Original Article

Title: Impact of Stopping Tumor Necrosis Factor-inhibitors on Rheumatoid Arthritis Patients' Burden of Disease.

Authors: Marjan Ghiti Moghadam, MD¹; Peter M. ten Klooster, PhD²; Harald E. Vonkeman, MD, PhD³; Eva L. Kneepkens, MD, PhD⁴; Ruth Klaasen, MD, PhD⁵; Jan N. Stolk, MD, PhD⁶; Ilja Tchetverikov, MD, PhD⁷; Simone A. Vreugdenhil, MD⁸; Jan M. van Woerkom, MD, PhD⁹; Yvonne PM Goekoop-Ruiterman, MD, PhD¹⁰; Robert B.M. Landewé, MD, PhD¹¹; Piet L.C.M. van Riel, MD, PhD¹²; Mart A.F.J. van de Laar, MD, PhD¹³; Tim L. Jansen, MD, PhD¹⁴; on behalf of the Dutch National POET Collaboration.

Affiliations:

- 1) Department of Rheumatology, Arthritis Centre Twente, University of Twente and Medisch Spectrum Twente, Enschede, The Netherlands.
- 2) Peter M. ten Klooster, Department of Psychology, Health & Technology, Arthritis Centre Twente, University of Twente and Medisch Spectrum Twente, Enschede, The Netherlands.
- 3) Harald E. Vonkeman, Department of Rheumatology, Arthritis Centre Twente, University of Twente and Medisch Spectrum Twente, Enschede, The Netherlands.
- 4) Eva L. Kneepkens, Department of Rheumatology, Reade, Amsterdam, The Netherlands.
- 5) Ruth Klaasen, Department of Rheumatology, Meander Medical Centre, Amersfoort, The Netherlands.
- 6) Jan N. Stolk, Department of Rheumatology, Gelderse Vallei Hospital, Ede, The Netherlands.
- 7) Ilja Tchetverikov, Department of Rheumatology, Albert Schweitzer Hospital, Dordrecht, The Netherlands.
- 8) Simone A. Vreugdenhil, Department of Rheumatology, St. Antonius Hospital, Nieuwegein, The Netherlands.
- 9) Jan M. van Woerkom, Department of Rheumatology, Gelre Hospitals, Apeldoorn, The Netherlands.

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10) Yvonne PM Goekoop-Ruiterman, Department of Rheumatology, Haga Hospital, The Hague, The Netherlands.

11) Robert B.M. Landewé, Department of Rheumatology, Academic Medical Center, Amsterdam, the Netherlands.

12) Piet L.C.M. van Riel, Department of IQ Healthcare, Radboud University Medical Center, Nijmegen, The Netherlands.

13) Mart A.F.J. van de Laar, Department of Rheumatology, Arthritis Centre Twente, University of Twente and Medisch Spectrum Twente, Enschede, The Netherlands.

14) Tim L. Jansen, Department of Rheumatology, VieCuri Medical Center, Venlo, The Netherlands.

Corresponding author and address for reprint requests:

Marjan Ghiti Moghadam:

University Hospital Leuven, Department of Rheumatology,

Herestraat 49, 3000 Leuven, Belgium

Tel: +32 16 34 25 41

Fax: +32 16 34 25 43

E-mail: marjan.ghitimoghadam@uzleuven.be

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ABSTRACT

Objective: To determine the impact of stopping tumor necrosis factor inhibitor (TNFi) treatment on patient-reported outcomes (PROs) of physical and mental health status, health utility, pain, disability and fatigue in patients with established rheumatoid arthritis (RA).

Methods: In the pragmatic 12-month POET trial, 817 RA patients with ≥ 6 months of remission or stable low disease activity were randomized 2:1 to stopping or continuing TNFi. In case of flare, TNFi was restarted at the discretion of the rheumatologist. PROs were assessed every 3 months.

Results: TNFi was restarted within 12 months in 252/531 patients (47.5%) in the stop group. At 3 months, mean PRO scores were significantly worse in the stop group and a larger proportion of patients experienced a minimal clinically important difference (MCID) on all PROs. Effect sizes (ES) were strongest for health utility (ES = -0.24) and pain (ES = -0.30). Mean scores improved again after this point but disability scores remained significantly different at 12 months. After 12 months, the relative risk of experiencing a MCID ranged from 1.16 for mental health status to 1.58 for fatigue. Mean PRO scores for patients restarting TNFi within 6 months were no longer significantly different from those that did not restart TNFi at 12 months.

