Treat-to-target in axial spondyloarthritis: an observational study in daily practice

Esther Beckers[1,2], Annelies Boonen[1,2], Casper Webers[1,2], Peter ten Klooster[3], Harald Vonkeman[3,4], Monique Efdé[5], Astrid van Tubergen[1,2]

1. Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands
2. Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, Netherlands
3. Department of Psychology, Health & Technology, University of Twente, Enschede, Netherlands
4. Rheumatology, Medisch Spectrum Twente, Enschede, Netherlands
5. Rheumatology, VieCuri Medical Center, Venlo, Netherlands

Corresponding author:

Esther Beckers

Department of Internal Medicine, Division of Rheumatology

Maastricht University Medical Center

P Debyelaan 25

6229 HX Maastricht

The Netherlands

Email: esther.beckers@maastrichtuniversity.nl

ORCiD iD: https://orcid.org/0000-0003-1098-8908

Abstract

Objectives: To evaluate the extent to which internationally agreed treat-to-target (T2T) recommendations were applied in clinical practice in patients with axial spondyloarthritis (axSpA).

Methods: Data were used from a web-based patient registry for monitoring SpA in daily practice in the Netherlands (SpA-Net). The extent to which T2T was applied was evaluated through four indicators: the proportion of patients 1) with ≥1 Ankylosing Spondylitis Disease Activity Score (ASDAS) assessed during a 1-year period, 2) having inactive disease/low disease activity (ID/LDA, i.e. ASDAS<2.1), 3) in whom re-evaluation of ASDAS within recommended intervals occurred, and 4) with high disease activity (HDA, i.e. ASDAS≥2.1) in whom treatment was adapted ≤6 weeks after obtaining ASDAS≥2.1. Patients with HDA with treatment adaptations were compared to patients with HDA without treatment adaptations.

Results: In 185 out of 219 patients (84%), disease activity was monitored with ≥1 ASDAS during a 1-year period, of whom 71 (38%) patients had a score below the target (ASDAS<2.1) at first measurement. Re-evaluation of ASDAS ≤3 months occurred in 11% and 23% of the patients with ID/LDA and HDA, respectively. Treatment adaptation occurred in 19 out of 114 patients (13%) with HDA. Patients in whom treatment was adapted, had significantly higher ASDAS ($p<0.01$), C-reactive protein levels ($p<0.05$), and physician global assessment ($p<0.05$) compared to patients without treatment adaptations.

Conclusions: T2T was applied to a limited extent in clinical practice in patients with axSpA. Available disease activity scores seemed not to be used for determining the frequency of re-evaluation nor treatment adaptation.

Keywords: Spondyloarthritis, Treat-to-Target, Disease management, Clinical decision making

Key messages:

1. Treat-to-target is applied to a limited extent in clinical practice in patients with axSpA.
2. Disease activity scores appear not to drive the frequency of re-evaluation nor treatment adaptation.
3. Barriers to application of treat-to-target in patients with axSpA in practice should be studied.

INTRODUCTION

Treat-to-target (T2T) is recommended as a management strategy for axial spondyloarthritis (axSpA)(1, 2). The formulation of these T2T recommendations was justified by observational studies revealing a longitudinal association between disease activity and radiographic progression in ankylosing spondylitis (AS), and studies that showed that the impact of TNF inhibitors on spinal radiographic progression is mediated by their effect on disease activity (3-5). In addition, achieving inactive disease (ID) is associated with improved physical activities and work productivity, all contributing to better overall functioning and health (6).

The international T2T recommendations for SpA, as well as the ASAS-EULAR management recommendations for axSpA and the 2019 international ASAS quality standard set for optimising access, treatment and patient outcomes in axSpA, all advise that disease activity should be monitored regularly with validated outcome measures to evaluate whether treatment targets have been achieved (7-9). In axSpA, the AS Disease Activity Score (ASDAS) is preferred; alternatively the Bath AS Disease Activity Index (BASDAI) can be used if CRP levels are not available (10, 11). Both the International T2T recommendations for SpA and the ASAS-EULAR management recommendations for axSpA advice that treatment should be guided towards predefined treatment targets. However, only the T2T recommendations explicitly define the target as ID or low disease activity (LDA) (2). In addition, experts from ASAS advise to initiate or resume treatment in patients who have demonstrated clinically important disease worsening, defined as an increase in ASDAS of 0.9 points or more (12). Furthermore, the T2T recommendations explicitly advise that the frequency of re-evaluation should be dependent on prior disease activity scores. In patients who have not achieved the target, disease activity should be re-evaluated within 3 months. Evaluation within 6 to 12 months may be considered in patients whose target is achieved.

Although the guidelines and management recommendations propose regular monitoring of disease activity and treatment towards predefined goals, clinicians report feasibility concerns in daily practice (13). In a review of medical files of patients with axSpA in 2013, it was shown that outcome measures for disease activity were only collected in a limited proportion of patients, ranging from 1% for the ASDAS to 51% for C-reactive protein (CRP) levels (14). Frequent monitoring of disease activity can be burdensome to both patients and care providers. For example, paper-based questionnaires are resource demanding in terms of distribution, gathering, score calculation and transfer of data into the existing electronic medical records (EMRs) (15). Integrating data collection into EMRs could pose a solution for these feasibility concerns, as patient reported outcome measures can be collected electronically (ePROMs) with equal or less time investment required. ePROMs generally provide high-quality data and most patients prefer electronic data collection (16, 17).

