Arthritis & Rheumatology
Vol. 73, No. 5, May 2021, pp 759–768
DOI 10.1002/art.41589

American College of Rheumatology
Empowering Rheumatology Professionals

Etanercept or Methotrexate Withdrawal in Rheumatoid Arthritis Patients in Sustained Remission

Jeffrey R. Curtis,[1] Paul Emery,[2] Elaine Karis,[3] Boulos Haraoui,[4] Vivian Bykerk,[5] Priscilla K. Yen,[3] Greg Kricorian,[3] and James B. Chung[3]

Objective. Patients with rheumatoid arthritis (RA) in whom remission is achieved following combination therapy with methotrexate plus etanercept face an ongoing medication burden. This study was undertaken to investigate whether sustained remission achieved on combination therapy can be maintained with either methotrexate or etanercept monotherapy, as assessed following discontinuation of one or the other medication from the combination.

Methods. Of the 371 adult patients with RA who received combination therapy with methotrexate plus etanercept, remission (defined as a Simplified Disease Activity Index [SDAI] score of ≤3.3) was sustained in 253 patients through a 24-week open-label period. These 253 patients then entered a 48-week, double-blind period and were randomized to receive either 1) methotrexate monotherapy (n = 101), 2) etanercept monotherapy (n = 101), or 3) methotrexate plus etanercept combination therapy (n = 51). Patients who subsequently experienced disease-worsening received rescue therapy with the combination regimen at the same dosages as used in the initial run-in period. The primary end point was the proportion of patients in whom SDAI-defined remission was maintained without disease-worsening at week 48 in the etanercept monotherapy group as compared to the methotrexate monotherapy group. Secondary end points included time to disease-worsening, and the proportion of patients in whom SDAI-defined remission was recaptured after initiation of rescue therapy.

Results. Baseline demographic and clinical characteristics of the RA patients were similar across the treatment groups. At week 48, SDAI-defined remission was maintained in significantly more patients in the etanercept monotherapy group than in the methotrexate monotherapy group (49.5% versus 28.7%; $P = 0.004$). Moreover, as a secondary end point, sustained SDAI-defined remission was achieved in significantly more patients who received combination therapy than in those who received methotrexate monotherapy (52.9% versus 28.7%; $P = 0.006$). Time to disease-worsening was shorter in those who received methotrexate monotherapy than in those who received etanercept monotherapy or those who received combination therapy (each $P < 0.001$ versus methotrexate monotherapy). Among the patients who received rescue therapy, SDAI-defined remission was recaptured in 70–80% in each treatment group. No new safety signals were reported.

Conclusion. The efficacy of etanercept monotherapy was superior to that of methotrexate monotherapy and similar to that of combination therapy in maintaining remission in patients with RA. SDAI-defined remission was recaptured in most of the patients who were given rescue therapy. These data could inform decision-making when withdrawal of therapy is being considered to reduce treatment burden in patients with well-controlled RA.

ClinicalTrials.gov identifier: NCT02373813.

Supported by Amgen Inc.

[1]Jeffrey R. Curtis, MD: University of Alabama at Birmingham; [2]Paul Emery, MD: Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK; [3]Elaine Karis, MD, Priscilla K. Yen, PhD, Greg Kricorian, MD, James B. Chung, MD, PhD: Amgen Inc., Thousand Oaks, California; [4]Boulos Haraoui, MD: Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada; [5]Vivian Bykerk, MD: Hospital for Special Surgery, New York, New York.

Dr. Curtis has received consulting fees, speaking fees, and/or honoraria from Amgen, Corrona, Janssen, Myriad, and Pfizer (more than $10,000 each) and AbbVie, Bristol Myers Squibb, Gilead, Eli Lilly, Novartis, Sanofi, and Scipher Medicine (less than $10,000 each). Dr. Emery has received consulting fees, speaking fees, and/or honoraria from AbbVie, Amgen, Bristol Myers Squibb, Celltrion, Gilead, Eli Lilly, MSD, Novartis, Pfizer, Roche, Samsung, and Sanofi (less than $10,000 each). Drs. Karis, Yen, Kricorian, and Chung own stock or stock options in Amgen. Dr. Haraoui has received consulting fees, speaking fees, and/or honoraria from AbbVie, Gilead, and Pfizer (more than $10,000 each) and Amgen, Bristol Myers Squibb, Janssen, Eli Lilly, Merck, Roche, Sandoz, Sanofi-Genzyme, and UCB (less than $10,000 each). Dr. Bykerk has received consulting fees, speaking fees, and/or honoraria from Amgen, Bristol Myers Squibb, Gilead, Pfizer, Sanofi-Genzyme, Regeneron, Scipher Medicine, and UCB (less than $10,000 each).

Qualified researchers may request data from Amgen clinical studies. Complete details are available at https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/.

Address correspondence to Jeffrey R. Curtis, MD, University of Alabama at Birmingham, 510 20th Street South, Birmingham, AL 35294. Email: jrcurtis@uabmc.edu.

Submitted for publication July 28, 2020; accepted in revised form November 10, 2020.