Conclusion: Stopping TNFi had a significant negative short-term impact on a broad range of PROs. Long-term negative consequences appeared to be limited and outcomes in patients needing to restart TNFi within the first 6 months tended to be restored at 12 months.

Significance and Innovations

1. This is the first large study to determine the effects of stopping TNFi treatment on a broad range of patient-reported outcomes.
2. Stopping TNFi resulted in a substantial short term worsening on all outcomes but mean 12-month outcome scores were comparable with those in the continuation group.
3. Mean PROs in patients restarting TNFi after a flare in the first 6 months tended to normalize at 12 months.

The introduction of biological agents such as tumor necrosis factor inhibitors (TNFi) has drastically improved the outcomes and clinical course of rheumatoid arthritis (RA). Their efficacy and effectiveness has been extensively demonstrated (1–3), and several trials have additionally demonstrated rapid and sustained improvements in a range of patient-reported outcomes (PROs), including health-related quality of life, general health, pain, disability, and fatigue (4–8).

As the long-term use of TNFi is costly and associated with increased risk of side effects (9–11), the possibility of stopping TNFi in patients with stable low disease activity or remission is receiving increasing interest. Several retrospective studies have suggested that stopping TNFi is possible in some patients (12,13), although two randomized trials showed that the majority of patients experienced a disease relapse within one year after stopping (14,15). This finding was recently confirmed in the POET trial (16), which showed that 51.2% of patients who stopped TNFi experienced a clinical flare within 12 months of follow-up compared to 18.2% of patients who continued TNFi treatment.

Current studies on stopping TNFi have primarily focused on the effects of discontinuation on disease activity status as the primary endpoint. However, clinical measures of disease activity may not adequately reflect the perception of illness and symptoms by RA patients themselves (17–20). Moreover, those studies that did report one or more patient-reported outcomes (PROs) as secondary endpoints only examined group-level changes, providing no information on the consequences of stopping TNFi at the individual patient level (21). Consequently, little is currently known about the effects of trying to stop TNFi on the burden of disease as experienced by patients, especially in those patients who cannot successfully stop. The objectives of the current study were to determine the effects of stopping TNFi treatment on important PROs and to explore the course of symptoms in patients restarting TNFi after a flare.

METHODS

Patients

Detailed study design and results of primary endpoints of the POET trial have been published (16). Briefly, the POET study was a pragmatic open-label trial in which RA patients with stable low disease activity (LDA), defined as 28-joint Disease Activity Score (DAS28) <3.2 for at least 6 months prior to inclusion, from 47 rheumatology centers throughout the Netherlands were randomized 2:1 to either stop or continue TNFi treatment. All participating patients were ≥ 18 years old, had RA per ACR 1987 criteria, and had received TNFi treatment for at least one year prior to inclusion. Concomitant treatment with conventional synthetic DMARDs (csDMARDs) was continued. If RA flared, defined as a DAS28 ≥ 3.2 with an increase >0.6 (22), TNFi could be restarted at the discretion of the treating rheumatologist. The study was approved by the Ethical Review Boards of all participating hospitals and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The POET study is registered in the Netherlands Trial Register, number NTR3112.

In total, 531 patients were allocated to the stop group and 286 to the continuation group and followed for 12 months (16). The primary outcome of the study was that significantly more people in the stop group (272/531 [51.2%]) experienced a DAS28 flare than in the continuation group (52/286 [18.2%]). Most of these flares (213/272 [78.3%]) occurred within 6 months after stopping TNFi. TNFi was restarted within 6 months in 211 patients (39.7%) and within 12 months in 252 patients (47.5%) in the stop group. Almost 85% of the patients who restarted TNFi within the first 6 months had regained low disease activity at 12 months.

Measurements

Patients were evaluated by their treating rheumatologist and rheumatology nurse at baseline and at least once every 3 months thereafter, for a period of one year. Baseline measures included: age, sex, weight, height, disease duration, medication use, rheumatoid factor (RF) and ACPA status, and concomitant use of csDMARDs. Clinical measurements were performed at every scheduled or unscheduled visit and included the ESR (mm/h), CRP (mg/l), 28-joint tender joint count (TJC28), 28-joint swollen joint count (SJC28), and a patient-reported assessment of general health on a 100-mm visual analog scale (VAS-GH). These component measures were combined to calculate the DAS28-ESR (23). Physician-reported flares and all changes in medication were continuously recorded throughout the study.