Since 2016, a web-based patient registry for monitoring patients with SpA in daily practice in the Netherlands (SpA-Net) is in use, available at www.mijnreumacentrum.nl (18). SpA-Net follows the patient journey in daily practice and facilitates monitoring of various disease aspects, including comorbidities, prescribed medication, adverse events, and patient- and physician-centered outcome measures for disease activity, physical functioning and overall health status. Results over time are graphically visualized in a dashboard, using color-coding to aid quick interpretation. These comprehensive up-to-date individual patient data are readily available to the physician during consultations, which facilitate informed treatment decision making based on a complete overview of the patient's history. In this particular situation where an electronic monitoring tool is available, we were interested in what the uptake of the T2T recommendations was. Therefore, the aim of this study was to evaluate the extent to which internationally agreed T2T recommendations were applied in patients with axSpA in rheumatology centers supported by SpA-Net.

METHODS

Design of the study and data collection

Data were used from SpA-Net, an electronic monitoring tool, registered in the Netherlands Trial Registry (NTR 6740).(18) The ethics committee of the university hospital Maastricht/Maastricht University determined that the Medical Research Involving Human Subjects Act did not apply as data were collected in routine care and official approval was not required for this study. Informed consent was obtained from each patient to use data for research purposes.

Rheumatologists and (specialised) nurses were trained to use SpA-Net in clinical practice and a standard operating procedure was provided for optimal record keeping. Patients were instructed by their care provider(s) to complete ePROMs in SpA-Net a few days prior to every visit at home or in the hospital's waiting room, where touch-screen tablets were available. If needed, a care provider offered assistance in completing the ePROMs during the visit. Care-providers were not notified if patients have completed a new outcome measure, nor have a high disease activity.

Study population

We used SpA-Net data from three participating centers from different geographical areas in the Netherlands; Maastricht University Medical Center is an academic center where a couple of SpA expert rheumatologists work, Medisch Spectrum Twente is a large general teaching hospital, and VieCuri is a top clinical hospital.

For the present study, patients were selected if they had a clinical diagnosis of axSpA for at least 6 months, were enrolled in SpA-Net before January 2018, and had at least one patient or

physician reported outcome measure registered in 2018 (January to December). Patients were excluded if they had participated in other clinical studies within this period.

Assessments

In SpA-Net, disease activity could be evaluated by CRP-based ASDAS and/or BASDAI.(19) CRP levels were usually assessed prior to the clinical visit using standard measurements. ID/LDA was defined as ASDAS<2.1 or BASDAI<4.0 and HDA was defined as ASDAS≥2.1 or BASDAI≥4.0 (19, 20). Overall functioning and health was monitored with the ASAS Health Index (ASAS HI) (21). Physical functioning was measured with the Bath AS Functional Index (BASFI) and the Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S) (11, 22). Health utility was measured with the EuroQoL 5 dimensions (EQ5D) and health-related quality of life (HR-QoL) with two summary scores of the Medical Outcomes Study Short Form Health Survey (MOS SF36): the physical and mental component summary (SF36-PCS and SF36-MCS, respectively) (23, 24). Symptom duration was calculated as the time between the onset of symptoms and the first ASDAS or BASDAI measurement in this study.

Study outcomes

The extent to which the T2T recommendations were followed was evaluated through four indicators: 1) the proportion of patients in whom disease activity was assessed with at least one ASDAS measurement during a 1-year period (January to December 2018); 2) the proportion of patients with ID/LDA at the first measurement; 3) the proportion of patients with ID/LDA or HDA in whom the ASDAS was re-evaluated within 3, 6 or 12 months after the first measurement; and 4) the proportion of patients in whom pharmacological treatment for axSpA was adapted within 6 weeks after a first measurement of ASDAS HDA.

Of note, for the third indicator, we used an extended time-window of 1 month, because in practice not all patients receive an appointment exactly within 3, 6 or 12 months, respectively.

For the fourth indicator, treatment adaptation was defined as increasing the dosage and/or frequency of drugs, starting an additional drug or switching between drugs. We investigated adaptations of the following medications: non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids, local steroid injections, conventional synthetic DMARDs (csDMARDs), targeted synthetic DMARDs (tsDMARDs) and biological DMARDs (bDMARDs). In parallel, we studied the proportion of patients with HDA in whom treatment was discontinued or the drug dosage and/or frequency of administration was decreased and reasons for this. For this fourth indicator a maximum period of 6 weeks was accepted between obtaining an HDA score and starting a new treatment, as time delays might occur in clinical practice. For example, time delays are expected as patients are

instructed to complete the questionnaires several days prior to the actual visit and when patients need to be screened for latent infectious diseases before commencement of a biological after a visit.

In extension to the fourth indicator, we evaluated treatment adaptation based on clinically important ASDAS worsening (12). This was done by calculating the proportion of patients in whom treatment was adapted among those patients with ASDAS ID/LDA at the first measurement, who showed a clinically important ASDAS worsening (ΔASDAS +0.9) at a second measurement, and consequentially changed from an ID/LDA state to an HDA state. Nearly all analyses were repeated with BASDAI instead of ASDAS.

Statistical analyses

Patient and disease characteristics were calculated with descriptive statistics. Differences in characteristics between patients with ID/LDA versus HDA at the first available measurement, and between patients with HDA in whom treatment was adapted versus not adapted were compared with independent samples t-tests, Mann-Whitney U-tests or Chi-square tests, whichever appropriate. Results were considered statistically significant when $p<0.05$. Analyses were performed in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics 24.