INTRODUCTION

In patients with rheumatoid arthritis (RA), remission became a more realistic and achievable goal with the introduction of tumor necrosis factor inhibitors (TNFi) (1–3). Combining a TNFi (such as etanercept) with methotrexate in the treatment of RA patients has resulted in a greater reduction in disease activity and decreased radiographic progression, as well as improvement in physical function, when compared to either therapy alone. Combination therapy has accordingly been established as a commonly used and effective regimen for achieving sustained remission and/or lowering disease activity in patients with RA (4–6).

For patients in whom stringent remission has been achieved and sustained, important questions remain about the need to continue combination therapy to maintain good disease control (3). Guidelines from the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recommend carefully tapering (though not stopping all) RA therapy for patients whose disease is in remission (7,8), but clear data are lacking on how best to manage this process. Informed guidance on minimizing therapy while maintaining excellent disease control in RA would be of significant value for patients and physicians, especially considering the aging population whose disease may be associated with more comorbidities and complex medication regimens, and also the safety and tolerability issues associated with long-term methotrexate use (9,10).

Prior studies examining how withdrawal of methotrexate or TNFi therapy (11–16) can impact disease control have had key limitations, including varying and inconsistent definitions of adequate disease control/remission and lack of an initial observational period of sustained control (remission) prior to treatment reduction; both may be important factors for determining whether good disease control can be maintained after treatment withdrawal (17,18). In addition, previous studies in which either a TNFi or methotrexate was withdrawn did not examine monotherapy strategies with either medication in a single, comparative study.

The Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Rheumatoid Arthritis (SEAM-RA) is a randomized, double-blind, controlled trial designed to study patients with RA whose disease is in stable, stringently defined remission after having received combination therapy with etanercept and methotrexate, and to rigorously investigate whether remission could be maintained with either etanercept or methotrexate monotherapy, as assessed after withdrawal of either treatment. This study aimed to directly address questions of practical importance to patients and physicians, with the goal of simplifying care and minimizing the medication burden in patients with RA.

PATIENTS AND METHODS

Trial design and oversight. This international, multicenter study (19) consisted of a 24-week open-label run-in period, a 48-week randomized, controlled double-blind period, and a 30-day safety follow-up period for all enrolled patients (see the Supplementary Notes for a list of the primary investigators and study sites, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41589/abstract). To be included in the SEAM-RA trial, patients with RA receiving combination therapy with methotrexate (dosage of 10–25 mg/week) plus etanercept (dosage of 50 mg/week) were required to have a score of ≤3.3 on the Simplified Disease Activity Index (SDAI; score range 0–86, with remission defined as ≤3.3, low disease activity as 3.4 to ≤11.0, moderate disease activity as 11.1 to 26, and high disease activity as >26) (20) at the time of screening, thereby satisfying the established ACR/EULAR criteria for remission (21). Once enrolled, patients continued combination therapy and entered a 24-week open-label run-in period, to identify patients whose disease remained stable and in remission. These patients were then selected for randomization into the subsequent double-blind, treatment-withdrawal period. Patients with an SDAI score of >3.3 and ≤11 on 2 or more visits or an SDAI score of >11 at any time during the run-in period were ineligible for the double-blind period.

Patients in whom SDAI-defined remission was achieved at the end of the run-in period and who met the above-described eligibility criteria at a subsequent baseline visit for the double-blind period were randomized 2:2:1 via an Interactive Voice and Web Response System to subsequently receive, on a weekly basis, either 1) oral methotrexate plus subcutaneous placebo (i.e., etanercept withdrawal), 2) subcutaneous etanercept plus oral placebo (i.e., methotrexate withdrawal), or 3) subcutaneous etanercept plus oral methotrexate (i.e., no change in therapy). During the double-blind period, patients and investigators were blinded with regard to the treatment assignments, and randomization was based on a computer-generated randomization schedule (prepared by staff at Amgen Inc.). During the double-blind period, patients randomized to receive methotrexate continued with the medication at the same dosage received during the screening and run-in period, and patients randomized to continue receiving etanercept received a dosage of 50 mg/week.

Randomized patients were considered to have disease-worsening if they had increased disease activity based on an SDAI score of >3.3 and ≤11 on 2 consecutive visits at least 2 weeks apart, an SDAI score of >3.3 and ≤11 at any time on 3 or more separate visits, or an SDAI score of >11 at any time. Patients with disease-worsening received weekly rescue treatment with the combination of etanercept plus methotrexate (i.e., reestablished or continued combination therapy using the same dosages received at the time of study enrollment).

During both the run-in and double-blind periods, etanercept (manufactured and supplied by Amgen Inc.) was administered using single-use, prefilled syringes in the dosages recommended in the prescribing information (22). Methotrexate (manufactured by Teva Pharmaceuticals and supplied by Amgen Inc.) was provided as 2.5-mg tablets during the run-in period and as 2.5-mg capsules

(to enable blinding) during the double-blind treatment period. Folic acid was prescribed at a dosage of 5–7 mg per week.