Patients additionally completed six established PROs at baseline and before every study visit, including the 36-item short-form (SF-36) health survey version 2.0 (24), five-dimensional EuroQol (EQ-5D) (25), the Health Assessment Questionnaire Disability Index (HAQ-DI) (26), and the Bristol RA Fatigue Multidimensional Questionnaire (BRAFM-DQ) (27). Except for the BRAFM-DQ, well-established values for minimal clinically important differences (MCIDs) are available for each of these PROs as described below. Patients in the stop group also rated their overall experience of stopping TNFi before each study visit.

Measures

Health status

The SF-36 assesses different aspects of health represented in 8 scales (24,28). The eight SF-36 scales are linearly transformed to range from 0 to 100, with higher scores representing better health status. Additionally, the scale scores can be aggregated into a physical component summary (PCS) and a mental component summary (MCS). The component summary scores are

standardized using normative data from the 1998 US general population with a mean score of 50 and a standard deviation of 10. Changes of 5 to 10 points on the 0 to 100 scales of the SF-36 and 2.5 to 5 on the norm-based component scales on the scales are considered to be clinically meaningful (29,30). The data were analyzed based on an MCID of ≥ 10 points on the bodily pain (BP) scale and ≥ 5 points on the component summaries as this corresponds closely with the half a standard deviation rule of thumb (31).

Health utility

Health-related quality of life was additionally measured with the EuroQol (EQ-5D) (32). The EQ-5D assesses problems in five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) on 3-point scales to produce a single, interval-level utility score. Utilities reflect the relative desirability of the health state where 0 refers to death and 1 refers to full health. Utility scores were calculated using the Dutch tariff (33). The MCID for the EQ-5D in RA was reported to be 0.05 (34).

Functional disability

The HAQ-DI contains 20 items measuring limitations over the past week in eight categories of daily living (26,35). Each item is scored on a 4-point rating scale from 0 (without any difficulty) to 3 (unable to do). The standard total disability score was calculated by determining the highest score in each of the eight categories, corrected for the use of aids and devices, and then averaging the category scores (36). Scores on the HAQ-DI range between 0 and 3, with higher values indicating more disability. A 2-step difference in score, or 0.25 units, is considered clinically significant (37).

Fatigue

The BRAF-MDQ is a disease-specific, 20-item questionnaire covering domains of physical fatigue (4 items), living (7 items), cognition (5 items), and emotion (4 items) (27). All 20 items can be summed to produce a global fatigue score (range 0 to 70), with higher scores representing worse fatigue. As no formal MCID has been established for the BRAF-MDQ, a minimal increase of 7 points was considered to indicate clinically relevant worsening, which corresponds to approximately half a standard deviation as reported in previous studies (27,38,39).

Patient-reported experience of stopping TNFi

Patients in the stop group rated their experience of stopping TNFi on a single item (“I experience stopping with the TNF blocker as...”) with a Likert-type response scale ranging from 1 (very positive) to 5 (very negative).

Statistical analysis

Analyses were conducted on the intent-to-treat (ITT) population which included all randomized patients. Mean scores on the PROs over time in the stop and continuation group were compared using generalized estimating equations (GEE) models with exchangeable correlation structures for repeated linear data with group (discontinuation vs. continuation), time (0, 3, 6, and 12 months), and group*time interaction as categorical factors to detect any difference in PRO trajectories over time. Post-hoc t-tests were performed to analyze between-group differences in scores at the different time points. Based on estimated marginal means and corresponding standard errors from the GEE models, between-group standardized effect sizes (ES) were expressed as Cohen’s d (Δ estimated marginal mean / pooled standard deviation) with 95% confidence intervals (95% CI) where 0.20 denotes a small, 0.50 a moderate, and 0.80 a large

effect (40). Besides comparing mean scores on a group level, individual patient-level analyses were performed by calculating the proportion of patients experiencing a clinically important worsening of symptoms on each PRO at each time point as compared to baseline. Proportions of patients experiencing a worsening of symptoms $\geq$ MCID were compared between the stop and continuation group using binary logistic GEE models, again with group, time (3, 6, and 12 months), and group*time as factors. Post-hoc chi-square tests and relative risks (RR) with 95% CI were used to examine the significance and magnitude of differences at each follow-up point. Additional descriptive analyses (linear GEE models without adjustment for covariates) were performed in the stop group only to compare longitudinal scores on each PRO between patients who needed to restart TNFi within 6 months versus those that did not restart during the full 12 months of the study.