RESULTS

In total, 307 patients had a clinical diagnosis of axSpA for at least 6 months, were enrolled in SpA-Net before January 2018 and did not participate in other clinical trials. Of these 307 patients, 219 (71%) also had at least one patient or physician reported outcome measure registered in 2018. A significant difference was found for the current and prior use of bDMARDs between patients with or without at least one completed outcome measure in 2018 (53.0% versus 34.1%, respectively) (supplementary table S1, available at *Rheumatology* online). Disease activity was assessed at least once in 2018 in 185 out of 219 patients (84%) with the ASDAS, and in 214 out of 219 patients (98%) with the BASDAI (figure 1 and table 1). In patients with at least one available ASDAS or BASDAI score in 2018, the average age of the patients was 51 (SD 14) years at the first measurement, average symptom duration was 16 (SD 13) years and 41% was female (table 2).

At the first measurement in 2018, 71 out of 185 patients (38%) had ID/LDA assessed with the ASDAS and 83 out of 214 patients (39%) had ID/LDA assessed with the BASDAI (figure 1). The mean symptom duration was significantly lower in patients with ID/LDA compared to patients with HDA and patients with ID/LDA were more often male (table 2). Scores for outcome measures assessing disease activity, physical function and overall functioning and health were significantly better in patients with ID/LDA compared to patients with HDA. Patient and disease characteristics of patients with BASDAI ID/LDA or HDA were comparable to ASDAS ID/LDA or HDA (table 2).

In patients who had HDA at the first measurement, the ASDAS was re-evaluated within 3, 6 or 12 months in 26, 56 and 83 out of 114 patients (23%, 49% and 73%, respectively) and the BASDAI in 34, 76, and 105 out of 131 patients (26%, 58% and 80%, respectively) (figure 1). The proportions of patients in whom disease activity was re-evaluated within 3 months was higher for patients with HDA compared to ID/LDA (23% versus 11% with the ASDAS and 26% and 19% with the BASDAI), while the proportions of patients in whom disease activity was re-evaluated within 6 or 12 months were comparable in patients with ID/LDA and HDA (figure 1).

In patients with ASDAS or BASDAI HDA at the first measurement, treatment was adapted within 6 weeks in, respectively, 19 out of 114 (13%) patients and 20 out of 131 (15%) patients (figure 2). For ASDAS HDA, this was done within the first week in 12 out of 19 (63%) patients, in the second week in 3 out of 19 (16%) patients and between the third and sixth week in 4 out of 19 (21%) patients. In 5 out of 21 patients (24%) with treatment adaptations at either the first or second measurement, the dosage and/or frequency of administration of the drug was increased (table 3). In 2 out of 16 (13%) patients without treatment adaptations despite HDA after the first measurement and with persistent ASDAS HDA at the next measurement, treatment was adapted after this second measurement (figure 2). Interestingly, in 8 out of the 114 patients (7%) with ASDAS HDA at the first measurement, the treatment was decreased (n=3) or (partially) discontinued (n=5) within 6 weeks. Reasons for this were that the disease activity was considered low by the physician (i.e. HDA state was not related to axSpA manifestations, n=3), drug ineffectiveness (n=2), drug side effects (n=1) or unknown reasons (n=1)).
In patients with ASDAS HDA and treatment intensification, the ASDAS, CRP and PhGA were significantly higher and the PGA was numerically, but non-significantly, higher compared to patients with ASDAS HDA in whom treatment was not adapted (table 4). Similarly, in patients with BASDAI HDA having a treatment intensification, the ASDAS, PGA, CRP and PhGA were significantly higher compared to patients with BASDAI HDA in whom treatment was not adapted (table 4). Thirteen out of 52 (25%) patients with ASDAS ID/LDA at the first measurement and in whom the ASDAS was re-evaluated within 1 year, had a clinically important worsening leading to HDA. In 2 out of these 13 (15%) patients, treatment was intensified.

DISCUSSION

This study showed that T2T is applied to a limited extent in clinical practice although a dashboard with disease activity scores was available supporting both care providers and patients. Disease activity was monitored at least once during a 1-year period in 86% of the patients with the ASDAS and in nearly all patients with the BASDAI. However, the available scores for disease activity did not appear to be used to drive re-evaluation nor treatment adaptation. In less than a quarter of the patients with HDA, ASDAS was re-evaluated within the recommended time period of 3 months, and treatment was adapted in a

small proportion of patients with HDA measured at one or two consecutive occasions. Also, clinically important worsening in ASDAS and consequently obtaining an HDA state did not appear to be used for making treatment decisions as advised by experts from ASAS (12). Analyses using the BASDAI instead of the ASDAS showed comparable results.

A T2T approach might not have been applied as the T2T recommendations have no official status, despite international agreement, were relatively new at the start of the study period, and were not yet justified by an RCT. Recently, the first results of an RCT evaluating the effect of application of T2T in axSpA towards predefined disease activity targets on health status, compared to routine care, were presented (Tight Control in SpA, TICOSPA, NCT03043846) (25). Although the primary endpoint (statistically significant difference of ≥30% improvement in the ASAS Health Index between T2T and usual care group) was not met, outcome measures for disease activity, physical functioning and HR-QoL showed a general trend in favour of T2T with a comparable safety profile. T2T was also found to be favourable from a health economics perspective.

In clinical practice, monitoring of disease activity within pre-defined time periods can be hampered as care providers and patients might not use an electronic monitoring tool due to lack of availability of such a system, lack of time, motivation or experience. The results of our study are in line with a 2015 UK physician survey which estimated that a limited proportion of care providers use a T2T approach or routinely include specific assessments in patients with psoriatic arthritis (PsA) (26). In addition, partial implementation of T2T recommendations is also still seen in patients with rheumatoid arthritis (RA) for whom applying T2T is strongly being advised now for over 10 years (27). The implementation of T2T in these patients was not universal, differed between specific recommendations and decreased over time (28). Furthermore, a discrepancy between rheumatologists agreeing with EULAR/T2T recommendations for patients with RA and their actual performance in clinical practice was observed in an international study (29).

