Running Head: Stopping TNFi in rheumatoid arthritis patients in stable low disease activity.

Title: Stopping Tumor Necrosis Factor-inhibitors in Patients with Established Rheumatoid Arthritis in Remission or Stable Low Disease Activity: A Pragmatic Randomized Multicenter Open-Label Controlled Trial.

Authors: Marjan Ghisti Moghadam, MD; Harald E. Vonkeman, MD, PhD; Peter M. ten Klooster, PhD; Janneke Tekstra, MD, PhD; Dirkjan van Schaardenburg, MD, PhD; Miriam Starmans-Kool, MD, PhD; Elisabeth Brouwer, MD, PhD; Reinhard Bos, MD, PhD; Willem F. Lems, MD, PhD; Edgar M. Colin, MD, PhD; Cornelia F. Allaart, MD, PhD; Inger L. Meek, MD, PhD; Robert Landewé, MD, PhD; Hein J. Bernelot Moens, MD, PhD; Piet L.C.M. van Riel, MD, PhD; Mart A.F.J. van de Laar, MD, PhD; Tim L. Jansen, MD, PhD; on behalf of the Dutch National POET Collaboration.

Affiliations: 1) Arthritis Center Twente MST & University of Twente, Enschede, The Netherlands.

2) University Medical Center Utrecht, Rheumatology, Utrecht, The Netherlands.

3) VU University Medical Center & Reade Medical Center, Rheumatology, Amsterdam, The Netherlands.

4) Atrium Medical Center, Rheumatology, Heerlen & Orbis Medical Center, Rheumatology, Geleen – Sittard, The Netherlands.

5) University Medical Center Groningen, Rheumatology, Groningen, The Netherlands.

6) Medical Center Leeuwarden, Rheumatology, Leeuwarden, The Netherlands.

7) VU University Medical Center & Reade Medical Center, Rheumatology, Amsterdam, The Netherlands.

8) Ziekenhuis groep Twente Almelo & Ziekenhuis groep Twente Hengelo, Rheumatology, The Netherlands.

9) Leiden University Medical Center, Rheumatology, Leiden, The Netherlands.

10) Radboud University Medical Center, Rheumatology, Nijmegen, The Netherlands.

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11) AMC Amsterdam, Rheumatology, Amsterdam, the Netherlands.

12) Ziekenhuis groep Twente Almelo & Ziekenhuis groep Twente Hengelo, Rheumatology, The Netherlands.

13) Viecuri Medical Center, Rheumatology, Venlo, The Netherlands.

**Corresponding Author and address for reprint requests:**

Marjan Ghiti Moghadam, MD,

Arthritis Center Twente MST & University of Twente,

Ariënsplein 1

7511 JX Enschede

The Netherlands

Ph: +31 53 487 2450

Fax: +31 53 487 3601

e-mail: m.ghitimoghadam@mst.nl

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ABSTRACT

Objective: TNF-inhibiting biologicals (TNFi) are effective treatments for rheumatoid arthritis (RA). It is unclear if patients in remission or in stable low disease activity need to continue TNFi or can stop this treatment. This study was undertaken to assess whether established RA patients in remission or stable low disease activity can effectively and safely stop their TNFi therapy.

Methods: Pragmatic multicenter open-label randomized controlled trial. Inclusion criteria: patients diagnosed with RA according to the ACR 1987 criteria, using a TNFi for at least 1 year with stable dose DMARDs over the last 6 months, DAS28 <3.2 over the last 6 months. Patients were randomized to either stop or continue their current TNFi in a 2:1 ratio. Flare was defined as DAS28 ≥3.2 with an increase ≥0.6 compared to the baseline DAS28.

Results: 531 patients were allocated to the stop group and 286 to the TNFi continuation group. At 12 months, more patients in the stop group (272/531 [51.2%]) had experienced a flare than in the continuation group (52/286 [18.2%]; P <0.001). The hazard ratio for flare after stopping TNFi was 3.50 (95% CI: 2.60-4.72). Mean DAS28 scores in the stop group were significantly higher during the follow-up period compared with the continuation group (p<0.001). Of the 195 patients that restarted TNFi after a flare within 26 weeks, 165 (84.6%) had regained DAS28 <3.2 six months later and median time to regained DAS28 <3.2 was 12 weeks (95% CI: 10.8-13.2). There were more hospitalizations in the stop group than in the continuation group (6.4% vs 2.4%).

