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Stopping Tumor Necrosis Factor Inhibitor Treatment in Patients With Established Rheumatoid Arthritis in Remission or With Stable Low Disease Activity

A Pragmatic Multicenter, Open-Label Randomized Controlled Trial

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Objective. **Tumor necrosis factor inhibitor (TNFi) biologic agents are an effective treatment for rheumatoid arthritis (RA). It is unclear whether patients whose disease is in remission or who have stable low disease activity need to continue use of TNFi or can stop this treatment. This study was undertaken to assess whether patients with established RA who are in remission or have stable low disease activity can effectively and safely stop their TNFi therapy.**

Methods. **The study was designed as a pragmatic multicenter, open-label randomized controlled trial. Inclusion criteria were a diagnosis of RA according to the American College of Rheumatology 1987 classification criteria, as well as use of a TNFi for at least 1 year along with a stable dose of disease-modifying antirheumatic drugs and a Disease Activity Score in 28 joints (DAS28) of <3.2 over the 6 months preceding trial inclusion. Patients were randomized in a 2:1 ratio to either stop or continue treatment with their current TNFi. Flare was defined as a DAS28 of ≥3.2 during the 12-month follow-up period and an increase in score of ≥0.6 compared to the baseline DAS28.**

Results. **In total, 531 patients were allocated to the stop group and 286 to the TNFi continuation group. At 12 months, more patients had experienced a flare in the stop group (272 [51.2%] of 531) than in the continuation group (52 [18.2%] of 286; $P < 0.001$). The hazard ratio for occurrence of a flare after stopping TNFi was 3.50 (95% confidence interval [95% CI] 2.60–4.72). The mean DAS28 in the stop group was significantly higher during the follow-up period compared to that in the continuation group ($P < 0.001$). Of the 195 patients who restarted TNFi treatment after experiencing a flare and within 26 weeks after stopping, 165 (84.6%) had regained a DAS28 of <3.2 by 6 months later, and the median time to a regained DAS28 of <3.2 was 12 weeks (95% CI 10.7–13.3). There were more**

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hospitalizations in the stop group than in the continuation group (6.4% versus 2.4%).

Conclusion. **Stopping TNFi treatment results in substantially more flares than does continuation of TNFi in patients with established RA in remission or with stable low disease activity.**

Modern pharmacotherapy in rheumatoid arthritis (RA) is characterized by early intensive therapy and treatment to the target of remission. Current guidelines recommend that RA patients start treatment with disease-modifying antirheumatic drugs (DMARDs) as soon as possible to achieve clinical remission. When targets are not met, treatment should be intensified by increasing the dose of DMARD or by combining it with a conventional synthetic DMARD, or by adding a biologic agent such as a tumor necrosis factor inhibitor (TNFi) (1–5). However, the current guidelines do not provide clear recommendations on treatment strategies after remission or stable low disease activity has been reached (4,5).

TNFi biologic agents 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 the regimen of conventional synthetic DMARDs in attaining disease remission (9–11), few randomized studies have addressed the effects of subsequently stopping or tapering the TNFi. Results of several small observational studies have suggested that 25–60% of RA patients receiving a combination of methotrexate and TNFi may retain a low level of disease activity after stopping their TNFi (12–17). Some studies have also suggested that in the majority of these patients, TNFi can be restarted, with similar efficacy (12,18).

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

PATIENTS AND METHODS

Setting and patients. The study was designed as a pragmatic open-label randomized controlled trial that was conducted at 47 rheumatology centers throughout The Netherlands. Written informed consent was obtained from all study patients. Eligibility criteria included age >18 years, a diagnosis of RA according to the American College of Rheumatology 1987 classification criteria (19), and TNFi treatment for at least 1 year, along with concomitant use of a stable dose of conventional synthetic DMARDs for at least 6 months prior to inclusion. Patients were required to be in remission or to have maintained stable low disease activity for at least six months, defined as either a Disease Activity Score in 28 joints (DAS28) (20) of <3.2 or the rheumatologist's clinical impression of remission or stable low disease activity, in combination with a baseline DAS28 of <3.2 and at least 1 C-reactive protein (CRP) level of <10 mg/liter, in the 6 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 Ethics Review Boards of all participating hospitals and was conducted in accordance with the Guidelines for Good Clinical Practice and the Declaration of Helsinki. The study (known as the POET study) is registered in The Netherlands Trial Register (clinical trials registry no. NTR3112).