Interpretation of the limited extent to which T2T is applied remains speculative, as it is unknown whether the lack of implementation is intentional or unintentional. Patients or care providers could decide to continue pharmacological treatment in patients with HDA for several reasons, for example, non-pharmacological treatment could have been initiated or intensified, irrespective of provided pharmacological treatment.(1) Treatment could also be guided towards alternative treatment targets in patients who are unlikely to achieve ID/LDA, such as patients with severe irreversible damage (30). Alternatively, care providers and patients might expect that disease activity will decrease without treatment intensification as a result of natural disease fluctuations (31). The latter was also seen in our study: approximately 20% of the patients with HDA at the first measurement had ID/LDA at a consecutive measurement without treatment modification. Furthermore, patients may be reluctant to adapt their current treatment, because of beliefs about potential ineffectiveness

of alternative treatment options or worries about potential adverse side effects of a new treatment (32). Finally, it is possible that the pharmacological treatment in some patients with HDA is decreased or (partially) discontinued instead of intensified because of non-response or adverse side effects (33). In our study, >20% of the patients with ASDAS HDA without treatment intensification had a medication history of ≥3 bDMARDs as opposed to 10% in those patients with treatment intensification. We also saw that treatment was decreased or (partially) discontinued in 7% of the patients with ASDAS HDA at the first measurement for various reasons.

Implementation of T2T guidelines in practice remains challenging. The above illustrates that barriers to application of a T2T approach can be found at several levels, for example the structure of the local health care and perceptions and preferences of the patients and physicians (28). As a next step, we would therefore recommend to develop studies identifying such barriers, but also facilitators for successful application of T2T in axSpA in practice, after which a multifaceted implementation strategy should be developed (34, 35).

An important limitation of our study is that data were collected in centers with an online EMR available, and results were not compared to centers without an online EMR available, which might affect the generalizability of the results. In addition, it is possible that patients had a visit that was not logged in SpA-Net as using this patient registry is voluntary for both patients and physicians. Furthermore, modifications in non-pharmacological treatments were not considered, however, these are also an important treatment aspect in axSpA.

In conclusion, T2T was applied to a limited extent in patients with axSpA in daily clinical practice, in a setting where care providers were supported by an electronic monitoring tool. Measured disease activity scores seemed not to be used in accordance with T2T recommendations as re-evaluation within recommended intervals and treatment modifications occurred only in a small proportion of patients with HDA.

Disclose statement: The authors have declared no conflicts of interest.

Data availability statement: The data underlying this article will be shared on reasonable request to the corresponding author.

Funding declaration: SpA-Net was financially supported by grants from The Netherlands Organisation for Health Research and Development (ZonMw; project number 836042001) and Dutch Arthritis Society, and was additionally sponsored by Abbvie, Biogen, Celgene, Janssen-Cilag, MSD, Novartis, Pfizer and UCB.

REFERENCES

1. van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Annals of the Rheumatic Diseases. 2017;76(6):978.
2. Smolen JS, Schöls M, Braun J, Dougados M, FitzGerald O, Gladman DD, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Annals of the rheumatic diseases. 2018;77(1):3-17.
3. Ramiro S, Stolwijk C, van Tubergen A, van der Heijde D, Dougados M, van den Bosch F, et al. Evolution of radiographic damage in ankylosing spondylitis: a 12 year prospective follow-up of the OASIS study. Ann Rheum Dis. 2015;74(1):52-9.
4. Poddubnyy D, Protopopov M, Haibel H, Braun J, Rudwaleit M, Sieper J. High disease activity according to the Ankylosing Spondylitis Disease Activity Score is associated with accelerated radiographic spinal progression in patients with early axial spondyloarthritis: results from the GErman SPondyloarthritis Inception Cohort. Annals of the rheumatic diseases. 2016;75(12):2114-8.
5. Molnar C, Scherer A, Baraliakos X, de Hooge M, Micheroli R, Exer P, et al. TNF blockers inhibit spinal radiographic progression in ankylosing spondylitis by reducing disease activity: results from the Swiss Clinical Quality Management cohort. Annals of the rheumatic diseases. 2018;77(1):63-9.
6. van der Heijde D, Joshi A, Pangan AL, Chen N, Betts K, Mittal M, et al. ASAS40 and ASDAS clinical responses in the ABILITY-1 clinical trial translate to meaningful improvements in physical function, health-related quality of life and work productivity in patients with non-radiographic axial spondyloarthritis. Rheumatology. 2016;55(1):80-8.
7. Kiltz U, Landewé RBM, van der Heijde D, Rudwaleit M, Weisman MH, Akkoc N, et al. Development of ASAS quality standards to improve the quality of health and care services for patients with axial spondyloarthritis. Ann Rheum Dis. 2020;79(2):193-201.
8. Smolen JS, Schols M, Braun J, Dougados M, FitzGerald O, Gladman DD, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Annals of the rheumatic diseases. 2018;77(1):3-17.
9. van der Heijde D, Ramiro S, Landewe R, Baraliakos X, Van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Annals of the rheumatic diseases. 2017;76(6):978-91.
10. Lukas C, Landewe R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Annals of the rheumatic diseases. 2009;68(1):18-24.
11. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 1994;21(12):2281-5.
12. Molto A, Gossec L, Meghnathi B, Landewe RBM, van der Heijde D, Atagunduz P, et al. An Assessment in SpondyloArthritis International Society (ASAS)-endorsed definition of clinically important worsening in axial spondyloarthritis based on ASDAS. Annals of the rheumatic diseases. 2018;77(1):124-7.
13. Machado PM, Deodhar A. Treat-to-target in axial spondyloarthritis: gold standard or fools' gold? Current opinion in rheumatology. 2019;31(4):344-8.
14. Che H, Etcheto A, Dernis E, Nataf H, Boumier P, Breuillard P, et al. Evaluation of collected outcome measures in axial spondyloarthritis in daily-care rheumatology settings: the experience of the RHEVER network. Clinical and experimental rheumatology. 2015;33(6):851-7.
15. Kiltz U, Boonen A, Braun J, Richter JG. Electronic assessment of disease activity and functioning in patients with axial spondyloarthritis: challenges and unmet needs. Clinical and experimental rheumatology. 2016;34(5 Suppl 101):S57-S61.

