integrated (AUC) disease activity and radiographic progression (from previous time point) for each time interval

	0 - 6 months (n=192)	6 months - 1 year (n=164)	1 - 2 year (n=150)	2 - 3 year (n=146)
DAS28-ESR	0.060	0.170*	0.109	0.209*

* P < 0.05; ** P < 0.01.

Figure 2. Intra-individual relations between time-integrated DAS28 scores (standardized in weeks) and cumulative radiological progression during 3 years of follow-up ($N = 229$). Every patient has its own line, composed of the 0 – 6 month, 6 month – 1 year, 1 year – 2 year, and 2 year – 3 year values for time integrated disease activity in relation to the cumulative SHS score at those time points.

Table 3: *Within-person Pearson correlations between time-integrated disease activity as measured by DAS28 (top diagonal) and radiographic progression over time.*

	0 - 6 months	6 months - 1 year	1 - 2 year	2 - 3 year
0 - 6 months	-	0.394***	0.527***	0.592***
6 months - 1 year	-	-	0.172*	0.252**
1 - 2 year	-	-	-	0.478***
2 - 3 year	-	-	-	-

* P<0.05; ** P<0.01; *** P<0.001.

Radiographic progression and the different categories of disease activity

Table 4 represents the proportion of patients experiencing radiographic progression within each category of time-integrated disease activity. Across the different time points, in 12% to 30% of the patient in time-integrated remission, radiographic damage continued to be 3 or more Sharp v/d Heijde points.

Table 4. Proportion of patients experiencing radiographic progression (Δ SHS ≥ 3) within each time interval against categories of diseases activity (time-integrated standardized DAS28 scores) in the same period.

Disease activity	0 - 6 months progression		6 months - 1 year progression		1 year - 2 year progression		2 year - 3 year progression	
	No	Yes	No	Yes	No	Yes	No	Yes
<i>Remission</i> (DAS28 <2.6)	21 (70.0%)	9 (30.0%)	99 (87.6%)	14 (12.4%)	83 (80.6%)	20 (19.4%)	90 (85.7%)	15 (14.3%)
<i>Low</i> (DAS28 2.6 – 3.2)	37 (82.2%)	8 (17.8%)	14 (60.9%)	9 (39.1%)	17 (65.4%)	9 (34.6%)	21 (77.8%)	6 (22.2%)
<i>Moderate</i> (DAS28 3.2-5.1)	79 (73.8%)	28 (26.2%)	20 (83.3%)	4 (16.7%)	15 (75.0%)	5 (25.0%)	8 (61.5%)	5 (38.5%)
<i>High</i> (DAS28 >5.1)	7 (70.0%)	3 (30.0%)	2 (66.7%)	1 (33.3%)	0 (0.0%)	1 (100%)	1 (100%)	0 (0.0%)
Total	144 (75.0%)	48 (25.0%)	135 (82.8%)	28 (17.2%)	115 (76.7%)	35 (23.3%)	120 (82.2%)	26 (17.8%)

Baseline characteristics of patient in remission but with progression

Since the first 6 months were strongly predictive for the future association between disease activity and outcome, characteristics of patients with a time-integrated DAS28 score < 2.6 but with relevant progression (3 or more sharp v/d Heijde points) between 0-6 months were compared.

The mean baseline joint space narrowing score in the group with progression and in remission was 3.8 (SD = 4.6) and the mean erosion score was 4.6 (SD = 3.8) versus a mean joint space narrowing score of 0.9 (SD = 1.8) and mean erosion score of 0.3 (SD = 0.7) in the group of patients in remission without progression. The majority of patients in remission but with relevant progression were men (66.7%; 6/9) versus 42.9% (9/21) of patients in remission without progression. Patients in the group with progression and in remission were on average 56 years old (SD = 7.1) versus an average age of 49.4 years (SD = 15.1) in patients without progression and in remission. The mean DAS28 score in the group with remission and progression was 3.8 (SD = 0.8) with a symptom duration of 14.9 weeks (SD = 9.0) versus a mean DAS28 score of 3.9 (SD = 0.9) with a symptom duration of 16.1 weeks (SD = 12.9) in the group of patients without progression and in remission. Most of the patients in the group of progression and in remission were anti-CCP positive (8/9, 88.9%) and had a positive rheumatoid factor (8/9, 88.9%). In the group of patients without progression and in remission 47.6% (n = 10/21) were anti-CCP positive and fewer patients had a positive rheumatoid factor (13/21, 61.9%).

DISCUSSION

In this study we examined the inter- and intra-individual relationship between disease activity and radiographic joint damage in an early treat-to-target (T2T) treatment strategy in daily clinical practice. Our study confirms the effectiveness of the application of a continuous T2T approach on achieving and maintaining mean DAS28 remission. However, despite the quick and sustained suppression of disease activity, mean radiographic damage still accumulated. We demonstrated that the relationship between disease activity and radiographic progression was highly variable between individuals. At group level there was only a weak correlation between mean time-integrated DAS28 and mean cumulative radiographic damage score after 3 years. However, within individual patients, the associations between joint inflammation and joint damage at different time-intervals were moderately correlated.

The overall radiographic progression in our study is substantially lower in comparison with studies from the last decades [27, 28]. This improvement is most likely due to the more intensive treatment strategy, such as more intensive use of csDMARDs and the availability of bDMARDs. Previously, we showed that implementation of T2T treatment strategies in daily clinical practice leads to more rapid and higher DAS28 remission rates after 1 year than usual care [29]. Even in the long-term, sustained suppression of disease activity resulted in limited radiographic damage [9]. However, some patients still have progressive joint destruction even with relatively low disease activity. Two other longitudinal cohort studies also demonstrated that a substantial proportions of patients (7 - 17%) in sustained remission still had relevant progression of joint damage and 15-20% developed erosion in a previously unaffected joints [30, 31]. Together with the current findings, this suggests that joint destruction may be to a considerable extent driven by factors other than disease activity, and instead may be an individually determined disease process.

Studies from the past have demonstrated a strong association between the cumulative amount of disease activity (as measured by time-integration of laboratory based disease activity parameters) and radiographic progression [2, 3, 6]. Van Leeuwen et al. showed in RA patients treated with NSAIDs and low dose conventional DMARDs (hydroxychloroquine, gold and sulphasalazine) a highly significant correlation of 0.638 between time-integrated c-reactive protein (CRP) values and radiographic progression over 3 years of follow-up [2]. Plant et al. demonstrated in RA patients treated with conventional DMARDs (hydroxychloroquine, penicillamine and intramuscular gold) a significant strong correlation of 0.50 between time-integrated CRP level and change in Larsen score after 5-years follow-up. This correlation increased to 0.59 in a subgroup of patients with disease duration shorter than 2 years [3]. Knijff et al. showed correlations between time-integrated CRP and rheumatoid factor (RF) and

radiographic progression of 0.38 and 0.25 Sharp/vanderHeijde points respectively [6]. In this study they also found a fairly individual constant slope between exposure to disease activity over time and radiographic progression. Indicating an individually determined, linear relationship between exposure to disease activity and progression of radiographic damage. In a later study Wick et al. demonstrated a much weaker correlation between time-integrated CRP and joint damage (as measured by Larsen score) over 2 years of follow-up at population level in RA patients treated with DMARDs (gold, sulphasalazine and MTX) starting within 2 months after diagnosis [11]. Our study confirmed these results, showing insignificant or only weak correlations between time-integrated DAS28 levels and cumulative radiographic progression over 3 years of follow-up in RA patients treated with a modern treat-to-target treatment strategy.

A plausible explanation for this finding might be changes in treatment over time such as other types and/or doses of disease modifying antirheumatic drug (DMARD). The association between time-integrated disease activity, as measured by a composites disease activity score (DAS28) and cumulative radiographic progression, was poor in both the study by Wick et al. and in our study. In addition, Wick et al. found strong and significant correlations between ratios of cumulative inflammatory burden and radiographic progression within patients at different time-intervals. According to Wick et al. joint destruction results from the cumulative burden of inflammation over time modified by an individual constant factor (similar to the individual slope in the current study) that accounts for the inter-individual differences in the degree of joint destruction at any given level of inflammation. Given our results, this individual constant factor seems to persist or may be even stronger in more intensive treatment strategies. Earlier studies demonstrated that, although radiographic progression seems to be approximately linear at the group level, individual RA patients may have highly variable patterns of radiologic progression over time [19, 20, 32, 33]. All these studies have found relationships within patients between exposure to disease activity and progression of radiographic damage characterized by an individual factor that remained constant over follow-up periods up to five years. In addition, Welsing et al. demonstrated that the course of radiographic progression in individual patients is determined more strongly by fluctuations in disease activity than by the average level of disease activity. He also found this relationship to be constant over time and especially in patients who were rheumatoid factor positive [34].

For daily clinical practice the results of these findings means that in all patients their individual slope of disease activity and progression seems to be reasonable linear. The majority of patients showed consistently low disease activity with little radiographic progression. However, there were also patients with consistently low disease activity who still developed radiographic

progression. As this relationship is quite linear, these patients might be identifiable early in the disease process. This suggests that radiographic evaluation after six months of treatment might be valuable, even in patients with low disease activity. For future treatment strategies, treatment decisions should ideally be based on measurements of disease activity as well as radiographic progression.

Our study shows that the association between time-integrated DAS28 and radiographic progression, especially during the first six months of treatment, remains constant further in the disease course. In this first time-interval, a substantial proportion of patients (30%) showed relevant radiographic progression while being in time-integrated DAS28 remission. The majority of these RA patients were men, antiCCP positive and the majority also already had radiographic damage at baseline.

As disease activity varies over time, transformation of serial measurements using time-integration, or area under the curve methods, is very useful and permits comparison with outcome measures such as radiographic progression. Another strong element of this study is the setting of real-life practice, which makes the results generalizable to other practices. However, several limitations may have affected the results. This observational study does not allow any causal inference about the association between disease activity and radiographic outcome. Also, there was a substantial number of patients with missing values on radiographic progression, especially at the 2- and 3-year follow-up assessments, which may have biased the results. Thirdly, the real-world nature of this study may also have introduced bias, including confounding by indication. Finally, the DAS28 does not take disease activity in the feet into account, while the Sharp/van der Heijde score does take progression in the feet into account.

In conclusion this study shows that time-integrated disease activity and radiographic progression were only very weakly associated at group level in the first 3 years of treatment. However, within individual patients a fairly linear relationship between disease activity and radiographic progression seemed to exist over time.

REFERENCES

1. Boers M, Kostense PJ, Verhoeven AC, van der Linden S, COBRA Trial Group. Combinatietherapie Bij Reumatoïde Artritis: Inflammation and damage in an individual joint predict further damage in that joint in patients with early rheumatoid arthritis. *Arthritis Rheum* 2001, 44:2242–6.
2. Leeuwen M van, Rijswijk M van: The acute-phase response in relation to radiographic progression in early rheumatoid arthritis: a prospective study during the first three years of the disease. *Br J Rheumatol* 1993, 32(suppl 3):9–13.
3. Plant MJ, Williams AL, O'Sullivan MM, Lewis PA, Coles EC, Jessop JD: Relationship between time-integrated C-reactive protein levels and radiologic progression in patients with rheumatoid arthritis. *Arthritis Rheum* 2000, 43:1473–7.
4. Kuper HH, van Leeuwen MA, van Riel PL, Prevoo ML, Houtman PM, Lolkema WF, van Rijswijk MH: Radiographic damage in large joints in early rheumatoid arthritis: relationship with radiographic damage in hands and feet, disease activity, and physical disability. *Br J Rheumatol* 1997, 36:855–60.
5. van Leeuwen MA, van Rijswijk MH, Sluiter WJ, van Riel PL, Kuper IH, van de Putte LB, Pepys MB, Limburg PC: Individual relationship between progression of radiological damage and the acute phase response in early rheumatoid arthritis. Towards development of a decision support system. *J Rheumatol* 1997, 24:20–7.
6. Knijff-Dutmer E, Drossaers-Bakker W, Verhoeven A, van der Sluijs Veer G, Boers M, van der Linden S, van de Laar M: Rheumatoid factor measured by fluoroimmunoassay: a responsive measure of rheumatoid arthritis disease activity that is associated with joint damage. *Ann Rheum Dis* 2002, 61:603–7.
7. Wick MC, Anderwald C, Weiss RJ, Imhof H, Kainberger F, Smolen JS: Radiological progression of joint damage in a longitudinal cohort of early DMARD-treated rheumatoid arthritis patients followed for 10 years. *Scand J Rheumatol* 2004, 33:162–6.
8. Klarenbeek NB, Güler-Yüksel M, van der Kooij SM, Han KH, Ronday HK, Kerstens PJSM, Seys PEH, Huizinga TWJ, Dijkmans BAC, Allaart CF: The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. *Ann Rheum Dis* 2011, 70:1039–46.
9. Vermeer M, Kuper HH, Moens HJB, Drossaers-Bakker KW, van der Bijl AE, van Riel PLCM, van de Laar MAFJ: Sustained beneficial effects of a protocolized treat-to-target strategy in very early rheumatoid arthritis: three-year results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort. *Arthritis Care Res (Hoboken)* 2013, 65:1219–26.
10. van den Broek M, Dirven L, de Vries-Bouwstra JK, Dehpoor AJ, Goekoop-Ruiterman YPM, Gerards AH, Kerstens PJSM, Huizinga TWJ, Lems W, Allaart CF: Rapid radiological progression in the first year of early rheumatoid arthritis is predictive of disability and joint damage progression during 8 years of follow-up. *Ann Rheum Dis* 2012, 71:1530–3.
11. Wick MC, Lindblad S, Klareskog L, Van Vollenhoven RF: Relationship between inflammation and joint destruction in early rheumatoid arthritis: a mathematical description. *Ann Rheum Dis* 2004, 63:848–52.
12. Smolen JS, Han C, Bala M, Maini RN, Kalden JR, van der Heijde D, Breedveld FC, Furst DE, Lipsky PE, ATTRACT Study Group: Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum* 2005, 52:1020–30.