Conclusion: Stopping TNFi treatment in established RA patients in remission or stable low disease activity results in substantially more flares than continuing.
Modern pharmacotherapy in rheumatoid arthritis (RA) is characterized by early intensive therapy and treatment to the target of remission. Guidelines propagate starting patients on Disease Modifying Anti-Rheumatic Drugs (DMARDs) as soon as possible to achieve clinical remission. When targets are not met treatment should be intensified by increasing or combining conventional synthetic (cs)DMARDs or by adding biologics such as tumor necrosis factor inhibitors (TNFi) (1–5). However, current guidelines do not provide clear recommendations on treatment strategies after remission or stable low disease activity has been reached (4,5).

TNFi are known to increase the risk of infections and possibly some forms of cancer (6–8). They are also expensive as compared to treatment with conventional synthetic DMARDs. While there have been many studies demonstrating the efficacy of adding TNFi to csDMARDs in attaining disease remission (9–11), few randomized studies into subsequent stopping or tapering TNFi are available. Several small observational studies have suggested that 25-60% of RA-patients on a combination of methotrexate and TNFi may retain low disease activity after stopping their TNFi (12–17). Some studies also suggest that in the majority of these patients TNFi can be restarted with similar efficacy (12,18).

There is growing evidence that it may be possible to discontinue TNFi in patients with remission or stable low disease activity. However, it is unclear if TNFi can be effectively and safely restarted if necessary. At present, patients without notable complications or side effects are often kept on TNFi indefinitely. Because of the potentially avoidable risks and expenses of long-term TNFi treatment, we undertook a nation-wide pragmatic randomized multicenter open-label controlled trial to examine whether established RA-patients with remission or stable low disease activity can safely and effectively stop TNFi.
PATIENTS AND METHODS

Setting and Patients

This pragmatic randomized open-label controlled trial was conducted at 47 rheumatology centers throughout the Netherlands. Written informed consent was obtained from all study patients. Eligibility criteria included: age >18 years, RA diagnosis according to the American College of Rheumatology 1987 criteria (19), TNFi treatment for at least one year with stable concomitant csDMARDs use for at least six months prior to inclusion. Patients were in remission or had stable low disease activity for at least six months, defined as either Disease Activity Scores in 28-joints (DAS28) (20) <3.2 or the rheumatologists’ clinical impression of remission or stable low disease activity in combination with a baseline DAS28 <3.2 and at least one C-reactive protein (CRP) level <10 mg/L in the six months prior to inclusion. There were no exclusion criteria. Study inclusion took place from March 2012 to March 2014.

The study was approved by the Ethical Review Boards of all participating hospitals. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The study (POET study) is registered in the Netherlands Trial Register, number NTR3112.

Intervention

Patients were randomized 2:1 to either stop or continue their TNFi. Computer block randomization was used to achieve balance in allocation per center. All other medications, including csDMARDs, glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs), were left at the discretion of the treating rheumatologists and were continued unchanged as much as possible. In case of flare, defined as a DAS28 ≥3.2 plus an increase ≥0.6 compared to the baseline DAS28, TNFi treatment could be restarted in the stop group or switched in the continuation group.

Outcomes and Follow-up

Baseline Measurements
Baseline characteristics included: age, sex, weight, length, disease duration, medication use, rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody status.

**Efficacy Assessments**

Patients were evaluated by the treating rheumatologist and rheumatology nurse, at baseline and at least once every three months thereafter, or more often if needed, for a period of one year, in accordance with current Dutch guidelines for the diagnosis and treatment of RA (3). Clinical measurements, which are part of standard rheumatology care, were performed at every visit and included a tender joint count in 28 joints (TJC28), a swollen joint count in 28 joints (SJC28), erythrocyte sedimentation rate (ESR), and a patient-reported assessment of general health on a 100 mm visual analog scale (VAS-GH). Together, these components were combined into the composite Disease Activity Score for 28 joints (DAS28) (12). DAS28 scores range from 0 to approximately 10 with scores ≤ 3.2, between 3.2 and 5.1, and > 5.1 indicating low, moderate and high disease activity, respectively (21). A score < 2.6 corresponds to clinical remission (22). Patients were encouraged to immediately report any adverse events or disease flares to their treating rheumatologist. Physician-reported flares and changes in medication were recorded at each scheduled or unscheduled visit. Patients additionally completed the health assessment questionnaire disability index (HAQ-DI; range 0–3, higher scores indicating more disability) (23) at baseline and before every study visit. All data were collected and stored using a tailor-made web based data management system.