16. Salaffi F, Gasparini S, Ciapetti A, Gutierrez M, Grassi W. Usability of an innovative and interactive electronic system for collection of patient-reported data in axial spondyloarthritis: comparison with the traditional paper-administered format. Rheumatology. 2013;52(11):2062-70.
17. Salaffi F, Gasparini S, Grassi W. The use of computer touch-screen technology for the collection of patient-reported outcome data in rheumatoid arthritis: comparison with standardized paper questionnaires. Clinical and experimental rheumatology. 2009;27(3):459-68.
18. Webers C, Beckers E, Boonen A, van Eijk-Hustings Y, Vonkeman H, van de Laar M, et al. Development, usability and acceptability of an integrated eHealth system for spondyloarthritis in the Netherlands (SpA-Net). RMD Open. 2019;5(1):e000860.
19. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994;21(12):2286-91.
20. Machado PM, Landewe R, Heijde DV. Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. Ann Rheum Dis. 2018;77(10):1539-40.
21. Kiltz U, van der Heijde D, Boonen A, Braun J. The ASAS Health Index (ASAS HI) - a new tool to assess the health status of patients with spondyloarthritis. Clin Exp Rheumatol. 2014;32(5 Suppl 85):S-105-8.
22. Daltroy LH, Larson MG, Roberts NW, Liang MH. A modification of the Health Assessment Questionnaire for the spondyloarthropathies. J Rheumatol. 1990;17(7):946-50.
23. Ware J, Sherbourne C. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care. 1992;30(6):473-83.
24. EuroQol-Group. EuroQol-A new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.
25. Moltó A, López-Medina C, Van den Bosch F, Boonen A, Webers C, Dernis E, et al. Cluster-randomized pragmatic clinical trial evaluating the potential benefit of a tight-control and treat-to-target strategy in axial spondyloarthritis: The results of the TICOSPA trial. Annals of the Rheumatic Diseases. 2020;79(Suppl 1):417.
26. Dures E, Taylor J, Shepperd S, Mukherjee S, Robson J, Vlaev I, et al. Mixed methods study of clinicians' perspectives on barriers to implementation of treat to target in psoriatic arthritis. Ann Rheum Dis. 2020;79(8):1031-6.
27. 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;76(6):960-77.
28. Batko B, Batko K, Krzanowski M, Zuber Z. Physician Adherence to Treat-to-Target and Practice Guidelines in Rheumatoid Arthritis. J Clin Med. 2019;8(9).
29. Gvozdenovic E, Allaart CF, van der Heijde D, Ferraccioli G, Smolen JS, Huizinga TW, et al. When rheumatologists report that they agree with a guideline, does this mean that they practise the guideline in clinical practice? Results of the International Recommendation Implementation Study (IRIS). RMD Open. 2016;2(1):e000221.
30. Smolen JS, Braun J, Dougados M, Emery P, Fitzgerald O, Helliwell P, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. Ann Rheum Dis. 2014;73(1):6-16.
31. Essers I, Boonen A, Busch M, van der Heijde D, Keszei AP, Landewe R, et al. Fluctuations in patient reported disease activity, pain and global being in patients with ankylosing spondylitis. Rheumatology. 2016;55(11):2014-22.
32. Nowell W HT, Gavigan K, Curtis J, Malatestinic W, Bolce R, Lisse J, Kronbergs A, Himelein C, Walker J, Walsh J. Treatment Decision Making Among Axial Spondyloarthritis Patients: Real-World Data from the ArthritisPower Registry [abstract]. Arthritis Rheumatol. 2020;72 (suppl 10).
33. Imkamp M, Lima Passos V, Boonen A, Arends S, Dougados M, Landewé R, et al. Uncovering the heterogeneity of disease impact in axial spondyloarthritis: bivariate trajectories of disease activity and quality of life. RMD Open. 2018;4(2):e000755.

34. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet. 2003;362(9391):1225-30.
35. Grol R, Wensing M. What drives change? Barriers to and incentives for achieving evidence-based practice. Med J Aust. 2004;180(S6):S57-60.

Figure 1. Flowchart of patients with axSpA and measurements of ASDAS (A) and BASDAI (B) in SpA-Net.

Figure 2. Flowchart of patients, re-evaluations and treatment adaptations based on ASDAS (A) and BASDAI (B).