13. Landewé R, van der Heijde D, Klareskog L, van Vollenhoven R, Fatenejad S: Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate: results from the trial of etanercept and methotrexate with radiographic and patient outcomes. *Arthritis Rheum* 2006, 54:3119–25.
14. Knevel R, van Nies JAB, le Cessie S, Huizinga TWJ, Brouwer E, van der Helm-van Mil AHM: Evaluation of the contribution of cumulative levels of inflammation to the variance in joint destruction in rheumatoid arthritis. *Ann Rheum Dis* 2013, 72:307–8.
15. Emery P, Van Vollenhoven R, Ostergaard M, Choy E, Combe B, Graninger W, Krueger K, Matucci-Cerinic M, Navarro F, van Riel P, Settas L, Steinfeld S: Guidelines for initiation of anti-tumour necrosis factor therapy in rheumatoid arthritis: similarities and differences across Europe. *Ann Rheum Dis* 2009, 68:456–9.
16. Putrik P, Ramiro S, Kvien TK, Sokka T, Uhlig T, Boonen A, Equity in Clinical Eligibility Criteria for RA treatment Working Group: Variations in criteria regulating treatment with reimbursed biologic DMARDs across European countries. Are differences related to country's wealth? *Ann Rheum Dis* 2014, 73:2010–21.
17. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, Kvien TK, Navarro-Compán MV, Oliver S, Schoels M, Scholte-Voshaar M, Stamm T, Stoffer M, Takeuchi T, Aletaha D, Andreu JL, Aringer M, Bergman M, Betteridge N, Bijlsma H, Burkhardt H, Cardiel M, Combe B, Durez P, Fonseca JE, Gibofsky A, Gomez-Reino JJ, Graninger W, Hannonen P, Haraoui B, et al.: Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016, 75:3–15.
18. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, Nam J, Ramiro S, Voshaar M, van Vollenhoven R, Aletaha D, Aringer M, Boers M, Buckley CD, Buttgerit F, Bykerk V, Cardiel M, Combe B, Cutolo M, van Eijk-Hustings Y, Emery P, Finckh A, Gabay C, Gomez-Reino J, Gossec L, Gottenberg J-E, Hazes JMW, Huizinga T, Jani M, Karateev D, et al.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017, 76:960–977.
19. Fex E, Jonsson K, Johnson U, Eberhardt K: Development of radiographic damage during the first 5-6 yr of rheumatoid arthritis. A prospective follow-up study of a Swedish cohort. *Br J Rheumatol* 1996, 35:1106–15.
20. Plant MJ, Jones PW, Saklatvala J, Ollier WE, Dawes PT: Patterns of radiological progression in early rheumatoid arthritis: results of an 8 year prospective study. *J Rheumatol* 1998, 25:417–26.
21. Vermeer M, Kuper HH, Hoekstra M, Haagsma CJ, Posthumus MD, Brus HLM, van Riel PLCM, van de Laar MAFJ: Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. *Arthritis Rheum* 2011, 63:2865–72.
22. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL: Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995, 38:44–8.
23. Fransen J, van Riel PLCM: The Disease Activity Score and the EULAR response criteria. *Clin Exp Rheumatol* , 23(5 Suppl 39):S93-9.
24. van der Heijde D: How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 2000, 27:261–3.

25. Bruynesteyn K, Boers M, Kostense P, van der Linden S, van der Heijde D: Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. *Ann Rheum Dis* 2005, 64:179–82.
26. Matthews JN, Altman DG, Campbell MJ, Royston P: Analysis of serial measurements in medical research. *BMJ* 1990, 300:230–5.
27. Wolfe F, Sharp JT: Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. *Arthritis Rheum* 1998, 41:1571–82.
28. Carpenter L, Norton S, Nikiphorou E, Jayakumar K, McWilliams DF, Rennie KL, Dixey J, Kiely P, Walsh DA, Young A, Early Rheumatoid Arthritis Study and the Early Rheumatoid Arthritis Network: Reductions in Radiographic Progression in Early Rheumatoid Arthritis Over Twenty-Five Years: Changing Contribution From Rheumatoid Factor in Two Multicenter UK Inception Cohorts. *Arthritis Care Res (Hoboken)* 2017, 69:1809–1817.
29. Schipper LG, Vermeer M, Kuper HH, Hoekstra MO, Haagsma CJ, Den Broeder AA, van Riel P, Fransen J, van de Laar MAFJ: A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. *Ann Rheum Dis* 2012, 71:845–50.
30. Cohen G, Gossec L, Dougados M, Cantagrel A, Goupille P, Daures JP, Rincheval N, Combe B: Radiological damage in patients with rheumatoid arthritis on sustained remission. *Ann Rheum Dis* 2007, 66:358–63.
31. Molenaar ETH, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M, Dijkmans BAC: Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. *Arthritis Rheum* 2004, 50:36–42.
32. Graudal NA, Jurik AG, de Carvalho A, Graudal HK: Radiographic progression in rheumatoid arthritis: a long-term prospective study of 109 patients. *Arthritis Rheum* 1998, 41:1470–80.
33. Lindqvist E, Jonsson K, Saxne T, Eberhardt K: Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis. *Ann Rheum Dis* 2003, 62:611–6.
34. Welsing PMJ, Landewé RBM, van Riel PLCM, Boers M, van Gestel AM, van der Linden S, Swinkels HL, van der Heijde DMFM: The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. *Arthritis Rheum* 2004, 50:2082–93.

CHAPTER 8

Summary and general discussion

Rheumatoid arthritis (RA) is an inflammatory disease of the connective tissues of the body, particularly the synovial joints. Persistent inflammation may lead to damage of the joint capsule and the articular cartilage. Several clinical trials and studies in daily clinical practice have shown that early, aggressive suppression of inflammation leading to sustained remission or at least a state of low disease activity can prevent or minimize joint damage and associated disability. Current treatment guidelines advocate treat-to-target (T2T) as the optimal treatment approach [1]. Within this treatment paradigm, successive medication adjustments are made until a predefined disease activity target (usually remission or low disease activity) is reached. Accumulating evidence suggests that a T2T approach leads to better clinical outcomes than alternative treatment approaches, but it is still unclear whether T2T can be further optimized. The main objective of this thesis was to compare and explore the effects of a step-up DMARD monotherapy versus an initial DMARD combination therapy according to a T2T strategy aiming at remission in early RA. For this, the **Dutch RhEumatoid Arthritis Monitoring (DREAM)** collaboration started two T2T remission induction cohorts, both with different medication protocols, the results of which were presented in this thesis.

SUMMARY AND MAIN FINDINGS

Chapter 3

This chapter presented remission rates and predictors of remission in a real-life T2T cohort (initial DMARD combination therapy) of consecutive patients with a recent clinical diagnosis of RA. Remission was achieved rapidly in almost 80% of recently diagnosed RA-patients during the first year of their disease. Among a wide range of possible prognostic factors for achieving remission, no accurate predictors could be identified. This provides additional evidence that a T2T strategy aiming at remission is universally beneficial for recently diagnosed RA patients in clinical practice and can therefore be implemented widely. The vast majority of the patients in the current study achieved the treatment target using csDMARDs only and only 10% of patients needed treatment with bDMARDs within the first 12 months. This study confirmed that remission is a realistic goal in daily clinical practice. Moreover, the current T2T strategy appears to be broadly applicable to all patients with recently diagnosed RA. Together with the absence of clear baseline predictors, this suggests that clinicians aiming at remission in daily clinical practice may focus on outcomes only, without needing to take other patients characteristics into account.

Chapter 4

This chapter aimed to compare the effectiveness of two 'T2T' strategies in early RA patients. For this purpose, a step-up approach starting with methotrexate (MTX) monotherapy (strategy I) was compared to an initial DMARD combination approach (strategy II). The results of this study suggest that the previously reported outcomes that were achieved by implementation of 'T2T' with initial MTX monotherapy in daily clinical practice may be reproduced, and even improved upon, using an initial DMARD combination approach. Initial DMARD combination therapy resulted in comparable remission rates after one year but a significantly shorter median time to remission. At 6 months, mean disease activity scores were lower in patients with initial DMARD combination treatment than in those with DMARD step-up therapy. At 12 months, no significant differences remained in mean DAS28 scores or the proportion of patients in remission. In conclusion, 'T2T' using initial combination therapy leads to a significantly shorter time to achieve first remission.

Chapter 5

This chapter compared the radiographic outcomes of step-up DMARD monotherapy (strategy I) versus initial DMARD combination therapy (strategy II). This study showed that patients with initial DMARD monotherapy had significantly more, and more frequently clinically relevant, radiographic progression after one year. A substantially larger number of patients within strategy II showed no radiographic progression at all and only a small portion of patients showed clinically relevant progression. For clinically relevant progression, fewer tender joints and higher ESR were significantly associated with reaching a MCID.

Chapter 6

This chapter explored the association between achieving favorable clinical outcomes and patients' perceived changes in overall health status after 12 months of 'T2T' in patients with early rheumatoid arthritis and aimed to identify determinants of subjective non-improvement. Results showed that more than one-third of the patients (35%) did not consider their overall health to have improved, despite having achieved favorable clinical outcomes. Relative change from baseline in VAS pain and VAS fatigue was independently associated with non-improved perceived overall health status. This study showed that clinical improvements do not equate with improved subjective health for all patients. Improvement in clinical signs and symptoms alone may not be enough to achieve favorable health outcomes for all early RA patients. Therefore, the association of non-improvement with changes in pain and fatigue suggests that it might be

worthwhile to monitor and address pain and fatigue in addition to and independently of disease activity in early rheumatoid arthritis.

Chapter 7

This study examined the longitudinal relationship between disease activity and radiographic progression in patients with early rheumatoid arthritis in the current era of intensive treat-to-target (T2T) in daily clinical practice. At the group level, no significant correlations between time-integrated disease activity and radiographic progression were observed at the 6 month and 2-year follow-up. At 1-year and 3-year follow-up there was only a very weak positive association. A wide inter-individual variation between disease activity and radiographic progression was also apparent from the individual trajectory plots. However, the slopes of the individual lines in each time interval confirmed a fairly proportional relationship between disease activity and radiographic progression within patients. Especially the slopes in the first 6 months were strongly related to the slopes in the later time points. In 12 – 30% of the patient in time-integrated remission, relevant radiographic damage (SHS ≥ 3) continued. These findings suggest that, in the era of T2T, radiographic damage is no longer caused by only (consistent) high disease activity, but is primarily an individually determined disease process.

GENERAL DISCUSSION

Treat to target

Rheumatoid arthritis (RA) is a heterogeneous disease whereby the outcome of the disease is difficult to predict. Over the past few decades there has been a huge change in preventing and controlling the disease process of RA patients. Many changes and improvements have contributed to providing better healthcare, treating patients earlier in their disease course, the practice of treating patients to a predefined target (T2T), the use of glucocorticoids, and the introduction of bDMARDs.

In this thesis we demonstrated again that a T2T strategy is effective in early RA patients in daily clinical practice. Almost 80% of the patients achieved first remission within one year with a median time to first remission of 17 weeks in the initial DMARD combination strategy group (chapter 3). Achieving remission earlier in the course of the disease might prevent joint damage and increase the chances of sustained remission [2]. In this thesis, the target of remission was defined as DAS28 < 2.6 [3, 4]. However, the definition of remission and the remission cut-off point of the DAS28 are subject to debate. In some contexts remission is used to indicate decreased disease severity, in other contexts it implies that the disease has disappeared or measurable disease activity is absent. Complete absence of all signs and symptoms related to disease activity is not achievable for many patients. For example, some patients may have tender joint counts caused by concomitant osteoarthritis, others may never reach low scores on patient global assessment and in other patients acute phase reactants may remain elevated because of comorbidities [5]. Following the development of the original DAS for 44 joints, a variety of indices to measure disease activity, such as the Disease Activity Score for 28 joints (DAS28) Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI), with different cut-offs for remission have been proposed. However, the outcomes of these different indices are not exactly the same. Previous studies showed that DAS28 classifies more patients in remission [6–9], while SDAI and CDAI are more strict, as is reflected by lower remission percentages [6, 10]. The SDAI and CDAI criteria appear to be the most stringent of those currently validated disease activity scores, allowing for only minimal residual joint counts and thus reflecting a state of no active disease more closely than other scores [6]. These differences also raise questions about the validity of the remission definitions. All definitions perform comparably despite considerable differences in classification. Which index should be preferred will depend on the reason for using the index and might be largely based on personal preferences.

Besides the comments on its remission criteria, the DAS28 may have further limitations. For instance, with exception of the original DAS, its joint count includes only the hands, wrists,

elbows, shoulders and knees and therefore ignores the ankles and feet in its joint evaluation. Moreover, some studies demonstrated that patients scoring remission according to the DAS28, may still have relatively large numbers of ‘residual joint counts’, especially swollen joints [6, 11]. As we already know, radiographic joint damage often starts earlier in the feet than in the hands, suggesting that the joints of the feet may be important to assess in individual patients [5]. One of the main causes of pain in the feet is synovitis of the metatarsophalangeal (MTP) joints and is generally accompanied by joint swelling. Furthermore, erosions in the small joints of the foot occur more quickly and these erosions affects a greater number of joints compared with the erosions in the joints of the hands [12]. The study by van der Leeden et al. (2010) showed that nearly 40% of RA patients with disease in remission, according to the DAS28, had forefoot involvement (pain and/or swelling in at least one MTP joint) [13].

As such, the DAS28 cut-off point of 2.6 for remission may have insufficient construct validity. Moreover, if the joints of the feet are involved in individual patients more often than other joints, or less often, this might lead to under- or over estimation of disease activity when assessing the 28 joints as defined in the DAS28. Therefore, the DAS28 should be used with caution in individual patient care in daily clinical practice. For example, the squeeze test of forefoot might be an alternative simple test to include feet at the assessment of disease activity at an early stage in the disease course [14].

Another important aspect of T2T is the logistics in daily clinical practice. Measuring the number of swollen and tender joints is difficult, poorly reproducible and time consuming in daily clinical practice [15]. The DAS28 is a complex tool because of the difficult mathematical formula used to calculate the sum score and therefore requires some sort of calculating device. Tools such as the DAS28 calculator and online tools such as MijnReumacentrum.nl (MRC) can facilitate this process. In the DREAM remission induction cohorts, the logistics were further simplified in practice because a trained doctors assistant evaluated patients prior to the patient’s visit to the rheumatologist. Trained physician assistants and trained nurses entered the detailed composite measures of the DAS28 (erythrocyte sedimentation rate (ESR), general health (GH), tender joint count (TJC), swollen joint count (SJC) in MRC and thus contributed to a uniform and efficient method of working. Because of these facilities, T2T in daily clinical practice did not require a lot of extra effort and is not time consuming for the nurses or the rheumatologists.