All patients provided written informed consent to participate in the trial, and each participating site obtained approval of the study protocol from an Institutional Review Board/Independent Ethics Committee. The statistical analyses were performed by the study sponsor.

Trial population. Key eligibility criteria at the time of screening included age ≥18 years, having a history of RA (consistent with the ACR/EULAR 2010 classification criteria [23]), having ≥6 months of good disease control (according to investigator opinion) before the run-in period, being in a state of disease remission based on an SDAI score of ≤3.3 at the time of screening (and at the end of the run-in period), having received etanercept at 50 mg weekly plus methotrexate at 10–25 mg weekly for ≥6 months, and having received a stable dose of oral methotrexate for ≥8 weeks prior to the first visit of the run-in period. Additional eligibility criteria are listed in the Supplementary Notes (http://onlinelibrary.wiley.com/doi/10.1002/art.41589/abstract).

End points for the double-blind period. During the double-blind period, patients were assessed on day 1 (baseline) and then at weeks 12, 24, 36, and 48. The primary end point was the proportion of patients having achieved SDAI-defined remission (an SDAI score of ≤3.3) without disease-worsening at week 48 in the etanercept monotherapy group as compared to the methotrexate monotherapy group. Secondary end points included the proportion of patients who experienced SDAI-defined remission without disease-worsening at week 48 in the combination therapy group as compared to the methotrexate monotherapy group. In those patients who experienced disease-worsening and were subsequently given rescue therapy, other secondary end points included the proportion of patients