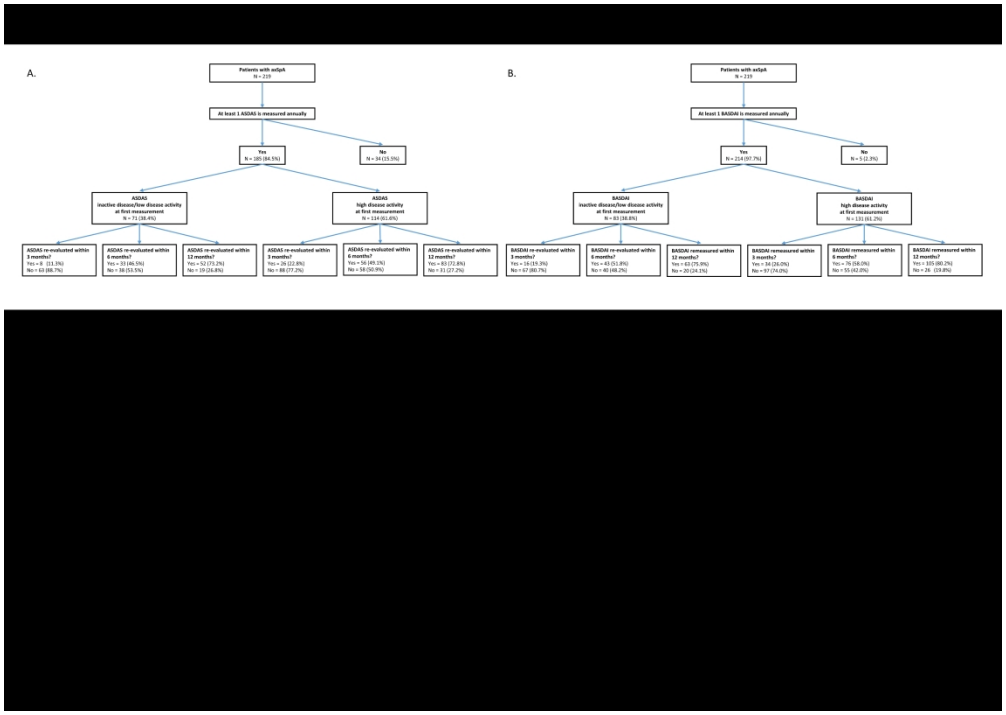

Figure 1 Flowchart of patients with axSpA and measurements of ASDAS (A) and BASDAI (B) in SpA-Net

755x534mm (118 x 118 DPI)

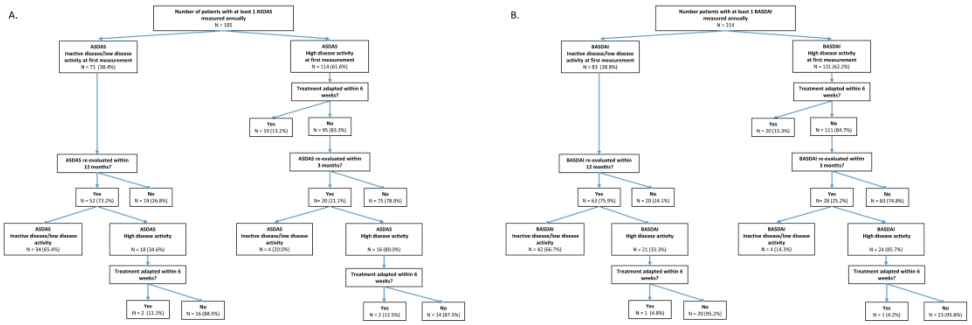

Figure 2 Flowchart of patients, re-evaluations and treatment adaptations based on ASDAS (A) and BASDAI (B)

295x108mm (300 x 300 DPI)

Table 1 Frequency of ASDAS or BASDAI measurements per patient during a 1-year period (2018)

ASDAS		BASDAI	
Number of measurements	Frequency n (%)	Number of measurements	Frequency n (%)
0	31 (14.4%)	0	2 (0.9%)
1	91 (42.1%)	1	101 (46.8%)
2	67 (31.0%)	2	69 (31.9%)
3	19 (8.8%)	3	32 (14.8%)
4	5 (2.3%)	4	6 (2.8%)
5	2 (0.9%)	5	2 (0.9%)
6	1 (0.5%)	6	3 (1.4%)
≥7	0 (0.0%)	≥7	1 (0.5%)

Table 2 Patient and disease characteristics of patients at time of measurement of first ASDAS and/or BASDAI