MRC is a web based online monitoring application for gathering patient characteristics, medication, clinical and laboratory measures and patient-reported outcome measures (PROMs). Data in MRC is immediately available for the nurses, rheumatologists and patients themselves

and supports the logistic process of the consultation, contributes to patient participation and shared decision-making, and also contributes to a well-streamed consult.

Start early

Early recognition of the disease and early initiation of treatment is another major paradigm change in the management of RA. This change will improve clinical outcomes and may even prevent or retard radiographic damage over the years [16–18]. However, it is still not exactly clear which treatment strategy is best for patients with early RA. Several different treatment strategies can be applied, but there may still be room for improvement and fine-tuning of the strategies. For instance, which strategy steps are useful? Is T2T with aggressive DMARD combination therapy better? Or step-up DMARD monotherapy? Is a personalized treatment approach better? According to the results of this thesis, initial DMARD combination therapy with an optional intramuscular injection of triamcinolone is recommended over step-up DMARD monotherapy, because treatment goals were attained faster in the combination strategy (Chapter 4) and resulted in less radiographic progression after one year (Chapter 5).

Current antirheumatic medications can be subdivided into conventional synthetic (cs)DMARDs, targeted synthetic (ts)DMARDs, biological (b)DMARDs and glucocorticoids. As has been described in this thesis, there have been major improvements in rheumatological therapy. In addition to starting with a combination of csDMARDs as soon as the diagnosis of RA is made, glucocorticoids have proven to be effective and preferable combined with csDMARDs [19, 20]. As the T2T strategy in clinical trials and daily clinical practice has resulted in large proportions of patients achieving sustained remission, the question is now whether it is possible to taper or discontinue DMARD therapy earlier in these patients. Studies with tapering schemes showed that many of these patients are able to stop their medication after a good response to the therapy [21–23].

Progression

Erosive joint damage is characteristic for RA and affects patients' physical function and quality of life [24]. The extent to which joint damage occurs differs from patient to patient and is relatively difficult to predict. For achieving optimal outcomes, patients who are susceptible for developing severe radiographic damage should be detected at an early stage in the treatment process. In this thesis fewer painful joints and a higher erythrocyte sedimentation rate (ESR) at baseline turned out to be predictive of minimal clinically relevant progression (Chapter 5). The finding that fewer tender joints turns out to be predictive of radiographic progression remains to

be explained. For example, it is possible that these patients have a higher pain threshold and therefore receive less optimal treatment (for example less frequent treatment intensifications and glucocorticosteroids). Or there is a sub-clinical cause. From previous studies, it became clear that sub-clinical inflammation is present in a significant proportion of RA patients in clinical remission, which may lead to radiographic progression [25–28]. These findings indicate that patients in clinical remission may still have a subclinical disease. This highlights the need for identifying new measures to add to the current clinical assessment of the disease.

Irrespective of clinical disease activity parameters, treatment changes should also be considered if patients show radiographic progression, which may lead in the long-term to limitations for the patient. Radiographic joint damage should be assessed according to a structured scoring method, such as the Sharp- van der Heijde method [29].

Initial combination therapy with DMARDs and glucocorticoids was more effective in achieving good clinical outcomes and preventing joint damage than step-up DMARD monotherapy in early RA patients. Additionally, those patients following an initial combination therapy approach had less radiographic progression after one year, despite higher disease activity at baseline (Chapter 5). This is in line with previous published literature, where several RCTs and observational studies in daily practice confirmed these results [16, 30–33].

Presently, the overall radiographic joint damage is much lower than in studies in the past [34, 35]. Even in the long-term, suppression of disease activity results in limited radiographic damage [36]. This change in the occurrence of radiographic joint damage is most likely due to the excellent treatment options available for RA patients, such as more intensive use of conventional synthetic disease modifying antirheumatic drugs (csDMARDs) and the availability of biological DMARDs (bDMARDs). Despite quick and sustained suppression of disease activity, there are still some patients that developed radiographic joint damage (Chapter 5 and 7). Achieving clinical remission is an important goal in RA, but such remission may be unsatisfactory if radiographic joint damage is not halted. Whether the absence of arthritis activity prevents further joint damage is still a matter of debate. Radiographic joint damage might be driven by other factors than disease activity and might be a more individual determined disease process. It is important to detect radiographic progression early in the disease process, because radiographic progression at an early stage predicts radiographic damage in the long-term [37]. Therefore, it is advised to perform X-rays at baseline and in the first 6 months of the disease process to evaluate early radiographic progression and take this into account in the choice for the best suitable treatment strategy for the patient.

Patient perspective and physician preference

Physicians have to make daily decisions concerning the best treatments for patients. From the biomedical perspective, this means selecting the right medicine for a patient's condition, keeping in mind the medicine's safety profile. It is very important to find a balance in the range of treatment options, to determine which is the optimum in the given circumstances and to bring this in line with the perception of health status of the patients themselves. Most outcome measurements focus on clinical and radiographic aspects and do not take the patient's perspective into account. Several studies have shown that physicians and patients focus on different aspects of the disease when evaluating the patient's general health status. Physicians emphasize the objective clinical measures of disease activity (i.e. joint counts and acute phase reactants), while patients emphasize the subjective outcomes measures such as, pain, fatigue, participation and physical functioning [38–40].

Despite the overall good clinical response of patients, about 36 percent of the patients who achieved at least a moderate EULAR response after 12 months perceived their overall health not to have improved at all (chapter 6). Independent determinants of perceived health improvement in relative change from baseline were pain and to a lesser extent fatigue. Pain has been expressed by RA patients as one of the most important impairments to reduce [41]. It is well established that relief from pain and fatigue are important treatment goals for patients with RA [38, 42–44]. A majority of RA patients still experienced pain and fatigue despite reduced disease activity [45]. Patients with higher fatigue levels are more likely to report their health as fair or poor [46]. Pain and fatigue have also been identified as some of the most important domains when developing a core set definition of a flare [47, 48].

Other previous cross-sectional studies have demonstrated that patients are more pessimistic about their health status than physicians or clinical assessments show and that patient-reported outcomes (PROMs) such as fatigue and pain are important determinants of patient global assessment of disease activity [39, 49]. The results of chapter 6 suggest that pain and fatigue are subjective aspects that need attention in treating patients with RA, even, or perhaps especially, when patients are treated according to the current optimal treatment strategies. Outcomes such as fatigue and pain would be worth including in the monitoring of the disease course of RA patients.

Safety

Targeted treatment with a predefined goal with treatment adjustments until that goal is reached, is recommended in RA treatment in daily clinical practice [50, 51]. In the past, RA was treated with nonspecific immunosuppressive therapies. Although patients experienced differential benefits, only few had lasting remission. In recent studies with combination csDMARD therapies and with biological(s) in combination with methotrexate (MTX), disease remission is reached much more frequently. Irrespective of these advantages in available treatment strategies, there may be another significant issue, which is the toxicity of the medication. Many patients on MTX-monotherapy experience adverse events, but these are usually of a mild and tolerable category [52, 53]. Adverse event rates for combination DMARD therapy are similar to those of monotherapy [54]. Hydroxychloroquine (HCQ) prolongs the initial benefit of combination therapy. Furthermore, the concomitant administration of HCQ with MTX has been shown to increase the bioavailability of MTX, thereby potentially increasing both its efficacy and the risk of toxicity [55]. The combination of HCQ and MTX appears to be effective and well-tolerated [56]. In our study, Chapter 5, there were significantly more patients with registered complications with DMARD combination therapy (35%) than with step-up monotherapy (12%; $P < 0.01$).

Future research suggestions

Data in this thesis suggest that treating RA according to an initial DMARD combination strategy is superior to step-up DMARD monotherapy. Remission can be achieved earlier in the disease course. Future results need to show how long patients will be in DAS28 remission and/or drug free remission, if tapering of medication and achieving drug free remission is also possible, how many and which patients will still develop radiographic progression in the long-term, and what will be the best treatment as a follow-up treatment strategy in which patients who do not achieve remission within the first 6 months. After six months, remission was achieved in 63.3% of the patients. To achieve these goals in more patients, or ultimately in all patients, treatment strategies still have to be further optimized.

Although several unresolved questions concerning treatment of RA patients in daily clinical practice were answered in this thesis, some remain unresolved. Future research is necessary to optimize the management of early RA. RA is treatable, and patients live longer which is partly due to better treatment options. But what are the results in the long-term? And what are the consequences of prolonged periods of DMARD use? Is the development of new erosions or new joint space narrowing in previously unaffected joints worse than progression of existing damage (i.e. enlargement of erosions and/or new erosions in a previously damaged

joint)? And what is the impact of lifestyle on RA? These are all interesting and exciting research areas. Now that large proportions of patients achieve the remission criteria, the question is also raised whether it is possible to taper and maybe even discontinue medication earlier in these patients. Data in this thesis show that remission is a feasible goal in RA, as was demonstrated in both T2T strategies. The introduction of early treatment, treating patients to the target and initial combination therapy have markedly improved the short-term outcomes of patients with RA. Given these facts, there are no major differences between both strategies in disease activity after one year. Arguably, we could suggest that it makes no big difference whether patients receive monotherapy or combination therapy. We could instead suggest that it is of major importance to initiate treatment early in the disease course and to follow a T2T strategy regardless of the exact medication protocol used. However, even in T2T strategies not everyone reaches remission and/or is free of medication, and therefore there is still room for improvement. Future results should show how long and in which patients' remission and drug free remission can be sustained.

With initial DMARD combination therapy there is still a number of patients with radiographic progression, which can hallmark irreversible functional disabilities, although the extent of the damage was lower than in patients who were treated according to a step-up DMARD monotherapy. In clinical practice, non-adherence, either intentional or non-intentional, might explain persistent disease activity as well as radiographic joint damage. Future research should focus on patients who show significant radiographic progression in their first year of treatment, instead of focusing on remission and/or low disease activity only. One of the factors associated with developing relevant radiographic progression was higher erythrocyte sedimentation rate (ESR), suggesting that these patients might benefit from even stronger suppression of inflammatory disease activity, i.e. a more stringent treatment. More research is needed to support the hypotheses that a more stringent treatment will be beneficial for patients with higher ESR. As mentioned before, there are at this moment a variety of definitions of the concept of remission that still allow residual disease activity which could potentially lead to progressive joint damage. Using a concept of radiographic remission parallel to the concept of remission of inflammatory disease activity (i.e. DAS28 < 2.6) could be an option [57–60] .

One of the principles of T2T is shared decision-making, involving patients in determining the treatment goals and in therapeutic decisions during their treatment process. Involving patients in their treatment process will optimize treatment results. In addition to minimizing disease activity, improving pain, fatigue, physical function, social functioning and labor participation are also paramount [61].

In RA, patients are effectively treated according to the principle of T2T. In the current guidelines for the management of RA, the treatment target is regarded to be the same for all patients: ‘one size fits all’. Despite very promising results, T2T strategies do not have the same impact on all patients [13]. A relevant proportion of patients still did not reach clinical remission within 12 months of treatment (Chapters 3 and 4) [14, 15]. On the other side, there is also a group of patients which may be over-treated. If not all patients can be treated successfully according to the same treatment protocol, we might need to personalize treatment and identify individual patient characteristics indicating specific personalized treatment approaches.

In the initial T2T recommendations, the task force already identified the importance of patient involvement in the treatment process, and published a patient version of these recommendations [16]. Patient involvement is a very important aspect for a number of reasons. Firstly, it can help patients to prepare their visit to the rheumatologist and help improve communication between patient and physician [17]. Secondly, it can also ensure that the target for treatment is appropriate for the patient. Open communication and increased patient involvement have been shown to increase treatment adherence and patient satisfaction [18]. Despite the recommendations to improve patient involvement, the success of the T2T strategy in clinical trials has primarily been assessed using clinical disease activity outcomes, such as remission, and not patient-centered outcomes. In many ways, this way of evaluation runs counter to both the T2T recommendations and the recent literature highlighting the importance of patient-centered care and the integration of patient priorities into treatment decision-making [62]. Thus, each patient is different and therefore, even within the same disease, patients can respond differently to the same treatment. The mapping of the human genome may also identify specific patient characteristics that can facilitate customized therapy. Future research will determine the feasibility of such an approach.

So far, one of the major challenges in RA research will be the search for effective strategies that can alter the disease course of RA patients toward a higher percentage of patients in sustained (drug-free) remission with prevention of radiographic joint damage. Secondly, major focus will be the shift towards a more personalized medicine approach based on knowledge of determinants of treating individual patients and treatment efficacy and safety.

In conclusion, the current T2T strategy with initial DMARD combination treatment has contributed to very high remission rates and a virtual stop of radiographic progression in most patients after one year. However, treatment strategies may still need to be further optimized and especially be personalized for each individual patient.

OVERALL CONCLUSIONS

Initial DMARD combination therapy is effective, safe and easy to implement in daily clinical practice by patients as well as for rheumatologists and nurses. Moreover, implementing DMARD combination therapy as a first choice approach for patients with newly diagnosed RA patients is sensible, not only from a medical perspective, but also from an economic perspective. Initial combination therapy is a highly cost-effective treatment approach. Patients will have many benefits from implementation of initial DMARD combination therapy, because this approach gives patients a better prognosis (fast remission, higher remission rates, and less radiographic damage) than patients who were treated according to a step-up DMARD monotherapy approach. Therefore, we recommend this treatment to all rheumatologists and to prescribe initial DMARD combination therapy to newly diagnosed RA patients. In case of treatment failure, patients can rapidly switch after 24 weeks to a biological in combination with a csDMARD. The combination treatment approach was confirmed a fast, effective as well as cost-effective treatment for patients with early RA to increase the chances of retrieving their quality of life and retarding or preventing long-term progression of damage to their joints. Previously, the implementation of 'T2T' has shown successful results. This thesis showed that the implementation of 'T2T' with initial DMARD combination therapy is even more successful and should now be the standard of care in all hospitals for all RA patients.