RESULTS

Patient characteristics and baseline scores

Baseline demographics, disease characteristics and PRO scores were similar in both groups (Table 1). Most patients had longstanding, RF positive, disease. The majority (85.9%) was on their first TNFi, predominantly adalimumab or etanercept. Scores on all PROs indicated relatively mild disease impact at baseline, as would be expected for RA patients in stable remission or low disease activity. Mean SF-36 component summary scores indicated that patients' mental health was comparable to general population norms, while their physical health score was approximately half a standard deviation below the population mean. PRO scores were significantly but modestly correlated with DAS28-ESR scores over the different time points (Pearson r 's ranging from 0.08 to 0.45), confirming that patient-perceived symptoms and clinical disease activity reflected related but distinct aspects of the disease (Supplementary Table 1).

PRO scores in patients stopping vs. continuing TNFi

The GEE analyses (Supplementary Table 2) showed a significant group by time interaction for all PROs, except for the EQ-5D, indicating that mean scores changed significantly different between both groups over time. Although all effect sizes were of small magnitude, post-hoc t-tests confirmed that mean scores at 3 months were significantly worse in the stop group than those in the continuation group on all PROs (Figures 1-3). Mean SF-36 MCS appeared to improve slightly between baseline and 3-month follow-up in the continuation group, but this improvement was not significant (paired t-test, $P = 0.192$).

The short-term impact of stopping TNFi was largest for pain with SF-36 BP scores being around 7 points lower ($ES = -0.30$) in the stop group at 3 months. After this point, PRO scores in the stop group tended to stabilize and steadily improve again. At 6 months, physical health status, pain and functional disability scores remained significantly worse in the stop group. Pain in the stop group improved further and was no longer significantly different at 12 months. Functional disability scores, however, remained slightly ($ES = 0.18$) but significantly higher in the stop group.

MCIDs in patients stopping vs. continuing TNFi

The proportion of patients experiencing a worsening $\geq$ MCID at 3 months was significantly larger in the stop group for all PROs (Supplementary Table 3 and Figures 1-3). Except for the SF-36 MCS, there was no interaction between group and time, indicating that this difference between groups remained stable over the remaining course of follow-up. A substantial number of patients continuing TNFi also experienced a MCID due to natural fluctuations or measurement error. The proportion of patients experiencing a MCID was largest for pain at all follow-up time

points in both the continuation (31.3% to 64.0%) and the stop group (49.5% to 80.0%). The RR for experiencing a MCID at 3 months ranged from 1.63 on the EQ-5D to 2.19 on the SF-36 MCS for patients stopping vs. continuing TNFi. Over the course of follow-up RRs decreased for all PROs, but the differences remained significant for all PROs except mental health status (Figures 1-3). After 12 months, trying to stop TNFi had resulted in an additional 5.5% (SF-36 MCS) to 18.6% (HAQ-DI) of patients experiencing a clinically important worsening on top of those observed in the continuation group.

PRO scores in patients restarting vs. not restarting TNFi

At 6 months, TNFi was restarted in 211 patients in the stop group (39.7%), whereas 279 patients (52.5%) did not restart TNFi during the entire 12 months of follow-up. Estimated mean scores in both subgroups are shown in Figures 4-5. In those patients experiencing a flare and needing to restart TNFi within the first 6 months after baseline, this was accompanied by a sharp worsening of physical health status, pain, health utility and disability scores at 3 and 6 months. Effect sizes were -0.42 (95% CI: -0.60 to -0.24) and -0.42 (95% CI: -0.60 to -0.24) for SF-36 PCS, -0.56 (95% CI: -0.74 to -0.37) and -0.41 (95% CI: -0.59 to -0.22) for SF-36 BP, -0.36 (95% CI: -0.54 to -0.18) and -0.21 (95% CI: -0.39 to -0.03) for EQ-5D, and 0.30 (95% CI: 0.12 to 0.48) and 0.29 (95% CI: 0.11 to 0.47) for HAQ-DI scores at 3 and 6 months, respectively. PRO scores improved rapidly after restart and were no longer significantly different from those that did not restart TNFi at all after 9 months.

Patient-reported experience of stopping TNFi

The proportion of patients who rated their experience of stopping TNFi as positive or very positive after 12 months was 38.8%, while 43.6% experienced stopping as negative or very

negative (Supplementary Table 4). At each time point, experience ratings were strongly associated with having restarted TNFi at that time or not. Across study visits, 72.4% to 76.2% of the patients that restarted TNFi rated their experience as negative as opposed to 12.1% to 18.9% of the patients that did not restart (Supplementary Table 5).