**Safety Assessments**

Patients were closely monitored for adverse events. Clinical and laboratory results were assessed at each three-monthly visit. Adverse events were recorded at every visit.

**Clinical End Point**

The primary end point of the study was the proportion of patients with a flare during 12-months follow-up. Flare was defined as at least one DAS28 ≥3.2 plus an increase >0.6
compared to the baseline DAS28 (24). Secondary endpoints were time to flare, change from baseline in DAS28 score, change in functional status, the number of patients and time to regaining remission (DAS28 <2.6) or low disease activity (DAS28 <3.2) after restarting TNFi (only in the stop group) and the proportion of patients with (serious) adverse events.

**Statistical Analysis**

The projected sample size for the POET study was based on an estimated proportion of 40% flares in the stop group (12) and a 2:1 randomization ratio. The formal sample size calculation indicated that 869 patients would be needed to provide 80% power to detect a difference of at least 10% between both groups (α=0.05). To compensate for an estimated 10–15% dropout, the study protocol conservatively aimed to include 1000 patients (667 in the stop group and 333 in the continuation group) within 1 year.

During the enrollment phase of the trial it became clear that recruitment was at a slower pace than anticipated and that the target sample size could not be achieved. After an extension of the planned inclusion period with one year, a total of 819 patients had been randomized. Because of slowing enrollment during the final months, while observing a lower than anticipated dropout rate, the steering committee decided to stop enrolment by the end of March 2014. Although not completely satisfactory, the estimated power of the study to detect a ≥10% difference between both groups remained as high as 77%.

If a DAS28 score could not be calculated because of a missing value for ESR or VAS-VGH, this value was imputed by means of the expectation-maximization algorithm using the patient's values of the remaining components of the DAS28. Missing values for all DAS28 assessments were 8.3%, 8.9%, 10.4% and 15.3% at 3, 6, 9 and 12 months visits, respectively. The primary analysis was performed on the basis of intention to treat in patients that were correctly included. The proportions of patients in both groups with a flare within 6 and 12 months of follow-up were compared by separate $\chi^2$ tests. Patients who dropped out early without flare were assumed to remain in remission. Additional modified intention to treat analyses were performed using a ‘worst-case scenario’, in which all correctly included
patients without flare but with a missing DAS28 score at 3 or 6 months, or 9 and 12 months, respectively, were counted as flare in the stop group and non-flare in the continuation group.

Time to DAS28 flare was examined using Kaplan-Meier survival analysis. In this analysis, patients who dropped out before 12 months without flare were censored at the time of withdrawal. Between-group difference in survival was tested by the log rank test. Additional stratified survival analysis in the stop group was performed by the type of TNFi.

Next, sensitivity analyses were performed by repeating the survival analyses using ‘physician-reported flare’ and ‘medication escalation’ (defined as reinitiating TNFi or starting or increasing any biological or non-biological DMARD (including glucocorticoids)) as dependent variables. An additional survival analysis compared the time course of incidence of patients remaining in DAS28 remission throughout the 12 months of follow-up in both groups.

Multivariable Cox proportional hazards regression with backward selection (P <0.05) was used to explore potential independent predictors of time to flare. Predictors considered (besides stopping TNFi) were sex, age (split at 60 yrs.), baseline DAS28 score, RF and anti-CCP status, disease duration (split at 10 yrs.), overweight (body mass index [BMI] ≥25) and number of TNFi used previously (12,16,25).

Mean DAS28 and HAQ-DI scores over time were compared using linear mixed modeling with a compound symmetry structure for the covariance matrix and the group*time interaction as fixed factor. Post-hoc analyses of covariance with baseline value as covariate were performed to test between-group differences at the different time points.

In the stop group, the number of patients regaining remission (DAS28 <2.6) or low disease activity (DAS28 <3.2) after restarting TNFi within 26 weeks after stopping and time to regained remission were examined using Kaplan-Meier survival analysis.