HIGHLIGHTS OF THE IMPORTANT FINDINGS

- Initial DMARD combination therapy is recommended over step-up DMARD monotherapy. Almost 80% of recently diagnosed RA patients, following a DMARD combination therapy, achieved rapid remission during the first year of their disease;
- Initial DMARD combination therapy leads to a significantly shorter time to achieve first remission;
- No accurate predictors of achieving remission could be identified, therefore this strategy appears to be generally applicable to RA patients;
- The majority of the patients achieved the treatment target of DAS28 remission using csDMARDS only;
- Median radiographic progression was significantly higher with step-up DMARD monotherapy;
- No radiographic progression at all occurred more frequent with initial DMARD combination therapy;
- Experiencing a minimal clinically important difference (MCID) in radiographic progression was independently associated with fewer tender joints and higher erythrocyte sedimentation rate at baseline;
- More than one-third of the patients who achieved at least a moderate EULAR response after 12 months, did not perceive their overall health to have improved at all;
- Perceived non-improvement was associated with less improvement from baseline in pain and fatigue
- Time-integrated disease activity and radiographic progression were only weakly associated at group level, but within individual patients a fairly linear relationship between disease activity exists over time.

REFERENCES

1. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, Kvien TK, Navarro-Compán MV, Oliver S, Schoels M, Scholte-Voshaar M, Stamm T, Stoffer M, Takeuchi T, Aletaha D, Andreu JL, Aringer M, Bergman M, Betteridge N, Bijlsma H, Burkhardt H, Cardiel M, Combe B, Durez P, Fonseca JE, Gibofsky A, Gomez-Reino JJ, Graninger W, Hannonen P, Haraoui B, et al.: Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016, 75:3–15.
2. Schipper LG, Fransen J, den Broeder AA, Van Riel PLCM: Time to achieve remission determines time to be in remission. *Arthritis Res Ther* 2010, 12:R97.
3. Prevoo ML, van Gestel AM, van T Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL: Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. *Br J Rheumatol* 1996, 35:1101–5.
4. Fransen J, Creemers MCW, Van Riel PLCM: Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. *Rheumatology (Oxford)* 2004, 43:1252–1255.
5. Aletaha D, Ward MM, Machold KP, Nell VPK, Stamm T, Smolen JS: Remission and active disease in rheumatoid arthritis: Defining criteria for disease activity states. *Arthritis Rheum* 2005, 52:2625–2636.
6. Mierau M, Schoels M, Gonda G, Fuchs J, Aletaha D, Smolen JS: Assessing remission in clinical practice. *Rheumatology (Oxford)* 2007, 46:975–9.
7. Mäkinen H, Kautiainen H, Hannonen P, Sokka T: Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? *Ann Rheum Dis* 2005, 64:1410–3.
8. Landewé R, van der Heijde D, van der Linden S, Boers M: Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. *Ann Rheum Dis* 2006, 65:637–41.
9. Balsa A, de Miguel E, Castillo C, Peiteado D, Martín-Mola E: Superiority of SDAI over DAS-28 in assessment of remission in rheumatoid arthritis patients using power Doppler ultrasonography as a gold standard. *Rheumatology (Oxford)* 2010, 49:683–90.
10. Rintelen B, Sautner J, Haindl P, Andel I, Maktari A, Leeb B: Comparison of three rheumatoid arthritis disease activity scores in clinical routine. *Scand J Rheumatol* 2009, 38:336–341.
11. Mäkinen H, Kautiainen H, Hannonen P, Sokka T: Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? *Ann Rheum Dis* 2005, 64:1410–3.
12. Hulsmans HM, Jacobs JW, van der Heijde DM, van Albada-Kuipers GA, Schenk Y, Bijlsma JW: The course of radiologic damage during the first six years of rheumatoid arthritis. *Arthritis Rheum* 2000, 43:1927–40.
13. van der Leeden M, Steultjens MP, van Schaardenburg D, Dekker J: Forefoot disease activity in rheumatoid arthritis patients in remission: results of a cohort study. *Arthritis Res Ther* 2010, 12:R3.
14. de Jong PH, Weel AE, de Man YA, Huisman AM, Gerards AH, van Krugten M V., Luime JJ, Hazes JM: Brief Report: To squeeze or not to squeeze, that is the question! Optimizing the Disease Activity Score in 28 joints by adding the squeeze test of metatarsophalangeal joints in early rheumatoid arthritis. *Arthritis Rheum* 2012, 64:3095–3101.
15. Pincus T: Limitations of a quantitative swollen and tender joint count to assess and monitor patients with rheumatoid arthritis. *Bull NYU Hosp Jt Dis* 2008, 66:216–23.

16. Möttönen T, Hannonen P, Leirisalo-Repo M, Nissilä M, Kautiainen H, Korpela M, Laasonen L, Julkunen H, Luukkainen R, Vuori K, Paimela L, Bläfield H, Hakala M, Ilva K, Yli-Kerttula U, Puolakka K, Järvinen P, Hakola M, Piirainen H, Ahonen J, Pälvimäki I, Forsberg S, Koota K, Friman C: Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* 1999, 353:1568–73.
17. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, Hazes JM: Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med* 2001, 111:446–51.
18. Möttönen T, Hannonen P, Korpela M, Nissilä M, Kautiainen H, Ilonen J, Laasonen L, Kaipainen-Seppänen O, Franzen P, Helve T, Koski J, Gripenberg-Gahmberg M, Myllykangas-Luosujärvi R, Leirisalo-Repo M: Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. *Arthritis Rheum* 2002, 46:894–8.
19. Donahue KE, Gartlehner G, Jonas DE, Lux LJ, Thieda P, Jonas BL, Hansen RA, Morgan LC, Lohr KN: Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. *Ann Intern Med* 2008, 148:124–34.
20. Verschueren P, De Cock D, Corluy L, Joos R, Langenaken C, Taelman V, Raeman F, Ravelingien I, Vandevyvere K, Lenaerts J, Geens E, Geusens P, Vanhoof J, Durnez A, Remans J, Vander Cruyssen B, Van Essche E, Sileghem A, De Brabanter G, Joly J, Meyfroidt S, Van der Elst K, Westhovens R: Effectiveness of methotrexate with step-down glucocorticoid remission induction (COBRA Slim) versus other intensive treatment strategies for early rheumatoid arthritis in a treat-to-target approach: 1-year results of CareRA, a randomised pragmatic open-label superiority trial. *Ann Rheum Dis* 2017, 76:511–520.
21. Klarenbeek NB, van der Kooij SM, Güler-Yüksel M, van Groenendael JHLM, Han KH, Kerstens PJSM, Huizinga TWJ, Dijkmans BAC, Allaart CF: Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission: exploratory analyses from the BeSt study. *Ann Rheum Dis* 2011, 70:315–9.
22. Wevers-de Boer KVC, Heimans L, Visser K, Schouffoer AA, Molenaar ETH, van Groenendael JHLM, Peeters AJ, Speyer I, Collée G, Huizinga TWJ, Allaart CF: Determinants of reaching drug-free remission in patients with early rheumatoid or undifferentiated arthritis after one year of remission-steered treatment. *Rheumatology (Oxford)* 2015, 54:1380–4.
23. van der Kooij SM, Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Güler-Yüksel M, Zwinderman AH, Kerstens PJSM, van der Lubbe PAHM, de Beus WM, Grillet BAM, Roday HK, Huizinga TWJ, Breedveld FC, Dijkmans BAC, Allaart CF: Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. *Ann Rheum Dis* 2009, 68:914–21.
24. Guillemin F: Functional disability and quality-of-life assessment in clinical practice. *Rheumatology (Oxford)* 2000, 39 Suppl 1:17–23.
25. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, Hensor E, Wakefield RJ, O'Connor PJ, Emery P: An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. *Arthritis Rheum* 2008, 58:2958–67.
26. Brown AK, Quinn MA, Karim Z, Conaghan PG, Peterfy CG, Hensor E, Wakefield RJ, O'Connor PJ, Emery P: Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. *Arthritis Rheum* 2006, 54:3761–73.

27. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Karim Z, Quinn M, Wakefield R, Hensor E, Conaghan PG, Emery P: Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: A clinical and imaging comparative study. *Arthritis Rheum* 2009, 60:1915–22.
28. Foltz V, Gandjbakhch F, Etchepare F, Rosenberg C, Tanguy ML, Rozenberg S, Bourgeois P, Fautrel B: Power Doppler ultrasound, but not low-field magnetic resonance imaging, predicts relapse and radiographic disease progression in rheumatoid arthritis patients with low levels of disease activity. *Arthritis Rheum* 2012, 64:67–76.
29. van der Heijde D: How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 2000, 27:261–3.
30. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, van Zeben D, Dijkmans BA, Peeters AJ, Jacobs P, van den Brink HR, Schouten HJ, van der Heijde DM, Boonen A, van der Linden S: Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997, 350:309–18.
31. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJSM, Hazes JMW, Zwinderman AH, Peeters AJ, de Jonge-Bok JM, Mallée C, de Beus WM, de Sonnaville PBJ, Ewals JAPM, Breedveld FC, Dijkmans BAC: Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007, 146:406–15.
32. Calgüneri M, Pay S, Calışkaner Z, Apraş S, Kiraz S, Ertenli I, Cobankara V: Combination therapy versus monotherapy for the treatment of patients with rheumatoid arthritis. *Clin Exp Rheumatol*, 17:699–704.
33. Verschueren P, Esselens G, Westhovens R: Daily practice effectiveness of a step-down treatment in comparison with a tight step-up for early rheumatoid arthritis. *Rheumatology (Oxford)* 2008, 47:59–64.
34. Wolfe F, Sharp JT: Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. *Arthritis Rheum* 1998, 41:1571–82.
35. Carpenter L, Norton S, Nikiphorou E, Jayakumar K, McWilliams DF, Rennie KL, Dixey J, Kiely P, Walsh DA, Young A, Early Rheumatoid Arthritis Study and the Early Rheumatoid Arthritis Network: Reductions in Radiographic Progression in Early Rheumatoid Arthritis Over Twenty-Five Years: Changing Contribution From Rheumatoid Factor in Two Multicenter UK Inception Cohorts. *Arthritis Care Res (Hoboken)* 2017, 69:1809–1817.
36. Vermeer M, Kuper HH, Moens HJB, Drossaers-Bakker KW, van der Bijl AE, van Riel PLCM, van de Laar MAFJ: Sustained beneficial effects of a protocolized treat-to-target strategy in very early rheumatoid arthritis: three-year results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort. *Arthritis Care Res (Hoboken)* 2013, 65:1219–26.
37. Versteeg L, Steunebrink L, Kuper I, Vonkeman H, ten Klooster P, van der Bijl A, van de Laar M: Early Radiological Progression in Rheumatoid Arthritis Leads to More Long-Term Joint Damage in Daily Clinical Practice; Six Year Radiological Outcomes of a Strict Treat-to-Target Cohort in the Netherlands [abstract]. *Arthritis Rheumatol* 2016, 68((suppl 10)).
38. Studenic P, Radner H, Smolen JS, Aletaha D: Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. *Arthritis Rheum* 2012, 64:2814–2823.
39. Khan NA, Spencer HJ, Abda E, Aggarwal A, Alten R, Ancuta C, Andersone D, Bergman M, Craig-Muller J, Detert J, Georgescu L, Gossec L, Hamoud H, Jacobs JWG, Laurindo IMM, Majdan M, Naranjo A, Pandya S, Pohl C, Schett G, Selim ZI, Toloza S, Yamanaka H, Sokka T: Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. *Arthritis Care Res (Hoboken)* 2012, 64:206–14.

40. Markenson JA, Koenig AS, Feng JY, Chaudhari S, Zack DJ, Collier D, Weaver A: Comparison of physician and patient global assessments over time in patients with rheumatoid arthritis: a retrospective analysis from the RADIUS cohort. *J Clin Rheumatol* 2013, 19:317–23.
41. Heiberg T, Kvien TK: Preferences for improved health examined in 1,024 patients with rheumatoid arthritis: pain has highest priority. *Arthritis Rheum* 2002, 47:391–7.
42. ten Klooster PM, Veehof MM, Taal E, van Riel PLCM, van de Laar MAFJ: Changes in priorities for improvement in patients with rheumatoid arthritis during 1 year of anti-tumour necrosis factor treatment. *Ann Rheum Dis* 2007, 66:1485–90.
43. Heiberg T, Finset A, Uhlig T, Kvien TK: Seven year changes in health status and priorities for improvement of health in patients with rheumatoid arthritis. *Ann Rheum Dis* 2005, 64:191–5.
44. Sanderson T, Morris M, Calnan M, Richards P, Hewlett S: Patient perspective of measuring treatment efficacy: the rheumatoid arthritis patient priorities for pharmacologic interventions outcomes. *Arthritis Care Res (Hoboken)* 2010, 62:647–56.
45. Ishida M, Kuroiwa Y, Yoshida E, Sato M, Krupa D, Henry N, Ikeda K, Kaneko Y: Residual symptoms and disease burden among patients with rheumatoid arthritis in remission or low disease activity: a systematic literature review. *Mod Rheumatol* 2018:1–11.
46. Wolfe F, Hawley DJ, Wilson K: The prevalence and meaning of fatigue in rheumatic disease. *J Rheumatol* 1996, 23:1407–17.
47. Bingham CO, Alten R, Bartlett SJ, Bykerk VP, Brooks PM, Choy E, Christensen R, Furst DE, Hewlett SE, Leong A, May JE, Montie P, Pohl C, Sanderson TC, Strand V, Woodworth TG, OMERACT RA Flare Definition Working Group: Identifying preliminary domains to detect and measure rheumatoid arthritis flares: report of the OMERACT 10 RA Flare Workshop. *J Rheumatol* 2011, 38:1751–8.
48. Berthelot J-M, De Bandt M, Morel J, Benatig F, Constantin A, Gaudin P, Le Loet X, Maillefert J-F, Meyer O, Pham T, Saraux A, Solau-Gervais E, Spitz E, Wendling D, Fautrel B, Guillemin F: A tool to identify recent or present rheumatoid arthritis flare from both patient and physician perspectives: the “FLARE” instrument. *Ann Rheum Dis* 2012, 71:1110–6.
49. Barton JL, Imboden J, Graf J, Glidden D, Yelin EH, Schillinger D: Patient-physician discordance in assessments of global disease severity in rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2010, 62:857–64.
50. Schipper LG, Vermeer M, Kuper HH, Hoekstra MO, Haagsma CJ, Den Broeder AA, van Riel P, Fransen J, van de Laar MAFJ: A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. *Ann Rheum Dis* 2012, 71:845–50.
51. Vermeer M, Kuper HH, Hoekstra M, Haagsma CJ, Posthumus MD, Brus HLM, van Riel PLCM, van de Laar MAFJ: Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. *Arthritis Rheum* 2011, 63:2865–72.
52. Salliot C, van der Heijde D: Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. *Ann Rheum Dis* 2009, 68:1100–4.
53. Kremer JM, Lee JK: The safety and efficacy of the use of methotrexate in long-term therapy for rheumatoid arthritis. *Arthritis Rheum* 1986, 29:822–31.
54. Dale J, Alcorn N, Capell H, Madhok R: Combination therapy for rheumatoid arthritis: methotrexate and sulfasalazine together or with other DMARDs. *Nat Clin Pract Rheumatol* 2007, 3:450–458.