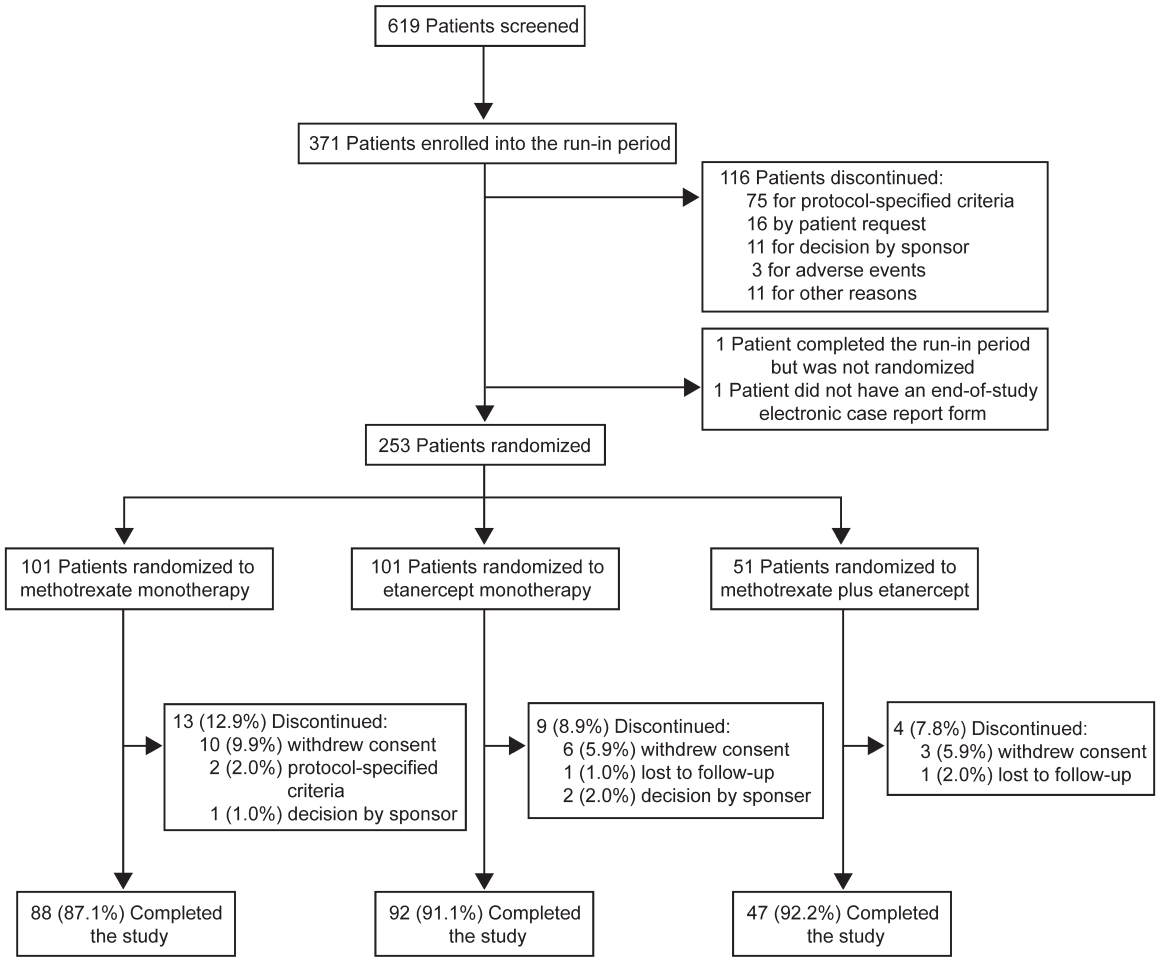


Figure 1. Flow chart of patient distribution in the study. At screening, patients with rheumatoid arthritis receiving methotrexate plus etanercept (combination therapy) were required to have a Simplified Disease Activity Index (SDAI) score of ≤3.3. After enrollment, patients continued receiving combination therapy and entered a 24-week open-label, run-in period to identify patients in whom stable remission was achieved for randomization into the subsequent double-blind, treatment-withdrawal period. Patients with an SDAI score of >3.3 and ≤11 on 2 or more visits or an SDAI score of >11 at any time during the run-in period were ineligible for the double-blind period. Patients with SDAI-defined remission at the end of the run-in period and who met eligibility for the double-blind period were randomized 2:2:1 into 1 of the 3 treatment groups.

in whom SDAI-defined remission was recaptured after initiation of rescue therapy, the SDAI scores in these patients over time after achievement of SDAI-defined remission, and the time to recapture SDAI-defined remission after initiation of rescue therapy. Safety end points included the percentage of patients who experienced adverse events, serious adverse events, fatal adverse events, and adverse events leading to withdrawal from the investigational product.

Statistical analysis. Data from prior treatment-withdrawal studies (12,16) were used to determine the SEAM-RA sample size. Based on a 2-sided chi-square test with 90% power to detect differences (at a significance level of 0.05) and assuming an effect size of 22% between the etanercept and methotrexate monotherapy groups, it was estimated that a sample size of 100 patients in the etanercept monotherapy group and 100 patients in the methotrexate monotherapy group would be required. Assuming a 30% attrition rate in the run-in period, it was estimated that ~358 patients were needed for enrollment, so that 250 patients could be randomized.

Analyses of the primary and secondary efficacy end points used the primary analysis set of all randomized patients, and these analyses were conducted according to treatment assignment. Analyses of safety end points used the safety analysis set of all randomized patients who received at least one dose of any investigational product, and these analyses were conducted according to the actual treatment received. Summary descriptive statistics were used for the baseline demographic and disease characteristics by treatment group.

For the primary end point, achievement of SDAI-defined remission at week 48 in patients in the etanercept monotherapy group was compared to that in the methotrexate monotherapy group, using a 2-sided chi-square test with a significance level of 0.05. Nonresponder imputation was used for missing values at week 48. Patients who dropped out of the study or experienced disease-worsening were considered nonresponders. Secondary end points were analyzed using the observed data set.

RESULTS

Patient characteristics. Between February 20, 2015 and June 26, 2018, the SEAM-RA study enrolled 371 patients into the 24-week, open-label run-in period, during which they continued combination therapy with methotrexate plus etanercept (Figure 1). The 253 patients eligible for the 48-week double-blind period were randomized from August 10, 2015 to December 5, 2018 to receive methotrexate monotherapy (101 patients), etanercept monotherapy (101 patients), or methotrexate plus etanercept (51 patients). The double-blind period was completed by 227 patients (89.7%); the most common reason for discontinuing was withdrawal of consent (Figure 1). The last day of the study was December 6, 2019. Among the 371 enrolled patients, 181 (49%) were from the US, and 62% of these patients were randomized to the treatment-withdrawal period. The overall percentage of

Table 1. Demographic and clinical characteristics of the RA patients at baseline*

Characteristic	Methotrexate monotherapy (n = 101)	Etanercept monotherapy (n = 101)	Combination therapy (n = 51)
Female sex, no. (%)	76 (75.2)	77 (76.2)	40 (78.4)
Age, years	56.2 ± 11.4	54.8 ± 12.8	55.9 ± 12.6
White, no. (%)	92 (91.1)	86 (85.1)	42 (82.4)
BMI, kg/m^2	27.8 ± 5.2	28.7 ± 5.7	28.7 ± 5.9
Duration of RA, years	9.7 ± 8.0	11.0 ± 7.4	10.3 ± 8.2
RF positive, no. (%)	59 (58.4)	64 (63.4)	35 (68.6)
Anti-CCP positive, no. (%)	66 (65.3)	67 (66.3)	35 (68.6)
Methotrexate dosage, mg/week	16.26 ± 4.56	15.97 ± 4.65	17.06 ± 4.99
Prednisone (≤5 mg daily), no. (%)	2 (2.0)	1 (1.0)	1 (2.0)
SDAI score	1.3 ± 1.0	1.3 ± 1.4	1.2 ± 1.2
Remission, no. (%)			
SDAI†	96 (95.0)	93 (92.1)	49 (96.1)
Boolean (in 28 joints)†	83 (82.2)	84 (83.2)	41 (80.4)
Tender joint count (of 28 joints)	0.1 ± 0.4	0.1 ± 0.4	0.2 ± 0.5
Swollen joint count (of 28 joints)	0.1 ± 0.4	0.0 ± 0.2	0.0 ± 0.2
Physician global assessment (scale 0–10)	0.30 ± 0.38	0.31 ± 0.91	0.17 ± 0.26
Patient global assessment (scale 0–10)	0.44 ± 0.58	0.45 ± 0.77	0.35 ± 0.55
CRP, mg/dl	0.27 ± 0.40	0.34 ± 0.54	0.47 ± 1.00
HAQ DI, mean ± SEM	0.32 ± 0.04	0.26 ± 0.04	0.28 ± 0.06