Safety data were reported descriptively and tested with Fisher's exact tests if appropriate. All analyses were performed using SPSS, version 22.
RESULTS
Baseline Characteristics of Patients

In total, 817 patients were correctly included, of which 531 were randomized into the TNFi stop group and 286 to the TNFi continuation group (Figure 1). From these, 672 patients (82.3%) were included based at least two available DAS28 scores <3.2 and 145 (17.7%) based on the rheumatologists’ impression in combination with at least one available CRP value. Two patients were incorrectly included and excluded immediately after randomization because they did not meet the criteria. Thirty-four patients dropped out during the first 12 months of follow-up on their own decision (n=28), because of comorbidity (n=5) or death (n=1). The proportion of dropouts was slightly higher in the continue group vs the stop group (17 out of 531 [3.2%] vs 17 out of 286 [5.9%] patients, P=0.06).

Baseline demographics and disease characteristics were similar in both groups (Table 1). Patients were typically older Dutch Caucasian females, with longstanding RF positive erosive RA. Most were on their first TNFi, primarily adalimumab (49.0%) or etanercept (42.4%). Around 4.9% were receiving glucocorticoids at baseline. Patients had stable low disease activity, in accordance with study inclusion criteria, and 653 patients (79.9%) were formally in remission (DAS28 <2.6).

Flare Rates and Survival

At the time of analysis, follow-up time for all patients was 12 months. Significantly more patients in the stop group experienced a flare within 6 months (213 out of 531 [40.1%] vs 34 out of 286 [11.9%] patients, p<0.001) or within 12 months (272 out of 531 [51.2%] vs 52 out of 286 [18.2%] patients, P<0.001) compared with the continuation group. There was no difference in the proportion of patients in the stop group experiencing a flare within 12 months between patients that were included based on available DAS28 scores vs those that were included based on the rheumatologists’ clinical impression plus CRP (51.2% vs 51.5%, respectively, P = 0.944). In worst-case scenario analyses, the number of patients with a flare in the stop group was 258 (48.6%) and 327 (61.6%) at 6 and 12 months, respectively.
Kaplan-Meier analysis confirmed that flare-free survival was significantly (P<0.001) lower in the stop group than in the continuation group (Figure 2). The hazard ratio (HR) for flare after stopping TNFi was 3.50 (95% CI: 2.60–4.72). There was no significant difference in time to flare by the type of TNFi that was stopped (log rank 2.24, P = 0.691). Sensitivity analysis with ‘physician-reported flare’ and ‘medication escalation’ as the criteria for flare gave similar results, although 12-month flare rates were somewhat higher for both ‘physician-reported flares’ (293 out of 531 [55.2%]) and ‘medication escalation’ (305 out of 531 [57.4%]) in the stop group and lower in the ‘continuation group’ (21 out of 531 [7.3%] and 32 out of 286 [11.2%], respectively) (Supplementary Figure 1). Flare-free survival was significantly (P <0.001) lower for the stop group using both alternative anchors for flare. From all patients in remission at baseline, 127 out of 428 (29.7%) in the stop group vs 128 out of 225 (56.9%) in the continuation group (P<0.001) remained in DAS28 remission throughout the 12-month study period (Supplementary Figure 2).

Predictors of time to flare
Besides stopping TNFi, higher baseline DAS28 scores (HR 1.39; 95% CI 1.21–1.60) and more than 10 years disease duration (HR 1.29; 95% CI 1.03–1.61) remained independently associated with a shorter time to flare in multivariable Cox regression. The adjusted HR for stopping TNFi was 3.70 (95% CI: 2.72–5.03).

Disease activity and functional status over time
The mixed effect model for disease activity showed a significant (P <0.001) interaction between time and group, indicating that mean DAS28 in the stop group was significantly different over time compared with the continuation group (Figure 3). Post-hoc analyses confirmed that DAS28 scores were significantly higher in the stop group at all follow-up time points (P’s <0.001). In both groups, mean DAS28 scores remained below the threshold for moderate disease activity. A similar, though less pronounced, pattern was seen for functional status. HAQ-DI scores also demonstrated a significant group*time interaction (P = 0.017) and
mean scores in the stop group were slightly, but significantly, higher at 3 (P = 0.023), 6 (P = 0.002) and 12 (P = 0.021) months.