	ASDAS					BASDAI				
	Total population with ≥1 ASDAS n = 185		**ASDAS <2.1** n = 71 (38.4%)	**ASDAS ≥2.1** n = 114 (61.6%)		**Total population with ≥1 BASDAI** n = 214		**BASDAI <4.0** n = 83 (38.8%)	**BASDAI ≥4.0** n = 131 (61.2%)	
Patient characteristics	**N patients**				**p-value**	**N patients**				**p-value**
Female, n (%)	76 (41.1)	185	23 (32.4)	53 (46.5)	0.06	88 (41.1)	214	29 (34.9)	59 (45.0)	0.14
Age, years	50.8 (13.8)	185	49.6 (14.6)	51.5 (13.3)	0.38	51.1 (13.7)	214	50.1 (14.2)	51.8 (13.4)	0.37
Occupational status					0.66					0.78
Employed, n (%)	67 (36.2)	-	29 (40.8)	38 (33.3)		70 (32.7)	-	31 (37.3)	39 (29.8)	
Retired, n (%)	13 (7.0)	-	6 (8.5)	7 (6.1)		14 (6.5)	-	6 (7.2)	8 (6.1)	
Disabled for work, n (%)	23 (12.4)	-	8 (11.3)	15 (13.2)		25 (11.7)	-	9 (10.8)	16 (12.2)	
Other, n (%)	9 (4.9)	-	2 (2.8)	7 (6.1)		10 (4.7)	-	3 (3.6)	7 (5.3)	
Unknown, n (%)	73 (39.5)	-	26 (36.6)	47 (41.2)		95 (44.4)	-	34 (41.0)	61 (46.6)	
Symptom duration, years	21.7 (13.6)	117	17.4 (12.7)	24.3 (13.6)	<0.01	21.1 (13.5)	129	17.5 (11.6)	23.3 (14.2)	<0.05
Disease duration, years	15.9 (12.9)	185	15.0 (13.1)	16.4 (12.8)	0.46	16.1 (12.9)	214	15.9 (13.4)	16.2 (12.7)	0.88
Current use of NSAIDs, n (%)	108 (58.4)	-	38 (53.5)	70 (61.4)	0.29	120 (56.1)	-	47 (56.6)	73 (55.7)	0.90
Current use of bDMARDs, n (%)	104 (56.2)	-	40 (56.3)	64 (56.1)	0.97	113 (52.8)	-	43 (51.8)	70 (53.4)	0.82
Number of current and prior bDMARDs					0.17					<0.05
None, n (%)	70 (37.8)	-	25 (35.2)	45 (39.5)		86 (40.2)	-	35 (42.2)	51 (38.9)	
1, n (%)	59 (31.9)	-	29 (40.8)	30 (26.3)		69 (32.2)	-	35 (39.8)	36 (27.5)	
2, n (%)	26 (14.1)	-	9 (12.7)	17 (14.9)		28 (13.1)	-	9 (10.8)	19 (14.5)	
≥3, n (%)	30 (16.2)	-	8 (11.3)	22 (19.3)		31 (14.5)	-	6 (7.2)	25 (19.1)	
Active peripheral arthritis (SJC66≥1), n (%)	6 (3.2)	84	0 (0.0)	6 (5.3)	<0.05	6 (2.8)	94	1 (1.2)	5 (3.8)	0.19
Active psoriasis (BSA ≥3%), n (%)	1 (0.5)	52	0 (0.0)	1 (0.9)	0.35	1 (0.5)	58	0 (0.0)	1 (0.8)	0.35
ASDAS (0-∞)*	2.4 (1.0)	185	1.4 (0.4)	3.0 (0.7)	<0.01	2.4 (1.0)	185	1.6 (0.6)	3.0 (0.7)	<0.01
BASDAI (0-10)	4.6 (2.1)	185	2.3 (1.2)	5.8 (1.6)	<0.01	4.6 (2.2)	214	2.4 (1.0)	6.0 (1.4)	<0.01
PGA (0-10)	4.5 (2.6)	185	2.4 (1.8)	5.7 (2.1)	<0.01	4.5 (2.6)	209	2.7 (1.9)	5.6 (2.4)	<0.01
CRP, mg/L (0-∞)	4.8 (7.0)	185	2.0 (1.7)	6.6 (8.4)	<0.01	4.8 (7.0)	188	3.6 (6.1)	5.6 (7.4)	<0.01
VAS pain (0-10)	4.3 (2.6)	71	2.3 (2.0)	5.7 (2.0)	<0.01	4.5 (2.7)	74	2.1 (1.8)	5.8 (2.1)	<0.01

PhGA (0-10)	1.8 (1.6)	79	1.2 (1.2)	2.2 (1.7)	<0.01	1.7 (1.5)	87	1.3 (1.3)	2.0 (1.6)	<0.05
ASAS-HI (0-17)	6.7 (3.3)	63	5.0 (3.1)	7.6 (3.0)	<0.01	6.9 (3.4)	66	5.0 (2.6)	7.8 (3.3)	<0.01
HAQ-S (0-3)	0.8 (0.5)	71	0.5 (0.4)	1.0 (0.5)	<0.01	0.9 (0.5)	74	0.5 (0.4)	1.1 (0.5)	<0.01
BASFI (0-10)	4.0 (2.3)	143	2.6 (1.7)	4.9 (2.2)	<0.01	4.2 (2.4)	165	2.5 (1.8)	5.1 (2.1)	<0.01
EQ-5D (0-1)	0.77 (0.19)	63	0.90 (0.10)	0.71 (0.19)	<0.01	0.76 (0.20)	66	0.86 (0.15)	0.71 (0.21)	<0.01
SF36 MCS (0-100)	45.9 (12.6)	74	49.2 (13.2)	44.0 (11.9)	<0.05	45.9 (12.6)	79	51.1 (9.6)	43.1 (13.2)	<0.05
SF36 PCS (0-100)	39.1 (9.5)	74	45.8 (7.4)	35.3 (8.4)	<0.01	38.7 (9.4)	79	44.2 (8.2)	35.8 (8.8)	<0.01

Values are expressed as mean (SD), unless stated otherwise. Included number of patients might be lower due to missing outcome measures. Correlations are statistically significant at the 0.05 level (two-tailed). * On average, CRP levels were measured -1.4 (SD 5.7) days prior to completing the BASDAI.

ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, N = Number, NSAIDs = Non-Steroid Anti-Inflammatory Drugs, bDMARDs = biological Disease Modifying Antirheumatic drugs, SJC66 = Swollen Joint Count of 66 joints, BSA = Body Surface Area, PGA = Patient Global Assessment, CRP = C-Reactive Protein, VAS= Visual Analog Scale, PhGA = Physician Global Assessment, ASAS-HI = Assessment of SpondyloArthritis international Society Health Index, HAQ-S = Health Assessment Questionnaire for Spondyloarthritis, BASFI = Bath Ankylosing Spondylitis Functional Index, EQ-5D = EuroQol 5D, SF36 = Medical Outcomes Study 36-Question Short Form, MCS = Mental Component Summary, PCS = Physical Component Summary

Table 3 Specifications of adapted treatment in patients with HDA at the first or second measurement within a 1-year period

	Patients with ASDAS HDA (≥2.1) and adapted treatment N = 21	**Patient with BASDAI HDA (≥4.0) and adapted treatment N = 21**
Started (additional) treatment, n (%)	9 (42.9)	9 (42.9)
Intensifying dosage and/or frequency of drug treatment, n (%)	5 (23.8)	3 (14.3)
Switched within treatment class*, n (%)	6 (28.6)	8 (38.1)
Switched to another treatment class*, n (%)	1 (4.8)	1 (4.8)