Intervention. Patients were randomized 2:1 to either stop or continue treatment with their TNFi. Computer block randomization was used to achieve balance in allocation per center. All other medications, including conventional synthetic DMARDs, glucocorticoids, and nonsteroidal antiinflammatory drugs, were left at the discretion of the treating rheumatologists and were continued unchanged as much as possible. In cases of disease flare, defined as a DAS28 of ≥3.2 and an increase in score of ≥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, height, disease duration, medication use, rheumatoid factor (RF) status, and anti–cyclic citrullinated peptide (anti-CCP) antibody status.

Efficacy assessments. Patients were evaluated by their treating rheumatologist and rheumatology nurse at baseline and at least once every 3 months thereafter, or more often if needed, for a period of 1 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 the tender joint count in 28 joints, the swollen joint count in 28 joints, erythrocyte sedimentation rate (ESR), and patient-reported assessment of general health on a 100-mm visual analog scale (VAS). Taken together, these components were combined into the composite DAS28 (12). DAS28 scores range from 0 to ~10, with scores of ≤3.2, between 3.2 and 5.1, and >5.1 indicating low, moderate, and high disease activity, respectively (21). A score of <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 (HAQ) Disability Index (DI) (range 0–3, with 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 3-month 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 the 12 months of follow-up. Flare was defined as at least one DAS28 score of ≥3.2 and an increase in score of >0.6 compared to the baseline DAS28 (24). Secondary end points were time to flare, change from baseline in the DAS28 score, change in functional status, number of patients, and time to regain remission (DAS28 of <2.6) or to achieve low disease activity (DAS28 of <3.2) after restarting TNFi treatment (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 flares of 40% 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 ($\alpha = 0.05$). To compensate for an estimated 10–15% dropout rate, the study protocol conservatively aimed to include 1,000 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 occurring at a slower pace than had been anticipated, and that the target sample size could not be achieved. After an extension of the planned inclusion period for 1 year, a total of 819 patients had been randomized. Because of slowing enrollment during the final months, and a dropout rate that was lower than anticipated, the steering committee decided to stop enrollment 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 an individual patient's DAS28 could not be calculated because of a missing value for the ESR or the VAS general health score, this value was imputed by means of the expectation-maximization algorithm, using the patient's values for the remaining components of the DAS28. The frequency of missing values for all DAS28 assessments was 8.3%, 8.9%, 10.4%, and 15.3% at the 3-, 6-, 9-, and 12-month visits, respectively. The primary analysis was performed on the basis of intention to treat in patients who were correctly included. The proportions of patients in both groups who experienced a flare within 6 months and 12 months of follow-up were compared by separate chi-square tests. Patients who dropped out early and were 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-defined flare was examined using Kaplan-Meier survival analysis. In this analysis, patients without flare who dropped out before 12 months were censored at the time of withdrawal. The between-group difference in survival was tested using the log rank test. Additional stratified survival analysis in the stop group was performed according to the type of TNFi. Sensitivity analyses were then performed by repeating the survival analyses using, as dependent variables, the physician-reported incidence of flare and medication escalation (defined as reinitiation of the TNFi or starting or increasing any biologic or non–biologic DMARD [including glucocorticoids]). An additional survival analysis was carried out to compare the time course of incidence of patients remaining in DAS28-defined 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 years), baseline DAS28 score, RF and anti-CCP status, disease duration (split at 10 years), being overweight (body mass index ≥25 kg/m^2), and number of TNFi previously taken (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-by-time interaction as a fixed factor. Post hoc analyses of covariance with baseline value as the covariate were performed to test between-group differences at the different time points.

In the stop group, the number of patients regaining remission (DAS28 of <2.6) or low disease activity (DAS28 of <3.2) after restarting TNFi treatment within 26 weeks after stopping, as well as the time to regained remission, were examined using Kaplan-Meijer 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 the patients. In total, 817 patients were correctly included, of whom 531 were randomized into the TNFi stop group and 286 into the TNFi continuation group (Figure 1). Among these patients, 672 (82.3%) were included on the basis of at least 2 available DAS28 scores of <3.2, and 145 (17.7%) were included on the basis of the rheumatologist's clinical impression of remission or stable low disease activity in combination with at least 1 available CRP value. Two patients were incorrectly included, and therefore were excluded immediately after randomization because they did not meet the criteria. Thirty-four patients dropped out during the first 12 months of follow-up because of their own decision to drop out (n = 28), presence of a comorbidity (n = 5), or occurrence of death (n = 1). The proportion of patients who dropped out was slightly lower in the TNFi stop group compared to the TNFi continuation group (17 [3.2%] of 531 versus 17 [5.9%] of 286; $P = 0.06$).