**Regained Disease Control**

In total, 252 of 531 patients (47.5%) in the stop group restarted TNFi after flare. Of the 195 patients that restarted within 26 weeks after inclusion, 132 (67.7%) achieved clinical remission and an additional 33 (16.9) regained low disease activity within 26 weeks. Median time to regained low disease activity or remission upon flare was 12 (95% CI: 10.7–13.3) and 14 weeks (95% CI: 11.2–16.8) respectively.

**Safety**

There were 42 reported serious adverse events (*Supplementary Table 1 and 2*); 1 death (due to an infection in the continuation group) and 41 hospitalizations (34 [6.4%] in the stop group vs 7 [2.4%] in the continuation group, P = 0.012). Eleven [2.1%] hospitalizations due to infection occurred in the stop group vs 4 [1.4%] in the continuation group. Hospitalization due to malignancy was reported in 5 patients [0.9%] in the stop group vs 3 patients [1.0%] in the continuation group. There were also 4 cases of elective surgery in the stop group: carpal tunnel syndrome, hip osteoarthritis, transurethral resection of the prostate, and fistula excision. Of the 34 hospitalizations in the stop group, 24 were judged as unrelated and 10 were judged as possibly related to (stopping) TNFi. In the continuation group, 2 of 7 hospitalizations were judged unrelated to, and 5 possibly related to continuing TNFi. Additionally, there were 143 adverse events (95 [17.9%] in the stop group vs 48 [16.8%] in the continuation group). Among the patients in the stop group that restarted TNFi, no allergic reactions were reported.
DISCUSSION

In this study we demonstrate that stopping TNFi in patients with established RA in remission or stable low disease activity results in significantly more flares than continuation of TNFi. Patients who stopped TNFi had a more than threefold increased risk of experiencing a flare within 12 months of follow-up as compared to those who continued. Mean disease activity in the stop group was significantly increased throughout the follow-up period compared with the continuation group, although the vast majority of patients remained well below the threshold for moderate disease activity. After restarting TNFi treatment most patients in the stop group quickly regained low disease activity or remission. There were no notable safety issues associated with stopping and restarting TNFi, but the total number of hospitalizations was significantly higher in the stop group.

The finding that stopping TNFi treatment resulted in more flares is robust, both statistically and clinically and because sensitivity analyses using other definitions of flare yielded similar results. Previous studies of stopping TNFi have shown more divergent results, possibly due to heterogeneity in study designs, definitions of flare and thresholds for disease activity before inclusion. Also, the use of concomitant csDMARDs was not clearly reported in most of these studies.

Recent results from the US Corrona registry suggested that 73.4% of 717 patients maintained benefit for more than 12 months after stopping their first TNFi (25). All other previous studies examined stopping specific TNFi. The results from an extension of the HONOR study, an open-label non-randomized trial in Japan, showed that 48% of 75 RA patients maintained remission and 62% maintained low disease activity for at least 12 months after stopping adalimumab (18). In the smaller retrospective BRIGHT study, however, only 18% of 22 patients who discontinued their adalimumab monotherapy maintained low disease activity after 12 months (26). In the observational RRR study, again from Japan, 55% of 102 patients who stopped infliximab maintained low disease activity at 12 months follow-up (13). Finally, a post-hoc analysis of the BeSt study from the Netherlands showed that 80% of 104 patients who stopped infliximab maintained low disease activity for
at least 12 months (16). The high rate of successful discontinuation of infliximab in the BeSt study may be explained by the very early initial treatment with the TNFi infliximab, whereas in the RRR study infliximab was only started after failure of multiple csDMARDs (16).

Although patients in the stop group were clearly at increased risk of experiencing a flare within 12 months, the finding that even in patients with established RA almost half could stop TNFi treatment could be considered a promising result. To date, only two randomized controlled trials of stopping TNFi have been published. Both studies addressed stopping the TNFi etanercept. In the PRESERVE study, a randomized placebo-controlled trial in 834 patients (80 centers world-wide), 604 patients with sustained low disease activity were randomized to stopping or continuing etanercept (27). Results of the PRESERVE study were very similar to the current trial, with 42.6% of the patients in the stop group vs 82.6% in the continuation group maintaining low disease activity at 12 months follow-up. In the DOSERA study, a European randomized placebo-controlled trial of 73 participants with low disease activity prior to discontinuation of etanercept, only 13% patients had flare-free survival after 48 weeks (28). In this study, however, different criteria were used to identify possible flare, including patient reported flare.