55. Carmichael SJ, Beal J, Day RO, Tett SE: Combination therapy with methotrexate and hydroxychloroquine for rheumatoid arthritis increases exposure to methotrexate. *J Rheumatol* 2002, 29:2077–83.
56. Clegg DO, Dietz F, Duffy J, Willkens RF, Hurd E, Germain BF, Wall B, Wallace DJ, Bell CL, Sleckman J: Safety and efficacy of hydroxychloroquine as maintenance therapy for rheumatoid arthritis after combination therapy with methotrexate and hydroxychloroquine. *J Rheumatol* 1997, 24:1896–902.
57. Gandjbakhch F, Haavardsholm EA, Conaghan PG, Ejbjerg B, Foltz V, Brown AK, Dohn UM, Lassere M, Freeston JE, Olsen IC, Boyesen P, Bird P, Fautrel B, Hetland ML, Emery P, Bourgeois P, Horslev-Petersen K, Kvien TK, McQueen FM, Ostergaard M: Determining a Magnetic Resonance Imaging Inflammatory Activity Acceptable State Without Subsequent Radiographic Progression in Rheumatoid Arthritis: Results from a Followup MRI Study of 254 Patients in Clinical Remission or Low Disease Activity. *J Rheumatol* 2014, 41:398–406.
58. Boutry N, Lardé A, Lapègue F, Solau-Gervais E, Flipo R-M, Cotten A: Magnetic resonance imaging appearance of the hands and feet in patients with early rheumatoid arthritis. *J Rheumatol* 2003, 30:671–9.
59. Peterfy CG: Magnetic resonance imaging in rheumatoid arthritis: current status and future directions. *J Rheumatol* 2001, 28:1134–42.
60. Anandarajah A, Thiele R, Giampoli E, Monu J, Seo G-S, Feng C, Ritchlin CT: Patients with rheumatoid arthritis in clinical remission manifest persistent joint inflammation on histology and imaging studies. *J Rheumatol* 2014, 41:2153–60.
61. Taylor PC, Moore A, Vasilescu R, Alvir J, Tarallo M: A structured literature review of the burden of illness and unmet needs in patients with rheumatoid arthritis: a current perspective. *Rheumatol Int* 2016, 36:685–95.
62. El Miedany Y: Adopting patient-centered care in standard practice: PROMs moving toward disease-specific era. *Clin Exp Rheumatol* , 32(5 Suppl 85):S-40-6.

Samenvatting en algemene discussie

Reumatoïde artritis (RA) is een ontstekingsziekte van het bindweefsel in het lichaam, met name de synoviale gewrichten. Aanhoudende ontsteking kan leiden tot beschadiging van de gewrichtscapsule en het gewrichtskraakbeen. Verschillende interventiestudies en onderzoeken in de dagelijkse klinische praktijk hebben aangetoond dat vroege, agressieve onderdrukking van ontstekingen tot aanhoudende remissie of op z'n minst een lage ziekteactiviteit kan leiden en gewrichtsschade en bijbehorende invaliditeit kan minimaliseren of zelfs voorkomen. De huidige behandelrichtlijnen pleiten voor treat-to-target (T2T) als de optimale behandelstrategie [1]. Binnen dit behandelingsparadigma worden opeenvolgende medicatieaanpassingen gemaakt totdat een vooraf bepaald doel van de mate van ziekteactiviteit (meestal remissie of lage ziekteactiviteit) wordt bereikt. De literatuur suggereert dat een T2T behandelstrategie leidt tot betere klinische uitkomsten dan alternatieve behandelstrategieën, maar het is nog steeds onduidelijk welke medicatiestrategie binnen T2T de beste resultaten oplevert. Het hoofddoel van dit proefschrift is om de effecten van twee T2T strategieën gericht op remissie in vroege RA, een *step-up* DMARD-monotherapie versus een initiële DMARD-combinatietherapie te vergelijken en te onderzoeken. De DREAM samenwerking startte deze twee T2T remissie inductie cohorten over de tijd op, beide met een verschillend medicatieprotocol, waarvan de resultaten in dit proefschrift worden gepresenteerd.

SAMENVATTING EN BEVINDINGEN

Hoofdstuk 3

Dit hoofdstuk presenteert de remissiepercentages en voorspellers van remissie in het meest recente *real-life* T2T cohort (initiële DMARD-combinatie therapie) van opeenvolgende patiënten met een recente klinische diagnose van RA. In bijna 80% van de recent gediagnosticeerde RA-patiënten werd remissie snel bereikt tijdens het eerste jaar van hun ziekte. Onder een breed scala van mogelijke prognostische factoren voor het bereiken van remissie, konden geen nauwkeurige voorspellers worden geïdentificeerd. Deze bevinding levert aanvullend bewijs dat een T2T-strategie gericht op remissie universeel gunstig lijkt voor recent gediagnosticeerde RA-patiënten in de klinische praktijk en daarom op grote schaal kan worden geïmplementeerd. De overgrote meerderheid van de patiënten in de huidige studie bereikte het behandeldoel alleen met conventionele synthetische *disease modifying antirheumatic drugs* (ziekteverloop beïnvloedende geneesmiddelen tegen reuma) (csDMARDs) en slechts 10% van de patiënten had binnen de eerste 12 maanden van de behandeling een biologische DMARD (bDMARD) nodig. Deze studie bevestigt dat remissie een realistisch doel is in de dagelijkse klinische praktijk. Bovendien lijkt de huidige T2T strategie breed toepasbaar te zijn voor patiënten met recent gediagnosticeerde RA.

Samen met de afwezigheid van duidelijke *baseline* voorspellers, suggereert dit dat artsen die zich richten op remissie in de dagelijkse klinische praktijk zich alleen op de uitkomsten, zoals ziekteactiviteit, kunnen richten, zonder rekening te hoeven houden met andere patiëntkarakteristieken.

Hoofdstuk 4

Dit hoofdstuk vergelijkt de effectiviteit van twee T2T strategieën bij vroege RA patiënten. Voor dit doel werd een *step-up* DMARD monotherapie, beginnend met methotrexaat (MTX) monotherapie (strategie I) vergeleken met de initiële DMARD combinatiestrategie (strategie II). De resultaten van deze studie suggereren dat de eerder gerapporteerde resultaten, die werden bereikt door implementatie van T2T met initiële MTX monotherapie in de dagelijkse klinische praktijk, kunnen worden gereproduceerd en zelfs verbeterd kunnen worden met behulp van initiële DMARD combinatietherapie. Initiële DMARD combinatietherapie resulteerde in vergelijkbare remissiepercentages na 1 jaar, maar een significant kortere mediane tijd tot remissie. Op 6 maanden waren de gemiddelde ziekteactiviteit scores lager in patiënten met initiële DMARD combinatietherapie, dan bij de patiënten die behandeld werden met *step-up* DMARD monotherapie. Op 12 maanden bleken er geen significante verschillen in gemiddelde ziekteactiviteit scores of het aantal patiënten in remissie. Concluderend leidt T2T met initiële combinatietherapie tot een significant kortere tijd tot het bereiken van een eerste remissie.

Hoofdstuk 5

Dit hoofdstuk vergelijkt de radiografische uitkomsten van de *step-up* DMARD monotherapie (strategie I) versus de initiële DMARD combinatietherapie (strategie II). Deze studie toonde aan dat patiënten met een initiële DMARD monotherapie na 1 jaar significant meer en vaker klinische relevante radiografische progressie vertoonden. Een aanzienlijk groter aantal patiënten binnen strategie II vertoonde helemaal geen radiografische progressie en slechts een klein deel van de patiënten vertoonde klinische relevante progressie. Minder gevoelige gewrichten en hogere bezinking op *baseline* waren significant geassocieerd met het bereiken van klinische relevante progressie in de totale patiëntengroep.

Hoofdstuk 6

Dit hoofdstuk onderzoekt de associatie tussen het bereiken van gunstige klinische uitkomsten en de waargenomen verandering van patiënten zelf in de algehele gezondheidstoestand na 12 maanden behandeling met T2T bij patiënten met vroege RA en heeft als doel om determinanten

van subjectieve verbetering te identificeren. De resultaten toonden aan dat meer dan een derde van de patiënten (35%) niet van mening was dat hun algehele gezondheid was verbeterd ondanks dat ze gunstige klinische resultaten hadden bereikt. Relatieve veranderingen ten opzichte van *baseline* pijn en *baseline* vermoeidheid waren onafhankelijk geassocieerd met een onverbeterde algehele gezondheidsstatus. Deze studie toont aan dat klinische verbetering niet per definitie gelijk staat aan een verbeterde subjectieve gezondheid voor alle patiënten. Verbetering in klinische signalen en symptomen alleen is niet genoeg om gunstige gezondheid uitkomsten te bereiken voor alle vroege RA patiënten. De voorspellende waarde van verandering in pijn en vermoeidheid suggereert daarom dat het de moeite waard kan zijn om pijn en vermoeidheid te monitoren en te meten naast het reguliere meten van ziekteactiviteit in vroege RA.

Hoofdstuk 7

Dit hoofdstuk onderzoekt de longitudinale relatie tussen ziekteactiviteit en radiografische progressie bij patiënten met RA met een intensieve T2T strategie in de dagelijkse klinische praktijk. Op groepsniveau werd er geen significante correlatie waargenomen tussen tijdgeïntegreerde ziekteactiviteit en radiografische progressie na 6 maanden en 2 jaar follow-up. Op 1-jaar en 3-jaar follow-up was er slechts een zeer zwakke positieve correlatie. Een brede interindividuele variatie tussen ziekteactiviteit en radiografische progressie was ook duidelijk te zien in de individuele trajecten van patiënten. De hellingen van de individuele lijnen bevestigen daarentegen in elk tijdsinterval een redelijk proportioneel verband tussen ziekteactiviteit en radiografische progressie. Vooral de hellingen in de eerste 6 maanden waren matig tot sterk geassocieerd met de hellingen op de latere tijdstippen. Zo'n 12 – 30% van de patiënten die over de tijd in remissie waren, liepen toch relevante radiografische schade op ($\text{SHS} \geq 3$). Deze bevindingen suggereren dat, in het tijdperk van T2T behandeling, radiografische schade niet langer wordt veroorzaakt door alleen (consistente) hoge ziekteactiviteit, maar in plaats daarvan vooral een individueel bepaald ziekteproces is.

ALGEMENE DISCUSSIE

Treat to target

Reumatoïde artritis is een heterogene ziekte waarbij de uitkomsten van de ziekte moeilijk te voorspellen zijn. In de afgelopen decennia is er een enorme verbetering opgetreden in het voorkomen en beheersen van het ziekteproces van RA patiënten. Veranderingen die met name hebben bijgedragen aan de betere behandeling van RA zijn het eerder behandelen van patiënten in het ziekteproces, patiënten behandelen volgens een vooraf bepaald doel (T2T), het gebruik van glucocorticosteroiden en de introductie van biologische DMARDs.

In dit proefschrift hebben we opnieuw aangetoond dat het behandelen volgens een T2T strategie effectief is bij vroege RA-patiënten in de dagelijkse klinische praktijk. Bijna 80% van de patiënten bereikte de eerste remissie binnen 1 jaar met een mediane tijd tot de eerste remissie van 17 weken in de initiële DMARD combinatiestrategie (hoofdstuk 3). Het bereiken van remissie vroeg in het ziekteproces kan gewrichtsschade voorkomen en de kans op langdurige remissie vergroten [2]. In dit proefschrift werd het doel van remissie telkens gedefinieerd als DAS28 < 2.6 [3, 4]. Echter, de definitie van remissie en het afkappunt van remissie is een onderwerp van voortdurende discussie. In sommige contexten wordt remissie gebruikt om de ernst van de ziekte aan te geven, in andere contexten betekent het dat de ziekte verdwenen is of dat meetbare ziekteactiviteit ontbreekt. Echter, een eenvoudige definitie zoals de volledige afwezigheid van alle signalen en symptomen die verband houden met ziekteactiviteit, is niet haalbaar voor veel RA patiënten. Sommige patiënten kunnen bijvoorbeeld gevoelige gewrichten hebben wat veroorzaakt wordt door gelijktijdige osteoartritis, andere patiënten bereiken misschien nooit lage scores op de *patient global* en bij andere patiënten kunnen biologische markers voor ziekteactiviteit (acute fase reactanten) verhoogd blijven vanwege co-morbiditeiten [5]. Na de ontwikkeling van de originele DAS voor 44 gewrichten zijn er verschillende samengestelde maten om ziekteactiviteit te meten ontwikkeld, zoals de *Disease Activity Score* voor 28 gewrichten (DAS28) *Clinical Disease Activity Index* (CDAI) en de *Simplified Disease Activity Index* (SDAI), met daarbij verschillende voorgestelde afkappunten voor remissie. Deze verschillende maten resulteren echter in verschillende uitkomsten met betrekking tot de classificatie van remissie. Eerdere studies toonden bijvoorbeeld aan dat de DAS28 meer patiënten in remissie classificeert [6–9], terwijl de SDAI en de CDAI veel strenger zijn, wat wordt weerspiegeld in lagere remissiepercentages [6, 10]. De SDAI en de CDAI criteria lijken de meest stringente uitkomstmaten te zijn van de huidige gevalideerde ziekteactiviteit scores, waardoor slechts minimale overgebleven gewrichtstellingen worden gemeten en wat dus resulteert in een zeer nauwkeurige status van geen ziekteactiviteit ten

opzichte van andere scores [6]. Deze verschillen roepen ook vragen op over de validiteit van de definitie van remissie. Alle definities presteren vergelijkbaar ondanks aanzienlijke verschillen in classificatie. Welke index de voorkeur heeft, lijkt vooral af te hangen van de reden van gebruik en is mogelijk grotendeels gebaseerd op persoonlijke voorkeuren.