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

Flare rates and survival. At the time of analysis, follow-up time for all patients was 12 months. Signif-

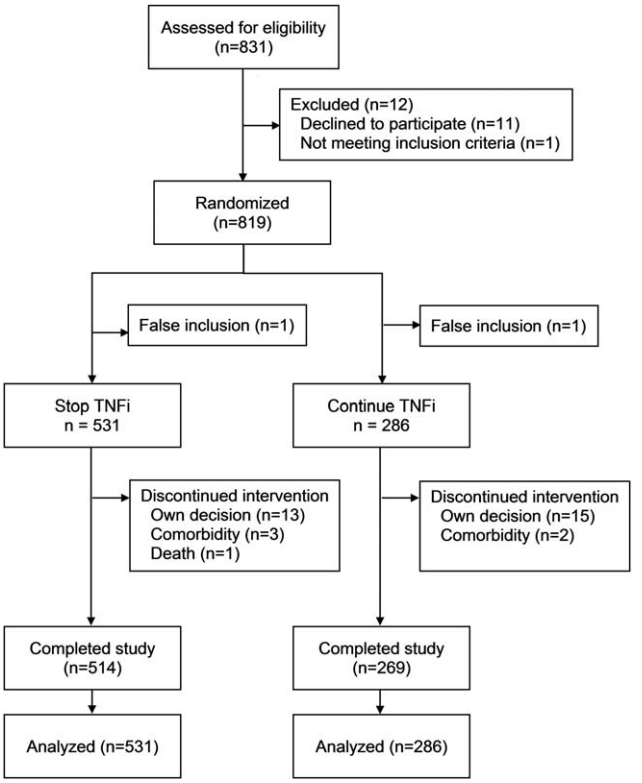

Figure 1. Study flow chart. TNFi = tumor necrosis factor inhibitor.

icantly more patients in the TNFi stop group than in the TNFi continuation group experienced a flare within 6 months (213 [40.1%] of 531 versus 34 [11.9%] of 286; $P < 0.001$) or within 12 months (272 [51.2%] of 531 versus 52 [18.2%] of 286; $P < 0.001$). There was no difference in the proportion of patients in the stop group experiencing a flare within 12 months between those who were included based on available DAS28 scores and those who were included based on the rheumatologist's clinical impression and the CRP value (51.2% versus 51.5%, respectively; $P = 0.944$). In the worst case scenario analyses, the number of patients with a flare in the stop group was 258 (48.6%) at 6 months and 327 (61.6%) at 12 months.

Kaplan-Meier survival analysis confirmed that the flare-free survival rate was significantly lower in the stop group than in the continuation group ($P < 0.001$) (Figure 2). The hazard ratio (HR) for occurrence of flare after stopping TNFi was 3.50 (95% confidence interval [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 analyses with physician-reported flare and medication escalation as the criteria for flare yielded similar results, although 12-month flare rates were somewhat higher in the stop group than in the continuation group when based on either physician-reported flare (293 [55.2%] of 531 versus 21 [7.3%] of 286) or medication escalation (305 [57.4%] of 531 versus 32 [11.2%] of 286) (details available upon request from the corresponding author). The flare-free survival rate was significantly lower in the stop group compared to the continuation group ($P < 0.001$) when both alternative anchors for flare were used. Among all patients in remission at baseline, 127 (29.7%) of 428 in the stop group compared to 128 (56.9%) of 225 in the continuation group ($P < 0.001$) remained in DAS28-defined remission throughout the 12-month study period (details available upon request from the corresponding author).