* Except where indicated otherwise, values are the mean ± SD. RA = rheumatoid arthritis; BMI = body mass index; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide; CRP = C-reactive protein; HAQ DI = Health Assessment Questionnaire disability index (score range 0–3).
† Clinical remission being defined as a Simplified Disease Activity Index (SDAI) score of ≤3.3 (score range 0–86) or meeting the Boolean criteria for remission according to the American College of Rheumatology/European League Against Rheumatism remission criteria (21).

enrolled patients who were randomized was 68%, and in some countries, as high as ~90% of their enrolled patients were randomized (in South Africa, 21 [91%] of 23 patients; in Poland, 19 [90%] of 21 patients).

The demographic and clinical characteristics of the patients at baseline were generally similar across the 3 randomized treatment groups (Table 1). Patients in each group were predominantly female and white, and the mean body mass index (BMI) of the study population was 28 kg/m^2 (Table 1). At the time of randomization, the overall mean age was 56 years, the mean duration of RA was 10.3 years, the mean dosage of methotrexate was 16.3 mg/week, the mean ± SD SDAI score was 1.3 ± 1.2, and the baseline mean ± SD Health Assessment Questionnaire disability index score (24) was 0.29 ± 0.03.

Maintenance of SDAI-defined remission. Analysis of the primary end point indicated that at week 48 of the double-blind period, SDAI-defined remission was maintained without disease-worsening in a significantly higher percentage of patients in the etanercept monotherapy group compared to the methotrexate monotherapy group (50 [49.5%] of 101 versus 29 [28.7%] of 101; $P = 0.004$) (Figure 2). Similarly, the disease remained in SDAI-defined remission by week 48 in a significantly higher percentage of patients in the continued combination therapy group compared to the methotrexate monotherapy group (27 [52.9%] of 51 versus 29 [28.7%] of 101; $P = 0.006$) (Figure 2).

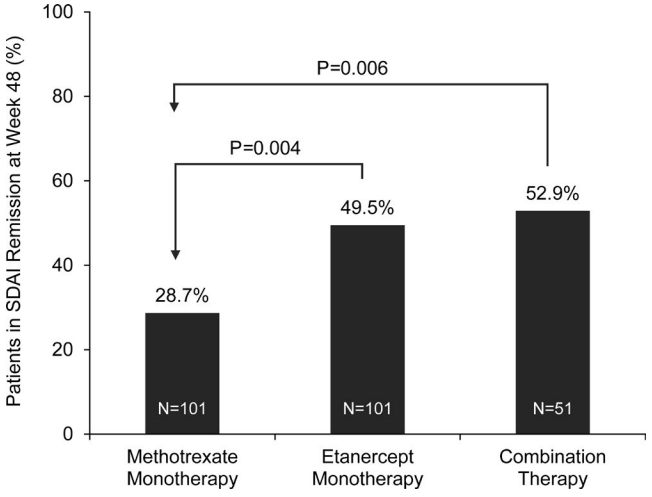


Figure 2. Patients in whom remission (as defined by a Simplified Disease Activity Index [SDAI] score of ≤3.3) was achieved without disease-worsening at week 48. The primary end point was comparison of the proportion of patients with SDAI-defined remission at week 48 between the etanercept and methotrexate monotherapy groups, among patients in the primary analysis set. A secondary end point was comparison of the methotrexate monotherapy and combination therapy groups. Missing data were imputed using nonresponder imputation (patients with disease-worsening were considered nonresponders). *P* values were estimated based on the chi-square test with continuity correction.

A univariate logistic regression analysis of selected covariates at baseline, in the data set including all patients, indicated potential predictors of remission maintenance. A higher baseline SDAI score was associated with a lower likelihood of maintaining remission, and a status of rheumatoid factor positivity was associated with a lower ability to maintain remission; positivity for anti–cyclic citrullinated peptide antibodies showed a similar trend.