*Treatments classes are non-Steroid Anti-Inflammatory Drugs (NSAIDs), Disease Modifying Anti-rheumatic drugs (DMARDs) or biological Disease Modifying Anti-rheumatic drugs (bDMARDs)

Table 4 Comparison of characteristics of patients with HDA in whom treatment was adapted or not adapted

	ASDAS ≥2.1			BASDAI ≥4.0		
Patient and disease characteristics	**Treatment not adapted** n = 93	**Treatment adapted** n = 21	**p-value**	**Treatment not adapted** n = 110	**Treatment adapted** n = 21	**p-value**
Female, n (%)	44 (47.3)	9 (42.9)	0.81	51 (46.4)	8 (38.1)	0.33
Age, years	51.8 (13.5)	50.0 (12.2)	0.58	52.3 (13.7)	49.1 (12.0)	0.32
Occupational status			0.10			0.16
Employed, n (%)	31 (33.3)	7 (33.3)	-	31 (28.2)	8 (38.1)	-
Retired, n (%)	7 (7.5)	0 (0.0)	-	8 (7.3)	0 (0.0)	-
Disabled for work, n (%)	9 (9.7)	6 (28.6)	-	11 (10.0)	5 (23.8)	-
Other, n (%)	7 (7.5)	0 (0.0)	-	7 (6.4)	0 (0.0)	-
Unknown, n (%)	39 (41.9)	8 (38.1)	-	53 (48.2)	8 (38.1)	-
Symptom duration, years	24.6 (13.9)	22.8 (12.7)	0.73	23.9 (14.1)	20.4 (14.7)	0.45
Disease duration, years	16.6 (13.2)	15.5 (11.4)	0.80	16.8 (12.8)	13.2 (11.7)	0.14
Current use of NSAIDs, n (%)	57 (61.3)	13 (61.9)	1.00	59 (53.6)	14 (66.7)	0.34
Current use of bDMARDs, n (%)	49 (52.7)	15 (71.4)	0.15	57 (51.8)	13 (61.9)	0.48
Number of current and prior used bDMARDs			0.19			<0.05
None, n (%)	39 (41.9)	6 (28.6)	-	45 (40.9)	6 (28.6)	-
1, n (%)	22 (23.7)	8 (38.1)	-	25 (22.7)	11 (52.4)	-
2, n (%)	12 (12.9)	5 (23.8)	-	17 (15.5)	2 (9.5)	-
≥3, n (%)	20 (21.5)	2 (9.5)	-	23 (20.9)	2 (9.5)	-
Active peripheral arthritis (SJC66>=1), n (%)	4 (4.3)	2 (9.5)	0.52	3 (2.7)	2 (9.5)	0.39
Active psoriasis (BSA >=3%), n (%)	1 (1.1)	0 (0.0)	0.64	0 (0.0)	0 (0.0)	0.65
ASDAS	2.9 (0.6)	3.4 (0.7)	<0.01	2.9 (0.7)	3.4 (0.8)	<0.01
BASDAI (0-10)	5.7 (1.6)	6.0 (1.7)	0.50	6.0 (1.4)	6.3 (1.3)	0.21
PGA (0-10)	5.6 (2.1)	6.5 (1.7)	0.06	5.4 (2.4)	6.8 (1.9)	<0.05
CRP, mg/L (0-∞)	6.0 (8.2)	8.9 (9.1)	<0.05	5.0 (6.9)	8.5 (9.1)	<0.05
VAS pain (0-10)	5.5 (2.1)	6.3 (1.7)	0.26	5.7 (2.1)	6.7 (1.7)	0.15
PhGA (0-10)	1.8 (1.4)	3.3 (1.9)	<0.05	1.6 (1.4)	3.0 (2.0)	<0.05
ASAS-HI (0-17)	7.5 (2.7)	8.0 (3.9)	0.62	7.5 (3.3)	9.0 (3.2)	0.22

HAQ-S (0-3)	1.0 (0.5)	1.1 (0.5)	0.50	1.1 (0.5)	1.1 (0.5)	0.88
BASFI (0-10)	4.9 (2.2)	5.0 (2.4)	0.84	5.1 (2.1)	5.4 (2.2)	0.61
EQ-5D (0-1)	0.70 (0.21)	0.73 (0.13)	0.96	0.70 (0.22)	0.72 (0.13)	0.68
SF36 MCS (0-100)	44.2 (12.8)	42.8 (9.6)	0.73	44.2 (12.9)	38.3 (13.7)	0.19
SF36 PCS (0-100)	35.6 (8.7)	33.5 (8.3)	0.48	35.8 (8.9)	34.9 (9.9)	0.75

Values are expressed as mean (SD), unless stated otherwise, Included number of patients might be lower due to missing outcome measures, Correlations are statistically significant at the 0.05 level (two-tailed).

ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, N = Number, NSAIDs = Non-Steroid Anti-Inflammatory Drugs, bDMARDs = biological Disease Modifying Antirheumatic drugs, SJC66 = Swollen Joint Count of 66 joints, BSA = Body Surface Area, PGA = Patient Global Assessment, CRP = C-Reactive Protein, VAS= Visual Analog Scale, PhGA = Physician Global Assessment, ASAS-HI = Assessment of SpondyloArthritis international Society Health Index, HAQ-S = Health Assessment Questionnaire for Spondyloarthritis, BASFI = Bath Ankylosing Spondylitis Functional Index, EQ-5D = EuroQol 5D, SF36 = Medical Outcomes Study 36-Question Short Form, MCS = Mental Component Summary, PCS = Physical Component Summary