Predictors of time to flare. Besides stopping the TNFi, higher baseline DAS28 scores (HR 1.39, 95% CI 1.21–1.60) and a disease duration of >10 years (HR 1.29, 95% CI 1.03–1.61) remained independently associated with a shorter time to flare in multivariable Cox regression analyses. The adjusted HR for a shorter time to flare after 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 interaction between time and group ($P < 0.001$), indicating that the mean DAS28 in the stop group was significantly different over time compared to that in the

Table 1. Baseline characteristics of the study patients*

Characteristic	Stop TNFi (n = 531)	Continue TNFi (n = 286)
Female, no. (%)	362 (68.2)	188 (66.0)
Age, mean ± SD years	60.0 ± 11.8	59.7 ± 10.6
Disease duration, mean ± SD years	12.0 ± 8.8	11.1 ± 8.4
DAS28, mean ± SD	1.98 ± 0.76	2.05 ± 0.73
BMI, mean ± SD kg/m^2	25.9 ± 4.3	26.2 ± 4.5
RF positive, no. (%)	328 (67.5)	178 (67.4)
Anti-CCP positive, no. (%)	332 (68.3)	179 (67.8)
Erosive disease, no. (%)	305 (62.8)	152 (57.6)
TNFi, no. (%)		
Adalimumab	271 (51.1)	129 (45.1)
Etanercept	213 (40.2)	133 (46.5)
Infliximab	25 (4.7)	14 (4.9)
Golimumab	15 (2.8)	8 (2.8)
Certolizumab	6 (1.1)	2 (0.7)
Number of TNFi taken, no. (%)		
First	459 (86.6)	243 (85.0)
Second	61 (11.5)	37 (12.9)
Third	10 (1.9)	6 (2.1)
Conventional synthetic DMARD, no. (%)		
Methotrexate	437 (82.3)	242 (84.6)
Methotrexate + glucocorticoids	22 (4.1)	10 (3.5)
Glucocorticoids	7 (1.3)	1 (0.3)
Other DMARD	36 (6.8)	22 (7.7)
No DMARD, no. (%)	29 (5.5)	11 (3.8)

* TNFi = tumor necrosis factor inhibitor; DAS28 = Disease Activity Score in 28 joints; BMI = body mass index; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide; DMARD = disease-modifying antirheumatic drug.

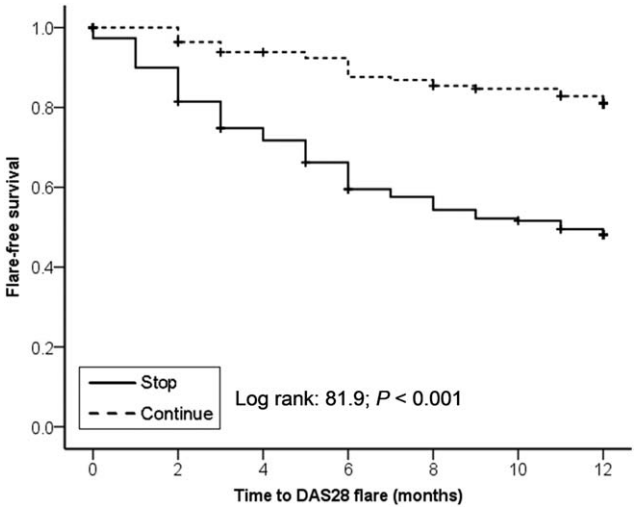

Figure 2. Kaplan-Meier curves for the rate of flare-free survival over the 12-month follow-up in patients who stopped their tumor necrosis factor inhibitor (TNFi) treatment compared to those who continued their TNFi treatment. Flare was defined as a Disease Activity Score in 28 joints (DAS28) of ≥3.2 and an increase in score of ≥0.6 compared to the baseline DAS28.

continuation group (Figure 3). Post hoc analyses confirmed that DAS28 scores were significantly higher in the stop group at all follow-up time points (all $P < 0.001$). In both groups, the mean DAS28 scores remained below the threshold for moderate disease activity.

A similar, although less pronounced, pattern was seen for functional status. HAQ DI scores also demonstrated a significant group-by-time interaction ($P = 0.017$). The mean HAQ DI scores in the stop group were slightly, but significantly, higher than those in the continuation group at 3 months ($P = 0.023$), 6 months ($P = 0.002$), and 12 months ($P = 0.021$) (Figure 3).

Regained disease control. In total, 252 (47.5%) of 531 patients in the stop group restarted their TNFi treatment after experiencing a flare. Of the 195 patients who restarted their TNFi treatment within 26 weeks after inclusion, 132 (67.7%) achieved clinical remission and an additional 33 patients (16.9%) regained low disease activity within the subsequent 26 weeks. The median time to regained low disease activity and regained remission upon flare was 12 weeks (95% CI 10.7–13.3) and 14 weeks (95% CI 11.2–16.8), respectively.