DISCUSSION

The POET trial showed that stopping TNFi treatment in patients with established RA in remission or with stable low disease activity resulted in substantially more clinical flares, but that most patients who restarted TNFi treatment quickly regained remission or low disease activity (16). The current study extends these findings by demonstrating that stopping TNFi also had a significant, but small, short-term negative impact on patient-reported physical and mental health status, health utility, pain, disability and fatigue. Except for physical disability, PRO scores did not remain significantly different at 12 months. However, the proportion of patients with worsening above MCID was higher and differed significantly for more PROs (Supplementary Table 2). Moreover, subgroup analyses showed that for patients who restarted TNFi after a flare within the first 6 months, 9- and 12-month PRO scores were no longer different from those that did not restart at all. As such, a strategy of trying to stop TNFi treatment and quickly restarting in case of flare, does not appear to have substantial long-term consequences for the burden of disease as experienced by patients.

To date, very few studies have thoroughly examined the longitudinal impact of stopping TNFi on patient-reported health-status and symptoms. The double-blind PRESERVE study showed that after 52 weeks patients maintaining 50 mg etanercept plus methotrexate treatment had significantly better scores than patients using placebo plus methotrexate on general health, pain, disability, health utility, sleep, and fatigue (14). Some other, non-randomized or

observational, studies specifically reported the effects of stopping TNFi on one or more PROs, usually by comparing long-term disability scores in patients who did and did not successfully discontinue TNFi. The observational RRR study showed that one-year mean HAQ-DI scores were significantly lower in patients who remained in DAS remission after stopping infliximab versus those that did not (41). Post-hoc analyses of 104 patients in the BeSt study who discontinued infliximab after achieving stable low disease activity showed that HAQ-DI scores at 1 and 3 years after discontinuation were similar to scores at discontinuation in both restarters and patients with sustained low disease activity (42). However, 5 years after discontinuation median disability scores were significantly increased in restarters. The open-label non-randomized HONOR study did not show a significant difference in one-year HAQ-DI scores between patients that did and did not sustain remission after adalimumab discontinuation (43). Another very small observational study in 21 RA patients did not find significant differences in one-year HAQ-DI scores either (44), although with only 21 analyzed patients this study was likely underpowered for this purpose.

The POET study is the first large pragmatic trial examining the impact of trying to stop TNFi on both clinical and patient-reported outcomes in realistic clinical settings. Overall, the current findings show that stopping TNFi resulted in significantly worse scores on all patient-reported outcome domains, particularly reflecting pain. However, the magnitude of differences was generally small and decreased again after 3-6 months. The proportion of patients experiencing a worsening $\geq$ the MCID within 3 months was also significantly larger in the stop group and remained significantly different at 12 months for most outcomes. At 12 months, the proportion of patients in the stop group that experienced an MCID was >50% on all PROs except mental health status. However, a substantial proportion of patients who continued TNFi also experienced an MCID, due to either natural disease fluctuations or measurement error. Like the

effect sizes for mean scores, relative risks for experiencing an MCID steadily decreased for all PROs over time.

In interpreting these findings, it is important to keep in mind that POET was an open label pragmatic trial in which, after randomization, rheumatologists were free to prescribe and adjust medications as considered clinically necessary. Consequently, it is not possible to attribute the differences between groups purely to the effects of stopping TNFi and the impact on PRO scores may be substantially confounded by other treatment decisions. For instance, rheumatologists are likely to have started or increased csDMARDs or NSAIDs in patients in the stop group with an increase in disease activity but not meeting the DAS28 flare criterion, resulting in an underestimation of impact. Moreover, as the follow-up period of POET was limited to one year, it is unclear how many patients experienced a disease relapse after this period. Finally, the POET study only examined the effects of completely stopping TNFi. Recently, several studies have suggested that TNFi dose reduction may be more effective in maintaining low disease activity (14,15). This may also translate into less impact on patient-reported symptoms. For instance, a recent trial on disease activity guided tapering of adalimumab or etanercept showed that HAQ-DI and EQ-5D scores remained stable in the dose reduction group and did not differ significantly over time from patients continuing TNFi (45).

An important strength of the current study is that it included a broad range of PROs, covering all patient-reported outcome domains as defined by the ACR and WHO/ILAR core set endpoints for RA clinical trials (46,47), as well as fatigue, which was more recently endorsed as a symptom important to patients (48). Moreover, well established and validated measures were used for all domains. For instance, we used the multi-item BRAF-MDQ to measure fatigue, which has better content validity and measurement precision than more commonly used single-item measures of fatigue (39).