Naast de opmerkingen over de remissiecriteria, heeft het meten van ziekteactiviteit met de huidige samengestelde scores nog verdere beperkingen. Dit type van beoordeling omvat, met uitzondering van de originele DAS, alleen de handen, polsen, ellebogen, schouders en knieën en negeert de enkels en voeten in de gewrichts-evaluatie. Bovendien hebben sommige onderzoeken aangetoond dat patiënten in remissie, volgens de DAS28, relatief nog steeds veel aangedane gewrichten hebben, en dan met name gezwollen gewrichten [6, 11]. Zoals we al weten, begint radiografische gewrichtsschade vaak eerder in de voeten dan in de handen, wat suggereert dat de gewrichten in de voeten belangrijk kunnen zijn om te beoordelen bij individuele patiënten [5]. Eén van de hoofdoorzaken van pijn in de voeten is synovitis van de metatarsofalangeale (MTP) gewrichten en gaat meestal gepaard met gewrichtszwelling. Verder treden erosies in de kleine gewrichten van de voeten sneller op en hebben deze erosies invloed op een groter aantal gewrichten vergeleken met de erosies in de gewrichten van de handen [12]. De studie van van der Leeden et al. toonde bijvoorbeeld aan dat bijna 40% van de RA patiënten met een ziekte in remissie volgens de DAS28 score, voorvoetbetrokkenheid had (pijn en/of zwelling in ten minste één MTP-gewricht) [13].

Het afkappunt voor de DAS28 van 2.6 voor remissie heeft dus mogelijk onvoldoende constructvaliditeit. Bovendien, als de gewrichten in de voeten bij individuele patiënten vaker betrokken zijn dan andere gewrichten, of minder vaak, dan kan dit leiden tot onder- of overschatting van ziekteactiviteit bij het beoordelen van 28 gewrichten zoals gedefinieerd in de DAS28. Het is van belang dat de DAS28 met enige voorzichtigheid wordt gebruikt bij de individuele patiëntenzorg in de dagelijkse klinische praktijk. Een alternatieve eenvoudige test die zou kunnen worden gebruikt als aanvulling op de beoordeling van ziekteactiviteit in een vroeg stadium van het ziekteverloop is de *squeeze test* van de voorvoet [14].

Een ander aspect van T2T is de logistiek in de dagelijkse klinische praktijk. Het meten van het aantal gezwollen en gevoelige gewrichten is moeilijk, slecht reproduceerbaar en tijdrovend in de dagelijkse klinische praktijk [15]. De DAS28 is een complex instrument vanwege de moeilijke wiskundige formules die wordt gebruikt om de somscore te berekenen en vereist vaak een soort calculator. Hulpmiddelen zoals de DAS28 calculator en de website MijnReumacentrum.nl (MRC) kunnen dit proces vergemakkelijken. In de DREAM remissie inductie cohorten werd de logistiek in de praktijk verder vereenvoudigd doordat een getrainde

doktersassistente, voorafgaand aan het consult van de patiënt aan de reumatoloog, de patiënten evalueert. Arts-assistenten in opleiding en getrainde verpleegkundigen vullen de gedetailleerde samengestelde metingen van de DAS28 (bezinking, algemene gezondheid, het aantal gevoelige gewrichten, het aantal gezwollen gewrichten) in MRC in en dragen zo bij aan een uniforme en efficiënte manier van werken. Vanwege deze faciliteiten is het toepassen van T2T in de dagelijkse klinische praktijk niet extra inspannend en tijdrovend voor verpleegkundigen en reumatologen.

MRC is een online monitoring applicatie voor het verzamelen van patiënten kenmerken, medicatiegegevens, klinische- en laboratoriummetingen en patiënt-gerapporteerde uitkomstmaten (PROMs). Gegevens in MRC zijn direct beschikbaar voor verpleegkundigen, reumatologen en voor de patiënten en ondersteunen de logistieke processen van de consulten en dit draagt bij aan patiënten-participatie en gedeelde besluitvorming (*shared decision making*), alsook aan een goed gestroomlijnd consult.

Vroeg starten

Vroege herkenning van de ziekte en de vroege start van de behandeling is een andere belangrijke paradigmaverschuiving in de management van RA. Deze verandering zal de klinische uitkomsten verbeteren en kan zelfs radiografische schade door de jaren heen voorkomen of vertragen [16–18]. Echter is het nog steeds niet duidelijk welke behandelstrategie nu precies het beste is voor RA patiënten. Uiteenlopende effectieve T2T behandelstrategieën kunnen worden toegepast, maar het is niet duidelijk welke strategie voor patiënten het best is. Is een T2T strategie met agressieve DMARD combinatietherapie het best of is *step-up* monotherapie beter? Of is een gepersonaliseerde behandelaanpak beter? Naar aanleiding van de resultaten van dit proefschrift wordt in eerste instantie initiële DMARD combinatie therapie met een optionele intramusculaire injectie van triamcinolon aanbevolen, omdat volgens deze strategie de behandelingsdoelstellingen eerder werden behaald dan in een *step-up* DMARD monotherapie (Hoofdstuk 4).

Huidige anti-reumatische medicijnen kunnen worden onderverdeeld in conventionele synthetische (cs) DMARD's, *targeted* synthetische (ts) DMARD's, *biological* (b) DMARDs en glucocorticosteroïden. Zoals bekend, is het belangrijk te starten met een combinatie van csDMARDs zo snel mogelijk wanneer de diagnose RA is vastgesteld. Daarnaast blijken glucocorticosteroïden bewezen effectief te zijn, bij voorkeur gecombineerd met csDMARDs [19, 20]. De T2T aanpak in klinische trials en in de dagelijkse klinische praktijk heeft aantoonbaar geleid tot een groot aantal patiënten met langdurige remissie. Dit roept nu de vraag op of het mogelijk is om de DMARD therapie eerder bij deze patiënten af te bouwen of zelfs te stoppen.

De huidige literatuur met betrekking tot afbouwschema's laten in ieder geval zien dat veel van de patiënten hun medicatie kunnen stoppen na een goede respons op de therapie [21–23].

Progressie

Erosieve gewrichtsschade is kenmerkend voor RA en tast het fysieke functioneren en kwaliteit van leven van de patiënt aan [24]. De mate waarin gewrichtsschade optreedt, verschilt van patiënt tot patiënt en is relatief moeilijk om te voorspellen. Voor het bereiken van optimale resultaten moeten patiënten die gevoelig zijn voor het ontwikkelen van ernstige radiografische schade vroeg in het behandelproces worden opgespoord. In dit proefschrift bleken alleen minder pijnlijke gewrichten en een hogere bezinking op baseline voorspellend te zijn voor minimale klinisch relevante progressie (MCID) (Hoofdstuk 5). De bevinding dat minder gevoelige gewrichten voorspellend waren voor radiografische progressie moet nog worden verklaard. Het is bijvoorbeeld mogelijk dat deze patiënten een hogere pijngrens hebben en hierdoor een minder optimale behandeling ontvangen (bijvoorbeeld minder vaak het intensiveren van de behandeling en minder gebruik van glucocorticosteroiden). Ook is een subklinische oorzaak mogelijk. Uit eerdere studies is immers gebleken dat subklinische ontsteking aanwezig is in een aanzienlijk deel van de RA patiënten in klinische remissie, wat kan leiden tot radiografische progressie [25–28]. Deze bevindingen wijzen erop dat patiënten in klinische remissie volgens de DAS28 nog steeds een subklinische ziekteactiviteit hebben. Dit benadrukt de noodzaak om nieuwe markers en definities voor ziekteactiviteit te identificeren en toe te voegen aan de huidige klinische beoordeling van deze ziekte.

Ongeacht de klinische parameters, moeten ook behandelingsveranderingen overwogen worden als patiënten ondanks goede ziektecontrole toch radiografische progressie vertonen, wat op lange termijn kan leiden tot fysieke beperkingen voor de patiënt. Radiografische gewrichtsschade moet dus nog steeds regelmatig worden beoordeeld tijdens de behandeling, bij voorkeur volgens een gestructureerde scoringsmethode, zoals de Sharp-van der Heijde methode [29].

Initiële combinatietherapie met DMARDs en glucocorticosteroiden bleek effectiever in het bereiken van goede klinische uitkomsten en het voorkomen van gewrichtsschade dan *step-up* DMARD monotherapie bij vroege RA patiënten. De patiënten die een initiële combinatietherapie ontvingen, hadden mindere radiografische progressie na 1 jaar ondanks een hogere ziekteactiviteit op baseline (Hoofdstuk 5). Deze bevinding komt overeen met eerder gepubliceerde literatuur, waaronder verschillende RCT's en observationele studies in de dagelijkse praktijk [16, 30–33].

Momenteel is de totale radiografische gewrichtsschade die vroege RA patiënten oplopen veel lager dan in eerder gedane studies [34, 35]. Zelfs op de lange termijn resulteert de onderdrukking van ziekteactiviteit in beperkte radiografische schade [36]. Deze verbetering in het optreden van radiografische gewrichtsschade is waarschijnlijk te wijten aan de uitstekende beschikbare behandelingsopties voor RA patiënten, zoals een intensiever gebruik van conventionele synthetische ziekte modifierende anti-reumatische geneesmiddelen (csDMARDs) en de beschikbaarheid van *biological* DMARDs (bDMARDs). Ondanks snelle en langdurige onderdrukking van ziekteactiviteit, zijn er echter nog steeds enkele patiënten die radiografische gewrichtsschade ontwikkelen (Hoofdstuk 5 en 7). Het bereiken van klinische remissie is een belangrijk doel in RA, maar een dergelijke remissie is niet voldoende als radiografische gewrichtsschade niet wordt gestopt. Of de afwezigheid van ziekteactiviteit verdere gewrichtsschade voorkomt, is nog steeds een punt van discussie. Radiografische gewrichtsschade kan worden veroorzaakt door andere factoren dan ziekteactiviteit en kan een meer individueel vastgesteld ziekteproces zijn. Het is belangrijk om radiografische progressie vroeg in het ziekteproces te detecteren, omdat radiografische progressie in een vroeg stadium voorspellend is voor radiografische schade op lange termijn [37]. Het is daarom aan te bevelen om röntgenfoto's op baseline en in de eerste 6 maanden van het ziekteproces te evalueren en mee te nemen in de keuze voor de best passende behandelingsstrategie voor de patiënt.

Patiënten perspectief en artsen voorkeur

Artsen moeten beslissingen nemen over de beste behandelingen voor patiënten. Vanuit biomedisch perspectief is dit het selecteren van het juiste medicijn voor de conditie van de patiënt, rekening houdend met het veiligheidsprofiel van het medicijn. Het is daarbij erg belangrijk om de optimale balans te vinden tussen biomedische uitkomsten en het perspectief van de gezondheidstoestand van de patiënt. De meeste uitkomstmaten zijn gericht op klinische en radiografische aspecten en houden geen rekening met het perspectief van de patiënt. Verschillende studies hebben echter aangetoond dat artsen en patiënten zich concentreren op andere aspecten van de ziekte bij het evalueren van de algemene gezondheidstoestand van de patiënt. Artsen benadrukken de objectieve klinische metingen van ziekteactiviteit (het aantal gezwollen en gevoelige gewrichten en acute fase reactanten), terwijl patiënten de nadruk leggen op de subjectieve uitkomstmaten zoals pijn, vermoeidheid, participatie en fysiek functioneren [38–40]. Dit werd bevestigd in het huidige onderzoek. Ondanks de goede algehele klinische respons van patiënten vond 36 procent van de patiënten, die na 12 maanden ten minste een matige EULAR respons hadden bereikt, dat hun algehele gezondheid helemaal niet was verbeterd

(Hoofdstuk 6). Onafhankelijke determinanten van geen waargenomen gezondheidsverbetering in deze groep waren de verandering in pijn en in mindere mate verandering in vermoeidheid. Pijn wordt algemeen door RA patiënten uitgedrukt als één van belangrijkste prioriteiten voor verbetering [41]. Het is duidelijk dat verlichting van pijn en vermoeidheid belangrijke behandelingsdoelen zijn voor RA patiënten [38, 42–44]. Een meerderheid van RA patiënten ervaart pijn en vermoeidheid ondanks een verminderde ziekteactiviteit [45]. Patiënten met een hoger vermoeidheidsniveau rapporteren bovendien hun gezondheid eerder als redelijk of slecht [46]. Pijn en vermoeidheid zijn recentelijk ook geïdentificeerd als één van de meest belangrijke domeinen bij de ontwikkeling van een kerndefinitie van een opvlamming van ziekteactiviteit [47, 48].

Eerdere cross-sectionele onderzoeken hebben aangetoond dat patiënten meer pessimistisch zijn over hun gezondheidstoestand dan artsen en dat patiënt-gerapporteerde uitkomstmaten (PROMs), zoals vermoeidheid en pijn, belangrijke bepalende factoren zijn voor de algehele patiënt beoordeling van ziekteactiviteit [39, 49]. De resultaten van hoofdstuk 6 suggereren dat pijn en vermoeidheid inderdaad subjectieve aspecten zijn die aandacht nodig hebben bij de behandeling van RA patiënten, zelfs wanneer patiënten worden behandeld volgens de huidige optimale behandelstrategieën. Uitkomsten zoals vermoeidheid en pijn zouden dus ook gemeten moeten worden bij het volgen van het ziekteverloop van RA-patiënten.

Veiligheid

Gerichte behandeling (T2T) met een vooraf bepaald doel met behandelingsaanpassingen totdat het doel is bereikt, wordt aanbevolen voor de behandeling van RA in de dagelijkse klinische praktijk [50, 51]. In het verleden werd RA behandeld met niet-specifieke immunosuppressieve therapieën. Hoewel patiënten verschillende voordelen ondervonden, behaalden slechts weinig patiënten langdurige remissie. In recente studies met combinatie csDMARDs therapieën en met een *biological* in combinatie met methotrexaat (MTX), wordt remissie van de ziekte veel vaker bereikt. Ongeacht deze voordelen van de huidige behandelstrategieën, kan er nog een ander probleem zijn, namelijk de toxiciteit van het medicijn. Veel patiënten met MTX monotherapie ondervinden bijwerkingen, maar deze zijn meestal van een milde en aanvaardbare categorie [52, 53]. De incidentie van bijwerkingen bij combinatie DMARD therapie is vergelijkbaar met die van een DMARD monotherapie [54]. Hydroxychloroquine (HCQ) verlengt het oorspronkelijke voordeel van combinatietherapie. Bovendien is aangetoond dat de gelijktijdige toediening van HCQ met MTX de biologische beschikbaarheid van MTX verhoogd, waardoor zowel de werkzaamheid als het risico op toxiciteit

mogelijk toenemen [55]. De combinatie van HCQ en MTX lijkt effectief te zijn en wordt goed verdragen [56]. In dit onderzoek, hoofdstuk 5, waren er echter significant meer patiënten met geregistreerde complicaties met DMARD combinatie therapie (35%) dan met *step-up* DMARD monotherapie (12%; $P < 0.01$).