Safety. There were 42 reported serious adverse events (details available upon request from the corresponding author), including 1 death (due to an infection in the continuation group) and 41 hospitalizations (34 [6.4%] in the stop group versus 7 [2.4%] in the continuation group; $P = 0.012$). Eleven (2.1%) of the hospitalizations due to infection occurred in the stop group, compared to 4 (1.4%) in the continuation group. Hospitalization due to malignancy was reported in 5 patients (0.9%) in the stop group compared to 3 patients (1.0%) in the continuation group. There were also 4 cases of elective surgery in the stop group, performed for carpal tunnel syndrome, hip osteoarthritis, transurethral resection of the prostate, and fistula excision. Of the 34 hospitalizations in the stop group, 24 were judged to be unrelated, and 10 were judged to be possibly related, to stopping TNFi. In the continuation group, 2 of 7 hospitalizations were judged to be unrelated, and 5 were judged to be possibly related, to continuing TNFi. Additionally, there were 143 adverse events (in 95 patients [17.9%]) in the stop group compared to 48 adverse events (in 43 patients [15.0%]) in the continuation group. Among the patients in the stop group who restarted their TNFi treatment, no allergic reactions were reported.

DISCUSSION

In this study, we have demonstrated that stopping treatment with TNFi in patients with established RA in

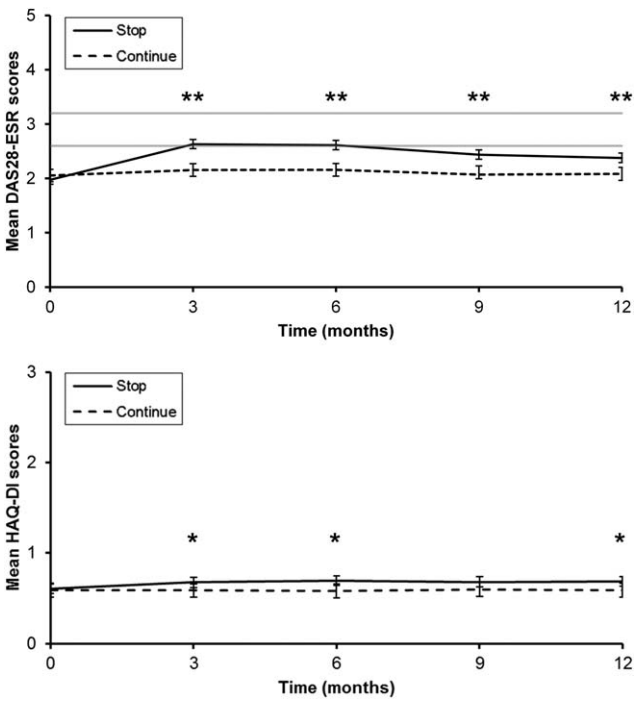

Figure 3. Mean Disease Activity Score in 28 joints using erythrocyte sedimentation rate (DAS28-ESR) (top) and mean Health Assessment Questionnaire (HAQ) Disability Index (DI) score (bottom) over time in patients who stopped their tumor necrosis factor inhibitor (TNFi) treatment compared to those who continued their TNFi treatment. Horizontal gray lines in the top panel represent thresholds for low disease activity (DAS28 <3.2) and remission (DAS28 <2.6). Results are shown as the mean ± 95% confidence interval. * = $P < 0.05$; ** = $P < 0.001$.

remission or with stable low disease activity results in significantly more flares than does continuation of TNFi. Patients who stopped their TNFi treatment had a >3-fold increased risk of experiencing a flare within 12 months of follow-up as compared to those who continued their TNFi. The level of disease activity according to the mean DAS28 was significantly increased in the stop group compared to the continuation group throughout the follow-up period, 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 was confirmed by the similar results observed in sensitivity analyses using other definitions of flare. Previous studies of stopping TNFi have shown more divergent results, possibly due to heterogeneity in the study designs, definitions of flare, and thresholds for disease activity before inclusion. Moreover, the use of concomitant conventional synthetic DMARDs was not clearly reported in most of those previous studies.