In summary, a strategy of trying to stop TNFi treatment in patients with stable low disease activity in daily clinical practice has a negative short-term impact on patient-perceived symptoms but does not appear to have substantial longer-term consequences for the burden of disease as experienced by patients.

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Table 1. Baseline characteristics of the patients

Characteristic	Stop TNFi (n=531)	Continue TNFi (n=286)
Female, n (%)	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)	1.97 (0.76)	2.05 (0.74)
RF positive, n (%)	328 (67.5)	178 (67.4)
TNFi, n (%)		
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, n (%)		
1 st	459 (86.6)	243 (85.0)
2 nd	61 (11.5)	37 (12.9)
3 rd	10 (1.9)	6 (2.1)
SF-36, mean (SD)		
Physical component summary score	45.6 (8.8)	45.3 (8.8)
Mental component summary score	52.0 (8.9)	51.64 (10.2)
Bodily pain score	71.9 (19.4)	72.1 (19.3)
EQ-5D, mean (SD)	0.84 (0.18)	0.85 (0.14)
HAQ-DI, mean (SD)	0.60 (0.62)	0.59 (0.59)
BRAF-MDQ, mean (SD)	14.7 (11.2)	15.4 (12.2)

BRAF-MDQ = Bristol RA Fatigue Multidimensional Questionnaire; DAS28 = disease activity score in 28 joints; EQ-5D = five-dimensional EuroQol; HAQ-DI = Health Assessment Questionnaire Disability Index; RF = rheumatoid factor; SF-36 = 36-item short-form health survey; TNFi = tumor necrosis factor- α inhibitor.

Figure 1. Estimated mean PRO scores on physical and mental health status in all patients over time (left panel), stratified into those who continued (dashed line) and stopped TNFi (solid line). Cumulative proportion of patients experiencing a MCID as compared with baseline (right panel), gray bars are patients in the stop group. Error bars are 95% Wald CIs for both mean scores and proportions. SF-36 = 36-item short-form health survey; PCS = physical component summary; MCS = mental component summary. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ for between-group t-tests or chi-square tests.

Figure 2. Estimated mean PRO scores on pain and health utility in all patients over time (left panel), stratified into those who continued (dashed line) and stopped TNFi (solid line). Cumulative proportion of patients experiencing a MCID as compared with baseline (right panel), gray bars are patients in the stop group. Error bars are 95% Wald confidence intervals for both mean scores and proportions. P-values are for between-group t-tests or chi-square tests. SF-36 = 36-item short-form health survey; BP = bodily pain; EQ-5D = five-dimensional EuroQol.

Figure 3. Estimated mean PRO scores on disability and fatigue in all patients over time (left panel), stratified into those who continued (dashed line) and stopped TNFi (solid line). Cumulative proportion of patients experiencing a MCID as compared with baseline (right panel), gray bars are patients in the stop group. Error bars are 95% Wald confidence intervals for both mean scores and proportions. P-values are for between-group t-tests or chi-square tests. HAQ-DI = Health Assessment Questionnaire Disability Index; BRAF-MDQ = Bristol RA Fatigue Multidimensional Questionnaire. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ for between-group t-tests or chi-square tests.

Figure 4. Estimated mean PRO scores on physical and mental health status, pain, and health utility of patients stopping TNFI, stratified into those who restarted within 6 months (solid line; $n = 211$) and remained off drug throughout the 12-month study period (dashed line; $n = 279$). Those who restarted after the 6-month visit were excluded. For comparison, mean scores in the total continuation group are plotted as solid grey lines (without error bars). Error bars are 95% Wald confidence intervals. P-values are for between-group t-tests or chi-square tests. SF-36 = 36-item short-form health survey version; PCS = physical component summary; MCS = mental component summary; BP = bodily pain; EQ-5D = five-dimensional EuroQol.

Figure 5. Estimated mean PRO scores on disability and fatigue of patients stopping TNFI, stratified into those who restarted within 6 months (solid line; n = 211) and remained off drug throughout the 12-month study period (dashed line; n = 279). Those who restarted after the 6-month visit were excluded. For comparison, mean scores in the total continuation group are plotted as solid grey lines (without error bars). Error bars are 95% Wald confidence intervals. P-values are for between-group t-tests or chi-square tests. HAQ-DI = Health Assessment Questionnaire Disability Index; BRAF-MDQ = Bristol RA Fatigue Multidimensional Questionnaire.