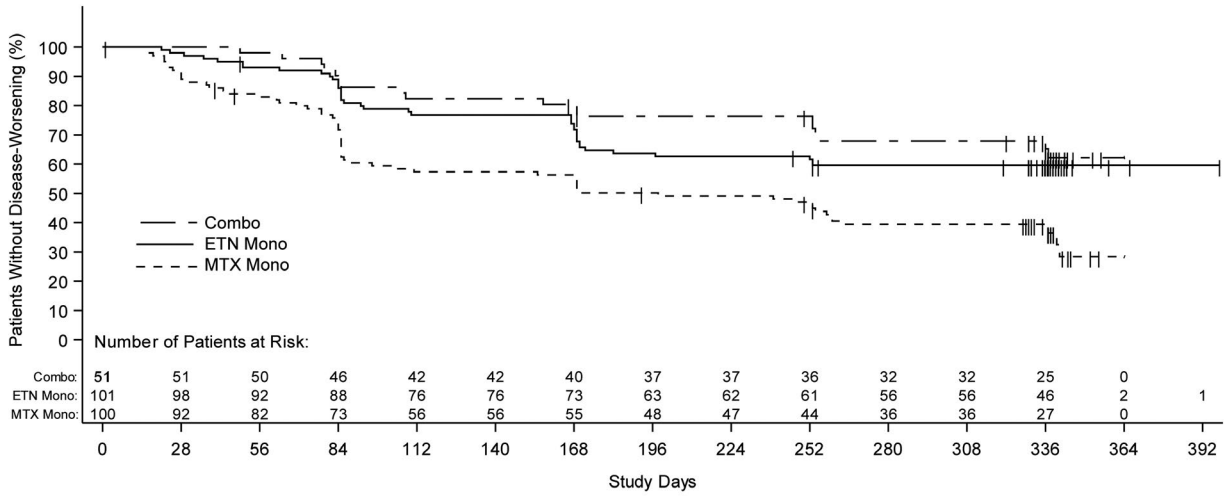
The BMI of the patients at baseline had a slight impact on remission maintenance, with a higher baseline BMI correlating with a decreased ability to maintain remission. Disease duration or prior duration of etanercept or methotrexate treatment was not shown to be a predictor of remission maintenance in this analysis (data not shown).

Disease-worsening and recapture of remission. During the 48-week double-blind period, the percentage of patients with disease-worsening was 63 (62.4%) of 101 in the methotrexate monotherapy group, 40 (39.6%) of 101 in the etanercept monotherapy group, and 18 (35.3%) of 51 in the combination therapy group. The median SDAI score at initiation of rescue therapy in each group was as follows: median 25.3 (interquartile range [IQR] 15.0–35.0) in the methotrexate monotherapy group, median 15.8 (IQR 7.7–32.1) in the etanercept monotherapy group, and median 14.0 (IQR 12.0–24.5) in the combination therapy group. The majority of patients who met the criteria for disease-worsening during the 48-week double-blind period were identified based on having an SDAI score of >11 (84%, 75%, and 78% of patients in the methotrexate monotherapy, etanercept monotherapy, and combination therapy groups, respectively). The highest SDAI scores in all 3 treatment groups occurred during the first 24 weeks of the double-blind period (see results in Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41589/abstract).

The time to disease-worsening was shorter in the methotrexate monotherapy group compared to either the etanercept monotherapy group ($P < 0.001$) or the combination therapy group ($P < 0.001$) (Figure 3). The differences between the methotrexate monotherapy and etanercept monotherapy groups were discernible as early as 4 weeks.

The cumulative Kaplan-Meier estimate (with 95% confidence interval [95% CI]) for the probability of not experiencing disease-worsening by week 48 was 38.0% (95% CI 28.2–47.6) in the methotrexate monotherapy group, 59.6% (95% CI 49.2–68.5) in the etanercept monotherapy group, and 65.2% (95% CI 49.9–76.8) in the combination therapy group (see the Kaplan-Meier estimates at all time points in Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41589/abstract).

During the double-blind period, rescue therapy was given to 52 (52%) of 101 patients in the methotrexate monotherapy group, 36 (36%) of 101 in the etanercept monotherapy group,



	MTX Mono (N = 101)	ETN Mono (N = 101)	Combo (N = 51)
Days to Disease-Worsening, Median (95% CI)	198 (96, 263)	NE (253, NE) P<0.001*	NE (336, NE) P<0.001*

Figure 3. Kaplan-Meier curves of time to disease-worsening in the 3 treatment groups (in the primary analysis set). The censor bars represent patients who did not have disease-worsening at their last Simplified Disease Activity Index–defined remission assessment date. One patient discontinued treatment with methotrexate (MTX) on study day 0, and thus was no longer at risk and was censored. The median time to disease-worsening in the etanercept (ETN) monotherapy (Mono) group and the combination (Combo) therapy group was not estimable (NE) because the cumulative event rate in these 2 groups at the end of the study period at 336 days (48 weeks) was 59.6% and 65.2%, respectively (i.e., did not reach or fall below 50%). **P* values are nominal and compare the etanercept-containing groups with the methotrexate monotherapy group using a 2-sided log-rank test. 95% CI = 95% confidence interval.

and 15 (29%) of 51 in the combination therapy group (a small number of patients who experienced disease-worsening withdrew from the study prior to receiving rescue therapy). Of the patients who received rescue therapy, 86 (83.5%) of 103 had ≥12 weeks of follow-up. The cumulative proportion of patients in whom SDAI-defined remission was recaptured after the initiation of rescue therapy (administered in response to disease-worsening) was 46%, 42%, and 47% by 12 weeks and 71%, 75%, and 80% by the end of the study in the methotrexate monotherapy, etanercept monotherapy, and combination therapy groups, respectively (Figure 4A). In comparison, the cumulative proportion of patients in whom SDAI-defined low disease activity was recaptured following rescue therapy was 71%, 81%, and 73% by 12 weeks and 96%, 92%, and 100% by the end of the study in the methotrexate monotherapy, etanercept monotherapy, and combination therapy groups, respectively (Figure 4B).