Recent results from the US Consortium of Rheumatology Researchers of North America registry have suggested that 73.4% of 717 RA patients maintained benefit for more than 12 months after stopping their first TNFi (25). All other previous studies examined stopping specific types of TNFi. The results from an extension of the HONOR Study (Humira Discontinuation without Functional and Radiographic Damage Progression following Sustained Remission of RA), an open-label, nonrandomized 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). However, in a smaller retrospective study, the BRIGHT Study (Efficacy and Safety of Bendamustine plus Rituximab compared with the Standard Rituximab-Chemotherapy Regimens for Patients with Treatment-Naive Indolent Non-Hodgkin's Lymphoma or Mantle Cell Lymphoma), only 18% of 22 patients who discontinued their adalimumab monotherapy maintained low disease activity after 12 months (26). In another observational study from Japan, the RRR Study (Remission Induction by Remicade in RA), 55% of 102 patients with RA or spondylarthritis and concurrent chronic B or C hepatitis who stopped treatment with infliximab maintained low disease activity at 12 months of follow-up (13). Finally, a post hoc analysis of the BeSt Study (Treatment Strategies for Early RA) from The Netherlands showed that 80% of 104 patients with early RA who stopped treatment with 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 conventional synthetic DMARDs (16).

Although patients in the TNFi stop group were clearly at increased risk of experiencing a flare within 12 months, the finding that even among patients with established RA, almost one-half were able to stop their TNFi treatment could be considered a promising result. To date, only 2 randomized controlled trials of stopping TNFi have been described in the literature. Both studies addressed stopping the TNFi etanercept. In the PRESERVE Study (Maintenance, Reduction, or Withdrawal of Etanercept after Treatment with Etanercept and Methotrexate in Patients with Moderate RA), a randomized placebo-controlled trial conducted in 834 RA patients (80 centers worldwide), 604 patients with sustained low disease activity were randomized to stop or continue treatment with etanercept (27). Results of the PRESERVE Study were very similar to those in the current trial, with 42.6% of the patients in the stop group compared to 82.6% in the continuation group maintaining low disease activity at 12 months of follow-up. In the DOSERA Study (Full Dose, Reduced Dose or Discontinuation of Etanercept in RA), a European randomized placebo-controlled trial of 73 RA patients with low disease activity prior to discontinuation of etanercept, only 13% of patients had flare-free survival after 48 weeks (28). In the present 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 dose reduction to stopping or continuation of etanercept (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 noninferior to dose maintenance with respect to the occurrence of major flares, defined on the basis of DAS28 scores, with a duration longer than 3 months. However, the incidence of DAS28-defined flares of shorter duration was significantly higher in the dose reduction group than in the continuation group, with proportions similar to those found in the current study.

Survival analysis in the present study showed that 83.1% of the patients regained low disease activity quickly

after restarting their TNFi, with a median time to regained low disease activity of 12 weeks. This corresponds well with previous studies that examined this end point. 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% of patients 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 of follow-up, it was not possible to assess whether 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 involving starting or increasing the dose of conventional synthetic DMARDs, compared to 11.2% of the patients in the continuation group. Only the BRIGHT Study also addressed this outcome, showing no significant differences between the patients who stopped adalimumab and those who continued treatment with adalimumab (26).

There was no significant difference in the dropout rate between the TNFi stop group and TNFi continuation group, 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% versus 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 demonstrated 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 the TNFi. One major concern in stopping and restarting infliximab is the possibility of augmented infusion reactions due to antibody development between administrations. In both the RRR Study and the BeSt Study, 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 to date the largest pragmatic randomized controlled trial assessing the safety and efficacy of stopping TNFi in RA patients in remission or with stable low disease activity. This non–industry-funded trial is the product of nationwide consensus among investigators in The Netherlands. Most patients had a long disease duration (established RA) and an average age of 60 years, which is representative of the RA population being treated with TNFi in The Netherlands.

Furthermore, we used a strict protocol for electronic data collection, including safety monitoring. In addition, we used a strict, discriminatory, and valid criterion for flare based on a combination of a threshold value for the DAS28 and a change in the DAS28 over time, whereas most other studies focused on achieving only an absolute cutoff value for the DAS28. The latter may be more sensitive but could lack specificity (24).

The study has some limitations. First, 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. Second, the study had a standard follow-up time of 12 months, which may have been too short to examine the persistence of the effects of stopping TNFi.

In conclusion, this study showed that stopping treatment with TNFi in RA patients whose disease is in remission or who have stable low disease activity results in substantially more flares than does continuation of TNFi treatment.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Ghiti Moghadam had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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