Suggesties voor toekomstig onderzoek

Resultaten van dit proefschrift suggereren dat de behandeling van RA volgens een initiële DMARD combinatie therapie beter is dan een *step-up* DMARD monotherapie. Remissie kan worden bereikt bij een groter deel van de patiënten en eerder in het ziekteverloop. Toekomstige resultaten zullen moeten aantonen hoe lang patiënten in DAS28 remissie en/of in medicatievrije remissie zullen zijn, of het afbouwen van medicatie en het bereiken van medicatievrije remissie ook mogelijk is, hoeveel en welke patiënten op lange termijn nog steeds radiografische progressie ontwikkelen en wat de beste behandeling zal zijn als vervolgstراتيجية voor de patiënten die nog geen remissie gedurende de eerste 6 maanden hebben bereikt. Na 6 maanden werd remissie bereikt bij 63.3% van de patiënten. Om dit doel bij meer patiënten te bereiken, of uiteindelijk bij alle patiënten, moet onderzocht worden of behandelingsstrategieën nog verder kunnen worden geoptimaliseerd, zonder ten koste te gaan van de veiligheid.

Hoewel verschillende openstaande vragen over de behandeling van RA patiënten in de dagelijkse klinische praktijk beantwoord zijn in dit proefschrift, blijven er nog steeds enkele vragen onopgelost. Toekomstig onderzoek is nodig voor het optimaliseren van het management van vroege RA. RA blijkt steeds beter behandelbaar en patiënten leven langer, wat deels te wijten is aan betere behandelopties. Echter, wat zijn de resultaten op lange termijn? En wat zijn de gevolgen van langdurige perioden van DMARD-gebruik? Is de ontwikkeling van nieuwe erosies of nieuwe gewrichtsspleetversmallingen in voorheen onaangetaste gewrichten slechter dan progressie van reeds bestaande schade (vergroting van erosies en/of nieuwe erosies in een eerder beschadigd gewricht)? En wat is de impact van levensstijl op RA? Dit zijn interessante en belangrijke onderzoeksgebieden. Nu een groot aantal patiënten de remissiecriteria bereiken, is er meer onderzoek nodig naar de mogelijkheid om eerder bij deze patiënten de medicatie af te bouwen en misschien zelfs stop te zetten.

Data in dit proefschrift laten zien dat remissie een haalbaar doel is bij RA patiënten, zoals in beide strategieën is aangetoond. De introductie van vroege behandeling, het behandelen van patiënten volgens het T2T principe en initiële combinatietherapie hebben de korte termijn uitkomsten van RA patiënten aanzienlijk verbeterd. Gezien deze uitkomsten, zijn er geen grote verschillen tussen beide strategieën. We zouden dus kunnen stellen dat het vooral van groot

belang is om vroeg met de behandeling te starten en een T2T strategie te volgen, ongeacht welk medicatieprotocol wordt gebruikt. Echter, niet iedereen bereikt (medicatievrije) remissie en daarom lijkt er nog steeds ruimte voor verbetering. Toekomstig onderzoek moet zich daarom vooral richten op hoe lang en in welke patiënten remissie en/of medicatievrije remissie voorkomt.

Bij initiële DMARD combinatietherapie zijn er bovendien nog steeds een aantal patiënten met radiografische progressie, wat onomkeerbare functionele beperkingen met zich meebrengt, hoewel de omvang van de schade minder is dan bij patiënten die zijn behandeld met *step-up* monotherapie. In de dagelijkse klinische praktijk kan niet-naleving van de behandelvoorschriften, opzettelijk of onopzettelijk, de aanhoudende ziekteactiviteit en radiografische gewrichtsschade mogelijk deels verklaren. Toekomstig onderzoek zou zich moeten richten op patiënten die in hun eerste behandeljaar radiografische progressie vertonen, in plaats van alleen te concentreren op remissie en/of lage ziekteactiviteit. Eén van de factoren die geassocieerd is met het ontwikkelen van klinisch relevante radiografische progressie is een hogere bezinking, hetgeen suggereert dat deze patiënten zouden profiteren van een nog sterkere onderdrukking van ontstekende ziekteactiviteit, dat wil zeggen een nog intensievere behandeling. Meer onderzoek is nodig om deze hypothese te ondersteunen dat een strengere behandeling gunstiger zal zijn voor patiënten met een hogere bezinking. Zoals eerder vermeld, zijn er verschillende definities van het begrip remissie, die meer of minder resterende ziekteactiviteit toelaten, wat zou kunnen leiden tot progressieve gewrichtsschade. Een mogelijke optie zou zijn om een definitie van radiografische remissie parallel aan de definitie remissie van inflammatoire ziekteactiviteit ($\text{DAS28} < 2.6$) te gebruiken [57–60].

Eén van de principes van T2T is gedeelde besluitvorming (*shared decision making*), waarbij patiënten betrokken worden bij het bepalen van de behandeldoelen en bij therapeutische beslissingen tijdens hun behandelproces. Het betrekken van patiënten bij hun behandelproces kan de behandelresultaten optimaliseren. Naast het minimaliseren van de ziekteactiviteit zijn ook de verbetering van pijn, vermoeidheid, lichamelijk functioneren, sociaal functioneren en arbeidsparticipatie van groot belang [61].

Momenteel wordt in de richtlijnen voor RA het behandeldoel voor alle patiënten gelijk beschouwd in een *‘one size fits all’* aanpak. Ondanks de veelbelovende resultaten, hebben T2T strategieën niet dezelfde impact op alle patiënten [13]. Een relevant deel van de patiënten bereikte binnen 12 maanden van de behandeling nog steeds geen klinische remissie (Hoofdstuk 3 en 4) [14, 15]. Aan de andere kant, is er ook een groep patiënten die mogelijk overbehandeld wordt. Als niet alle patiënten met succes behandeld kunnen worden volgens hetzelfde behandelprotocol,

dient misschien de behandeling verder gepersonaliseerd te worden door de individuele kenmerken van de patiënt te identificeren en de behandeling te richten op specifieke gepersonaliseerde behandelmethoden (*personalized medicine*).

In de oorspronkelijke T2T aanbevelingen heeft de *task force* het belang van de betrokkenheid van patiënten al bij het behandelproces geïdentificeerd en een patiëntenversie van deze aanbevelingen gepubliceerd [16]. De betrokkenheid van patiënten is om een aantal redenen een zeer belangrijk aspect. Ten eerste kan het patiënten helpen om hun bezoek aan de reumatoloog voor te bereiden en de communicatie tussen patiënt en reumatoloog verbeteren [17]. Ten tweede kan het helpen bij het vaststellen van een geschikt behandeldoel voor de patiënt. Een open communicatie en een verhoogde betrokkenheid verhoogt de therapietrouw en de patiënttevredenheid [18]. Ondanks de aanbevelingen om de betrokkenheid van patiënten te verbeteren, is het succes van de T2T strategie in klinische trials primair beoordeeld op klinische ziekteactiviteit uitkomsten, zoals remissie en niet op patiëntgerichte uitkomsten. In veel opzichten is deze manier van evaluatie niet in overeenstemming met de T2T aanbevelingen en de recente literatuur die het belang van de patiëntgerichte zorg en de integratie van prioriteiten van patiënten in de behandelbeslissingen benadrukken [62]. Elke patiënt is anders en daarom kunnen patiënten, zelfs met dezelfde ziekte, anders reageren op dezelfde behandeling. Het in kaart brengen van het menselijk genoom identificeert mogelijk specifieke kenmerken van de patiënt, wat therapie op maat in de toekomst mogelijk kan vergemakkelijken. Toekomstig onderzoek zal echter de haalbaarheid van een dergelijke aanpak moeten uitwijzen.

Tot nu toe is één van de grootste uitdagingen in RA onderzoek het blijven zoeken naar effectieve strategieën die het ziekteverloop van RA patiënten kunnen veranderen naar een hoger percentage patiënten in aanhoudende (medicatievrije) remissie met preventie van radiografische gewrichtsschade. Ten tweede zal de nadruk worden gelegd op de verschuiving naar een meer gepersonaliseerde geneeskundige benadering gebaseerd op kennis van determinanten van het behandelen van individuele patiënten en de werkzaamheid en veiligheid van de behandeling.

Concluderend heeft de huidige T2T strategie met initiële DMARD combinatie behandeling bijgedragen aan zeer hoge remissie percentages en een virtuele stop van radiografische progressie na 1 jaar. Behandelstrategieën moeten echter nog wel verder geoptimaliseerd worden en indien mogelijk gepersonaliseerd worden voor elke patiënt.

ALGEHELE CONCLUSIE

Initiële DMARD combinatietherapie is effectief, veilig en gemakkelijk te implementeren in de dagelijkse klinische praktijk voor zowel patiënten als voor reumatologen en verpleegkundigen. Bovendien is het implementeren van DMARD combinatietherapie een eerste verstandig keuze voor nieuw gediagnosticeerde RA patiënten, niet alleen vanuit medisch perspectief, maar ook vanuit economisch perspectief. De initiële combinatie therapie is zeer kosteneffectief. Patiënten zullen veel baat hebben bij de implementatie van een initiële DMARD combinatietherapie, omdat deze benadering patiënten een betere prognose geeft (snellere remissie, hoge remissie percentages, en minder radiografische gewrichtsschade) dan patiënten die behandeld zijn volgens een *step-up* DMARD monotherapie. We bevelen deze behandeling aan alle reumatologen aan om initiële DMARD combinatie therapie voor te schrijven aan nieuw gediagnosticeerde RA patiënten. In geval van het falen van de behandeling, kunnen patiënten snel overschakelen naar een *biological* in combinatie met een csDMARD. De gecombineerde behandelmethode werd bevestigd als een snelle, effectieve en kosteneffectieve behandeling voor patiënten met vroege RA om de kans van kwaliteit van leven te vergroten en om langdurige schade of progressie van de gewrichten te vertragen of zelfs te voorkomen. Al eerder werd aangetoond dat de implementatie van 'T2T' succesvolle resultaten oplevert. Dit proefschrift laat zien dat de implementatie van 'T2T' met initiële DMARD combinatietherapie nog succesvoller is en dat dit nu de standaardbehandeling zou moeten zijn in alle ziekenhuizen voor alle RA-patiënten.

HOOFDPUNTEN VAN DE BELANGRIJKE BEVINDINGEN

- Initiële DMARD combinatietherapie wordt aanbevolen in plaats van *step-up* monotherapie. Bijna 80% van de recent gediagnosticeerde RA patiënten bereikte, na behandeling volgens een DMARD combinatietherapie, snel remissie tijdens het eerste jaar van hun ziekte;
- Initiële DMARD combinatie therapie leidt tot een aanzienlijk kortere tijd om eerste remissie te bereiken;
- Er waren geen nauwkeurige voorspellers te identificeren voor het bereiken van remissie, daarom lijkt deze strategie toepasbaar voor alle RA patiënten;
- De meerderheid van de patiënten behaalde het behandeldoel van DAS28-remissie met alleen het gebruik van csDMARDs;
- De mediane radiografische progressie was significant hoger bij *step-up* DMARD monotherapie;
- De grootste groep patiënten waarbij helemaal geen radiografische progressie optrad, volgden de initiële DMARD combinatietherapie;
- Het ervaren van een minimale klinisch belangrijk verschil (MCID) in radiografische progressie was onafhankelijk geassocieerd met minder gevoelige gewrichten en een hogere bezinking op baseline;
- Meer dan 1/3 van de patiënten die na 12 maanden ten minste een matige EULAR-respons hadden bereikt, vonden niet dat hun algehele gezondheid was verbeterd.
- Waargenomen verbetering was geassocieerd met minder verbetering vanaf baseline in VAS pijn en VAS vermoeidheid;
- Tijd geïntegreerde ziekteactiviteit en radiografische progressie was slechts zwak geassocieerd op groepsniveau, maar binnen individuele patiënten bestond er een vrij lineair verband tussen ziekteactiviteit in de loop van de tijd.

REFERENCES

1. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, Kvien TK, Navarro-Compán MV, Oliver S, Schoels M, Scholte-Voshaar M, Stamm T, Stoffer M, Takeuchi T, Aletaha D, Andreu JL, Aringer M, Bergman M, Betteridge N, Bijlsma H, Burkhardt H, Cardiel M, Combe B, Durez P, Fonseca JE, Gibofsky A, Gomez-Reino JJ, Graninger W, Hannonen P, Haraoui B, et al.: Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016, 75:3–15.
2. Schipper LG, Fransen J, den Broeder AA, Van Riel PLCM: Time to achieve remission determines time to be in remission. *Arthritis Res Ther* 2010, 12:R97.
3. Prevoo ML, van Gestel AM, van T Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL: Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. *Br J Rheumatol* 1996, 35:1101–5.
4. Fransen J, Creemers MCW, Van Riel PLCM: Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. *Rheumatology (Oxford)* 2004, 43:1252–1255.
5. Aletaha D, Ward MM, Machold KP, Nell VPK, Stamm T, Smolen JS: Remission and active disease in rheumatoid arthritis: Defining criteria for disease activity states. *Arthritis Rheum* 2005, 52:2625–2636.
6. Mierau M, Schoels M, Gonda G, Fuchs J, Aletaha D, Smolen JS: Assessing remission in clinical practice. *Rheumatology (Oxford)* 2007, 46:975–9.
7. Mäkinen H, Kautiainen H, Hannonen P, Sokka T: Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? *Ann Rheum Dis* 2005, 64:1410–3.
8. Landewé R, van der Heijde D, van der Linden S, Boers M: Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. *Ann Rheum Dis* 2006, 65:637–41.
9. Balsa A, de Miguel E, Castillo C, Peiteado D, Martín-Mola E: Superiority of SDAI over DAS-28 in assessment of remission in rheumatoid arthritis patients using power Doppler ultrasonography as a gold standard. *Rheumatology (Oxford)* 2010, 49:683–90.
10. Rintelen B, Sautner J, Haindl P, Andel I, Maktari A, Leeb B: Comparison of three rheumatoid arthritis disease activity scores in clinical routine. *Scand J Rheumatol* 2009, 38:336–341.
11. Mäkinen H, Kautiainen H, Hannonen P, Sokka T: Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? *Ann Rheum Dis* 2005, 64:1410–3.
12. Hulsmans HM, Jacobs JW, van der Heijde DM, van Albada-Kuipers GA, Schenk Y, Bijlsma JW: The course of radiologic damage during the first six years of rheumatoid arthritis. *Arthritis Rheum* 2000, 43:1927–40.
13. van der Leeden M, Steultjens MP, van Schaardenburg D, Dekker J: Forefoot disease activity in rheumatoid arthritis patients in remission: results of a cohort study. *Arthritis Res Ther* 2010, 12:R3.
14. de Jong PH, Weel AE, de Man YA, Huisman AM, Gerards AH, van Krugten M V., Luime JJ, Hazes JM: Brief Report: To squeeze or not to squeeze, that is the question! Optimizing the Disease Activity Score in 28 joints by adding the squeeze test of metatarsophalangeal joints in early rheumatoid arthritis. *Arthritis Rheum* 2012, 64:3095–3101.
15. Pincus T: Limitations of a quantitative swollen and tender joint count to assess and monitor patients with rheumatoid arthritis. *Bull NYU Hosp Jt Dis* 2008, 66:216–23.