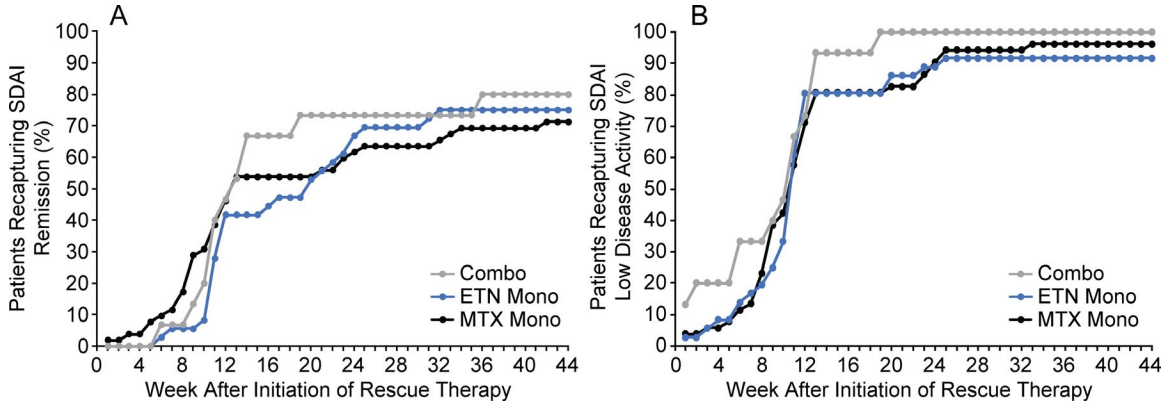


Figure 4. Cumulative proportion of patients in whom Simplified Disease Activity Index (SDAI)–defined remission (**A**) and low disease activity (**B**) were recaptured after initiation of rescue therapy (the rescue analysis set). The rescue analysis set consisted of 52 patients in the methotrexate (MTX) monotherapy (Mono) group, 36 patients in the etanercept (ETN) monotherapy group, and 15 patients in the combination (Combo) therapy group. On the X-axis, the value of 0 represents the time point of initiation of rescue therapy. Once SDAI-defined remission or low disease activity was recaptured, patient numbers remained as is for the subsequent weeks (even if remission or low disease activity status was lost at a later time).

Table 2. Summary of safety results from the double-blind period (safety analysis set)*

	Methotrexate monotherapy (n = 100)	Etanercept monotherapy (n = 99)	Combination therapy (n = 53)
All treatment-emergent AEs	63 (63.0)	55 (55.6)	33 (62.3)
Serious AEs	4 (4.0)	4 (4.0)	3 (5.7)
AEs leading to discontinuation of investigational product	3 (3.0)	2 (2.0)	0 (0.0)
Fatal AEs	0 (0.0)	0 (0.0)	0 (0.0)
AEs occurring in ≥5% of patients			
Infections	28 (28.0)	31 (31.3)	14 (26.4)
Musculoskeletal and connective tissue disorders	33 (33.0)	19 (19.2)	11 (20.8)
Injury and procedural complications	10 (10.0)	9 (9.1)	3 (5.7)
Respiratory, thoracic, and mediastinal disorders	6 (6.0)	4 (4.0)	3 (5.7)
Gastrointestinal disorders	4 (4.0)	6 (6.1)	2 (3.8)
Nervous system disorders	5 (5.0)	4 (4.0)	2 (3.8)

* Values are the number (%) of patients. The safety analysis set comprises patients in whom actual treatment was received. Patients in the monotherapy groups were included in the combination therapy group for the safety analysis set if they additionally received at least one dose of the other drug (i.e., nonassigned) during the double-blind period. Adverse events (AEs) were captured from randomization through the safety follow-up period (30 days after a patient's end of study) and were categorized using the Medical Dictionary for Regulatory Activities version 2.2. Serious AEs included aortic pseudoaneurysm, reactive arthritis, pneumonia, respiratory syncytial virus infection, concussion, spinal fracture, (worsening of) rheumatoid arthritis, gastric ulcer hemorrhage, ankle fracture, osteoarthritis, and herpes zoster.

There was no difference in the cumulative time to recapture SDAI-defined remission between the 3 treatment groups (see Supplementary Figure 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41589/abstract).

Safety outcomes. No new safety signals with the use of methotrexate or etanercept were observed (Table 2). Over the double-blind period, rates of treatment-emergent adverse events, serious adverse events, and events leading to discontinuation of the investigational product were similar across the 3 treatment groups. No fatal adverse events occurred. The most common adverse events were infections and musculoskeletal and connective tissue disorders.

DISCUSSION

Results from the SEAM-RA trial show that in patients in whom sustained SDAI-defined remission was achieved following treatment with the combination of methotrexate and etanercept, withdrawal of methotrexate resulted in a significantly greater ability to maintain remission over 1 year compared to withdrawal of etanercept. In addition, in patients in whom methotrexate was withdrawn (i.e., group receiving etanercept monotherapy), maintenance of remission was similar to that in the combination therapy group, and etanercept monotherapy was associated with a longer time to disease-worsening and a lower degree and proportion of patients with disease-worsening when compared to methotrexate monotherapy.