The current study only examined stopping TNFi completely. Several previous studies (additionally) examined the effects of TNFi dose reduction. Four randomized controlled trials compared etanercept reduction vs stopping or continuation (27–30). Although reduced dosing generally resulted in an increased flare risk, outcomes were better than with stopping. Recently, van Herwaarden et al. (31) showed that disease activity guided dose reduction of adalimumab and etanercept was non-inferior to dose maintenance with respect to the occurrence of major flares, defined as DAS28 flares with a duration longer than 3 months. However, the incidence of DAS28 flares of shorter duration was significantly higher in the dose reduction group than the continuation group, with proportions similar to those found in the current study.

Survival analysis showed that 83.1% of the patients regained low disease activity quickly after restarting TNFi, with a median time to regained low disease activity of 12 weeks.
This corresponds well with previous studies that examined this endpoint. In the HONOR study, restarting adalimumab was effective in regaining low disease activity in 90% of patients within 6 months and in 100% of patients after 9 months (18). In the BeSt study, 84% regained low disease activity after restarting infliximab within a median of 3 months (16). In the RRR study, re-treatment with infliximab also resulted in regained low disease activity in the majority of patients within 6 months (12). As the current study was limited to 12 months follow-up, it was not possible to assess if and when the remaining 16.9% of patients regained low disease activity.

In the current study, 57.4% of the patients needed a medication escalation after stopping their TNFi, usually starting or increasing csDMARDs, compared with 11.2% of the patients in the continuation group. Only the BRIGHT study also reported on this outcome, showing no significant differences between the patients who stopped or continued adalimumab (26).

There was no significant difference in drop-out rate between the stop and continuation groups, although the rate was numerically higher in the stop group. There were more hospitalizations in the stop group than in the continuation group (6.4% vs 2.4%). Most hospitalizations in the stop group were due to infections, elective surgery or surgery because of malignancies or fractures. Most of these hospitalizations were not considered to be related to the intervention. The PRESERVE study likewise reported no statistically significant difference in the total number of adverse events between the etanercept stop and continuation groups (27). Additionally, there were no notable (serious) adverse events after restarting TNFi. One major concern in stopping and restarting infliximab is the possibility of augmented infusion reactions due to antibody development between administrations. In the RRR and BeSt studies minimal infusion reactions were seen after restarting infliximab in 4.9% and 10% of patients, respectively (12,16).

Our study has several strengths. It is the largest pragmatic randomized controlled trial on stopping TNFi in RA patients in remission or stable low disease activity to date. This non-industry-funded trial is the product of nationwide consensus among investigators in the
Netherlands. Most patients had long disease duration (established RA) and an average age of 60 years, which is representative of the TNFi using RA population in the Netherlands. We further used strictly protocolled electronic data collection, including safety monitoring. Additionally, we used a strict, discriminatory and valid criterion for flare based on a combination of a threshold and a change over time in DAS28, whereas most other studies focused on achieving an absolute DAS28 cut-off only. The latter may be more sensitive but may lack specificity (24).

The study has some limitations. It is an open-label study, which may have influenced patients and rheumatologists in their interpretation of disease activity and their decisions to change medication. Secondly, the study had a standard follow-up of 12 months, which may have been too short to examine the persistence of the effects of stopping TNFi.

In conclusion, stopping TNFi treatment in RA patients in remission or stable low disease activity results in substantially more flares than continuing.
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Table 1. Baseline Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stop TNFi (n=531)</th>
<th>Continue TNFi (n=286)</th>
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<tr>
<td>Female, n (%)</td>
<td>362 (68.2%)</td>
<td>188 (66.0%)</td>
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<tr>
<td>Mean age (SD), y</td>
<td>60.0 (11.8)</td>
<td>59.7 (10.6)</td>
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<tr>
<td>Mean disease duration (SD), y</td>
<td>12.0 (8.8)</td>
<td>11.1 (8.4)</td>
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<td>Mean DAS28 (SD)</td>
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<td>2.05 (0.73)</td>
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<tr>
<td>Mean BMI (SD), kg/m²</td>
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<td>26.2 (4.5)</td>
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<td>RF positive, n (%)</td>
<td>328 (67.5%)</td>
<td>178 (67.4%)</td>
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<td>Anti-CCP positive, n (%)</td>
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TNFi = tumor necrosis factor-alpha inhibitor; DAS28 = disease activity score in 28 joints; RF = rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide; BMI = Body Mass Index; csDMARD = conventional synthetic disease modifying anti-rheumatic drug.
Figure 1. **Study flow chart**