16. Möttönen T, Hannonen P, Leirisalo-Repo M, Nissilä M, Kautiainen H, Korpela M, Laasonen L, Julkunen H, Luukkainen R, Vuori K, Paimela L, Bläfield H, Hakala M, Ilva K, Yli-Kerttula U, Puolakka K, Järvinen P, Hakola M, Piirainen H, Ahonen J, Pälvimäki I, Forsberg S, Koota K, Friman C: Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* 1999, 353:1568–73.
17. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, Hazes JM: Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am J Med* 2001, 111:446–51.
18. Möttönen T, Hannonen P, Korpela M, Nissilä M, Kautiainen H, Ilonen J, Laasonen L, Kaipainen-Seppänen O, Franzen P, Helve T, Koski J, Gripenberg-Gahmberg M, Myllykangas-Luosujärvi R, Leirisalo-Repo M: Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. *Arthritis Rheum* 2002, 46:894–8.
19. Donahue KE, Gartlehner G, Jonas DE, Lux LJ, Thieda P, Jonas BL, Hansen RA, Morgan LC, Lohr KN: Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. *Ann Intern Med* 2008, 148:124–34.
20. Verschueren P, De Cock D, Corluy L, Joos R, Langenaken C, Taelman V, Raeman F, Ravelingien I, Vandevyvere K, Lenaerts J, Geens E, Geusens P, Vanhoof J, Durnez A, Remans J, Vander Cruyssen B, Van Essche E, Sileghem A, De Brabanter G, Joly J, Meyfroidt S, Van der Elst K, Westhovens R: Effectiveness of methotrexate with step-down glucocorticoid remission induction (COBRA Slim) versus other intensive treatment strategies for early rheumatoid arthritis in a treat-to-target approach: 1-year results of CareRA, a randomised pragmatic open-label superiority trial. *Ann Rheum Dis* 2017, 76:511–520.
21. Klarenbeek NB, van der Kooij SM, Güler-Yüksel M, van Groenendael JHLM, Han KH, Kerstens PJSM, Huizinga TWJ, Dijkmans BAC, Allaart CF: Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission: exploratory analyses from the BeSt study. *Ann Rheum Dis* 2011, 70:315–9.
22. Wevers-de Boer KVC, Heimans L, Visser K, Schouffoer AA, Molenaar ETH, van Groenendael JHLM, Peeters AJ, Speyer I, Collée G, Huizinga TWJ, Allaart CF: Determinants of reaching drug-free remission in patients with early rheumatoid or undifferentiated arthritis after one year of remission-steered treatment. *Rheumatology (Oxford)* 2015, 54:1380–4.
23. van der Kooij SM, Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Güler-Yüksel M, Zwinderman AH, Kerstens PJSM, van der Lubbe PAHM, de Beus WM, Grillet BAM, Roday HK, Huizinga TWJ, Breedveld FC, Dijkmans BAC, Allaart CF: Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. *Ann Rheum Dis* 2009, 68:914–21.
24. Guillemin F: Functional disability and quality-of-life assessment in clinical practice. *Rheumatology (Oxford)* 2000, 39 Suppl 1:17–23.
25. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, Hensor E, Wakefield RJ, O'Connor PJ, Emery P: An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. *Arthritis Rheum* 2008, 58:2958–67.
26. Brown AK, Quinn MA, Karim Z, Conaghan PG, Peterfy CG, Hensor E, Wakefield RJ, O'Connor PJ, Emery P: Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. *Arthritis Rheum* 2006, 54:3761–73.

27. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Karim Z, Quinn M, Wakefield R, Hensor E, Conaghan PG, Emery P: Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: A clinical and imaging comparative study. *Arthritis Rheum* 2009, 60:1915–22.
28. Foltz V, Gandjbakhch F, Etchepare F, Rosenberg C, Tanguy ML, Rozenberg S, Bourgeois P, Fautrel B: Power Doppler ultrasound, but not low-field magnetic resonance imaging, predicts relapse and radiographic disease progression in rheumatoid arthritis patients with low levels of disease activity. *Arthritis Rheum* 2012, 64:67–76.
29. van der Heijde D: How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 2000, 27:261–3.
30. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, van Zeben D, Dijkmans BA, Peeters AJ, Jacobs P, van den Brink HR, Schouten HJ, van der Heijde DM, Boonen A, van der Linden S: Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997, 350:309–18.
31. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJSM, Hazes JMW, Zwinderman AH, Peeters AJ, de Jonge-Bok JM, Mallée C, de Beus WM, de Sonnaville PBJ, Ewals JAPM, Breedveld FC, Dijkmans BAC: Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007, 146:406–15.
32. Calgüneri M, Pay S, Calışkaner Z, Apraş S, Kiraz S, Ertenli I, Cobankara V: Combination therapy versus monotherapy for the treatment of patients with rheumatoid arthritis. *Clin Exp Rheumatol*, 17:699–704.
33. Verschueren P, Esselens G, Westhovens R: Daily practice effectiveness of a step-down treatment in comparison with a tight step-up for early rheumatoid arthritis. *Rheumatology (Oxford)* 2008, 47:59–64.
34. Wolfe F, Sharp JT: Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. *Arthritis Rheum* 1998, 41:1571–82.
35. Carpenter L, Norton S, Nikiphorou E, Jayakumar K, McWilliams DF, Rennie KL, Dixey J, Kiely P, Walsh DA, Young A, Early Rheumatoid Arthritis Study and the Early Rheumatoid Arthritis Network: Reductions in Radiographic Progression in Early Rheumatoid Arthritis Over Twenty-Five Years: Changing Contribution From Rheumatoid Factor in Two Multicenter UK Inception Cohorts. *Arthritis Care Res (Hoboken)* 2017, 69:1809–1817.
36. Vermeer M, Kuper HH, Moens HJB, Drossaers-Bakker KW, van der Bijl AE, van Riel PLCM, van de Laar MAFJ: Sustained beneficial effects of a protocolized treat-to-target strategy in very early rheumatoid arthritis: three-year results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort. *Arthritis Care Res (Hoboken)* 2013, 65:1219–26.
37. Versteeg L, Steunebrink L, Kuper I, Vonkeman H, ten Klooster P, van der Bijl A, van de Laar M: Early Radiological Progression in Rheumatoid Arthritis Leads to More Long-Term Joint Damage in Daily Clinical Practice; Six Year Radiological Outcomes of a Strict Treat-to-Target Cohort in the Netherlands [abstract]. *Arthritis Rheumatol* 2016, 68((suppl 10)).
38. Studenic P, Radner H, Smolen JS, Aletaha D: Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. *Arthritis Rheum* 2012, 64:2814–2823.
39. Khan NA, Spencer HJ, Abda E, Aggarwal A, Alten R, Ancuta C, Andersone D, Bergman M, Craig-Muller J, Detert J, Georgescu L, Gossec L, Hamoud H, Jacobs JWG, Laurindo IMM, Majdan M, Naranjo A, Pandya S, Pohl C, Schett G, Selim ZI, Toloza S, Yamanaka H, Sokka T: Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. *Arthritis Care Res (Hoboken)* 2012, 64:206–14.

40. Markenson JA, Koenig AS, Feng JY, Chaudhari S, Zack DJ, Collier D, Weaver A: Comparison of physician and patient global assessments over time in patients with rheumatoid arthritis: a retrospective analysis from the RADIUS cohort. *J Clin Rheumatol* 2013, 19:317–23.
41. Heiberg T, Kvien TK: Preferences for improved health examined in 1,024 patients with rheumatoid arthritis: pain has highest priority. *Arthritis Rheum* 2002, 47:391–7.
42. ten Klooster PM, Veehof MM, Taal E, van Riel PLCM, van de Laar MAFJ: Changes in priorities for improvement in patients with rheumatoid arthritis during 1 year of anti-tumour necrosis factor treatment. *Ann Rheum Dis* 2007, 66:1485–90.
43. Heiberg T, Finset A, Uhlig T, Kvien TK: Seven year changes in health status and priorities for improvement of health in patients with rheumatoid arthritis. *Ann Rheum Dis* 2005, 64:191–5.
44. Sanderson T, Morris M, Calnan M, Richards P, Hewlett S: Patient perspective of measuring treatment efficacy: the rheumatoid arthritis patient priorities for pharmacologic interventions outcomes. *Arthritis Care Res (Hoboken)* 2010, 62:647–56.
45. Ishida M, Kuroiwa Y, Yoshida E, Sato M, Krupa D, Henry N, Ikeda K, Kaneko Y: Residual symptoms and disease burden among patients with rheumatoid arthritis in remission or low disease activity: a systematic literature review. *Mod Rheumatol* 2018:1–11.
46. Wolfe F, Hawley DJ, Wilson K: The prevalence and meaning of fatigue in rheumatic disease. *J Rheumatol* 1996, 23:1407–17.
47. Bingham CO, Alten R, Bartlett SJ, Bykerk VP, Brooks PM, Choy E, Christensen R, Furst DE, Hewlett SE, Leong A, May JE, Montie P, Pohl C, Sanderson TC, Strand V, Woodworth TG, OMERACT RA Flare Definition Working Group: Identifying preliminary domains to detect and measure rheumatoid arthritis flares: report of the OMERACT 10 RA Flare Workshop. *J Rheumatol* 2011, 38:1751–8.
48. Berthelot J-M, De Bandt M, Morel J, Benatig F, Constantin A, Gaudin P, Le Loet X, Maillefert J-F, Meyer O, Pham T, Saraux A, Solau-Gervais E, Spitz E, Wendling D, Fautrel B, Guillemin F: A tool to identify recent or present rheumatoid arthritis flare from both patient and physician perspectives: the “FLARE” instrument. *Ann Rheum Dis* 2012, 71:1110–6.
49. Barton JL, Imboden J, Graf J, Glidden D, Yelin EH, Schillinger D: Patient-physician discordance in assessments of global disease severity in rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2010, 62:857–64.
50. Schipper LG, Vermeer M, Kuper HH, Hoekstra MO, Haagsma CJ, Den Broeder AA, van Riel P, Fransen J, van de Laar MAFJ: A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. *Ann Rheum Dis* 2012, 71:845–50.
51. Vermeer M, Kuper HH, Hoekstra M, Haagsma CJ, Posthumus MD, Brus HLM, van Riel PLCM, van de Laar MAFJ: Implementation of a treat-to-target strategy in very early rheumatoid arthritis: results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. *Arthritis Rheum* 2011, 63:2865–72.
52. Salliot C, van der Heijde D: Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. *Ann Rheum Dis* 2009, 68:1100–4.
53. Kremer JM, Lee JK: The safety and efficacy of the use of methotrexate in long-term therapy for rheumatoid arthritis. *Arthritis Rheum* 1986, 29:822–31.
54. Dale J, Alcorn N, Capell H, Madhok R: Combination therapy for rheumatoid arthritis: methotrexate and sulfasalazine together or with other DMARDs. *Nat Clin Pract Rheumatol* 2007, 3:450–458.

55. Carmichael SJ, Beal J, Day RO, Tett SE: Combination therapy with methotrexate and hydroxychloroquine for rheumatoid arthritis increases exposure to methotrexate. *J Rheumatol* 2002, 29:2077–83.
56. Clegg DO, Dietz F, Duffy J, Willkens RF, Hurd E, Germain BF, Wall B, Wallace DJ, Bell CL, Sleckman J: Safety and efficacy of hydroxychloroquine as maintenance therapy for rheumatoid arthritis after combination therapy with methotrexate and hydroxychloroquine. *J Rheumatol* 1997, 24:1896–902.
57. Gandjbakhch F, Haavardsholm EA, Conaghan PG, Ejbjerg B, Foltz V, Brown AK, Dohn UM, Lassere M, Freeston JE, Olsen IC, Boyesen P, Bird P, Fautrel B, Hetland ML, Emery P, Bourgeois P, Horslev-Petersen K, Kvien TK, McQueen FM, Ostergaard M: Determining a Magnetic Resonance Imaging Inflammatory Activity Acceptable State Without Subsequent Radiographic Progression in Rheumatoid Arthritis: Results from a Followup MRI Study of 254 Patients in Clinical Remission or Low Disease Activity. *J Rheumatol* 2014, 41:398–406.
58. Boutry N, Lardé A, Lapègue F, Solau-Gervais E, Flipo R-M, Cotten A: Magnetic resonance imaging appearance of the hands and feet in patients with early rheumatoid arthritis. *J Rheumatol* 2003, 30:671–9.
59. Peterfy CG: Magnetic resonance imaging in rheumatoid arthritis: current status and future directions. *J Rheumatol* 2001, 28:1134–42.
60. Anandarajah A, Thiele R, Giampoli E, Monu J, Seo G-S, Feng C, Ritchlin CT: Patients with rheumatoid arthritis in clinical remission manifest persistent joint inflammation on histology and imaging studies. *J Rheumatol* 2014, 41:2153–60.
61. Taylor PC, Moore A, Vasilescu R, Alvir J, Tarallo M: A structured literature review of the burden of illness and unmet needs in patients with rheumatoid arthritis: a current perspective. *Rheumatol Int* 2016, 36:685–95.
62. El Miedany Y: Adopting patient-centered care in standard practice: PROMs moving toward disease-specific era. *Clin Exp Rheumatol* , 32(5 Suppl 85):S-40-6.

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