Figure 2. **Kaplan-Meier curves for DAS28 flare-free survival.** The solid line represents the stop group, the dashed line represents the continuation group.

Figure 3. **Mean DAS28 (top panel) and HAQ-DI (bottom panel) scores over time.** The grey lines in the upper panel represent thresholds for low disease activity (DAS28 <3.2) and remission (DAS28 <2.6). Error bars represent 95% confidence intervals. * $P < 0.05$ and ** $P < 0.001$ for between group differences.
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<td>Adalimumab, n (%)</td>
<td>271 (51.1%)</td>
<td>129 (45.1%)</td>
</tr>
<tr>
<td>Etanercept, n (%)</td>
<td>213 (40.2%)</td>
<td>133 (46.5%)</td>
</tr>
<tr>
<td>Infliximab, n (%)</td>
<td>25 (4.7%)</td>
<td>14 (4.9%)</td>
</tr>
<tr>
<td>Golimumab, n (%)</td>
<td>15 (2.8%)</td>
<td>8 (2.8%)</td>
</tr>
<tr>
<td>Certolizumab, n (%)</td>
<td>6 (1.1%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Number of TNFi</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st, n (%)</td>
<td>459 (86.6%)</td>
<td>243 (85.0%)</td>
</tr>
<tr>
<td>2nd, n (%)</td>
<td>61 (11.5%)</td>
<td>37 (12.9%)</td>
</tr>
<tr>
<td>3rd, n (%)</td>
<td>10 (1.9%)</td>
<td>6 (2.1%)</td>
</tr>
<tr>
<td>csDMARD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate, n (%)</td>
<td>437 (82.3%)</td>
<td>242 (84.6%)</td>
</tr>
<tr>
<td>Methotrexate + glucocorticoids, n (%)</td>
<td>22 (4.1%)</td>
<td>10 (3.5%)</td>
</tr>
<tr>
<td>Glucocorticoids, n (%)</td>
<td>7 (1.3%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Other DMARD, n (%)</td>
<td>36 (6.8%)</td>
<td>22 (7.7%)</td>
</tr>
<tr>
<td>No DMARD, n (%)</td>
<td>29 (5.5%)</td>
<td>11 (3.8%)</td>
</tr>
</tbody>
</table>

TNFi = tumor necrosis factor-alpha inhibitor; DAS28 = disease activity score in 28 joints; RF = rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide; BMI = Body Mass Index; csDMARD = conventional synthetic disease modifying anti-rheumatic drug.
Figure 1. Study flow chart

Assessed for eligibility (n=311)
- Excluded (n=12)
  - Declined to participate (n=11)
  - Not meeting inclusion criteria (n=1)

Randomized (n=819)
- False inclusion (n=1)

Stop TNFi
  - n = 531
    - Discontinued intervention
      - Own decision (n=13)
      - Comorbidity (n=3)
      - Death (n=1)

Completed study (n=514)
- Analyzed (n=531)

Continue TNFi
  - n = 286
    - Discontinued intervention
      - Own decision (n=15)
      - Comorbidity (n=2)

Completed study (n=209)
- Analyzed (n=286)
Figure 2. Kaplan-Meier curves for DAS28 flare-free survival. The solid line represents the stop group, the dashed line represents the continuation group.

Log rank: 81.9; $P < 0.001$
Figure 3. Mean DAS28 (top panel) and HAQ-DI (bottom panel) scores over time. The grey lines in the upper panel represent thresholds for low disease activity (DAS28 <3.2) and remission (DAS28 <2.6). Error bars represent 95% confidence intervals. * P < 0.05 and ** P < 0.001 for between group differences.