Disease flares in the setting of treatment withdrawal are a key concern. Though flares occurred with therapy withdrawal, these study results overall are reassuring, in that they demonstrate that when combination therapy was reinstituted following disease-worsening, remission was recaptured in the majority of patients in both treatment-withdrawal groups. Among all patients with disease-worsening, remission was recaptured in 70–80%, and low disease activity was recaptured in 90–100% by the end of the study. Patients receiving etanercept or methotrexate monotherapy achieved similar recapture rates to the combination therapy group. The high rate of recapture achieved in the combination therapy group without a change in treatment has been previously observed (13). Among those patients in whom remission was recaptured, the median time to fully recapture remission after initiation of rescue therapy was 11 weeks in the methotrexate monotherapy group, 12 weeks in the etanercept monotherapy group, and 11.4 weeks in the combination therapy group. SDAI-defined low disease activity was recaptured in even more patients, with ~70–80% of patients showing recapturing of low disease activity by 12 weeks after initiation of rescue therapy. Time to recapture remission may be shorter when these strategies are implemented in real-world clinical practice, as very few patients received prednisone for disease flares in this trial. These results provide a conservative estimate as to how methotrexate plus etanercept can induce recapture of remission without the use of steroids.

A univariate analysis of selected covariates provided insights into potential predictors of maintaining remission, with data suggesting that there is a greater potential likelihood of maintaining remission in seronegative patients with lower disease activity and

a lower BMI. However, further and more sophisticated analysis of factors associated with maintaining remission is beyond the scope of this report.

Several features of the study should be noted. The combination therapy group served as a comparator to the monotherapy groups, and also showed the extent to which patients with sustained remission can experience disease-worsening over an extended period of time because of the inherent variability in RA disease activity. Consistent with the findings in a previous study (17), remission was not maintained in approximately one-half of the patients in the combination therapy group over the 48-week double-blind period. The majority of these patients met the criteria for disease-worsening, with a meaningful increase in disease activity (75–84% of patients having an SDAI score of >11) as opposed to multiple smaller fluctuations around an SDAI score of 3.3.

The etanercept monotherapy and combination therapy groups were not formally compared against each other, as the anticipated modest difference would have required a prohibitive sample size to demonstrate definitively. By including the combination therapy group, the study does provide meaningful information about the relative ability of etanercept to maintain remission.

Radiographs were not collected in the SEAM-RA trial. In the COMET trial (Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe RA), a difference in the proportion of patients with radiographic nonprogression was observed between the etanercept and methotrexate combination groups compared to the etanercept monotherapy group (16). However, the patients enrolled in the COMET trial had early disease, at a stage when there is a higher rate of radiographic progression, and the trial targeted remission defined by the Disease Activity Score in 28 joints, a less stringent definition of remission compared to the SDAI definition of remission. Given that patients in the SEAM-RA trial had a relatively long duration of disease, a very good level of disease control, and rapid institution of rescue therapy upon disease-worsening, differences in radiographic progression between the 3 treatment groups would be small and challenging to detect. However, the inverse correlation between disease control and radiographic progression is well known (25), and etanercept monotherapy and etanercept plus methotrexate combination therapy have been shown to elicit better radiographic outcomes as compared to methotrexate monotherapy (26,27).

Randomized patients had sustained good disease control for at least 1 year (6-month history plus 24-week observed run-in period) prior to therapy withdrawal, a duration designed to reflect the real-world clinical setting. This trial used the stringent SDAI definition of remission, which along with Boolean-defined remission, is both widely accepted and recommended by the ACR and EULAR (7,8) and accepted by the US Food and Drug Administration (28). Although SDAI-defined remission may be achievable in a relatively small proportion of RA patients, by adopting such a stringent criterion and enrolling patients in whom very good disease control has been sustained, with a mean SDAI score of 1.3 prior to randomization, this study investigated the effects of treatment withdrawal in near-ideal conditions. The study did not address gradual drug tapering, but the treatment-withdrawal design in the setting of sustained stringent remission does provide a "best case" scenario for patients in whom reduction of therapy is being considered. Moreover, simply reducing therapy may not lessen the long-term safety concerns and the need for monitoring.

Overall, the results of the SEAM-RA study provide information on the likelihood of success of discontinuing methotrexate and can inform general decision-making around RA treatment strategies. These results may be of particular interest to physicians and patients concerned about adverse events, such as nausea and fatigue, and long-term safety issues associated with methotrexate (10,29). Differences among the various TNFi, in terms of the need for long-term administration of monotherapy as compared to combination therapy, have been reported and may be related, in part, to the differences in immunogenicity profiles, with etanercept showing potential benefits (30–34). Thus, sustained efficacy, tolerability, and possible safety risks should be carefully weighed in clinical decisions related to treatment choice and withdrawal. The results from the SEAM-RA trial have practical implications and may inform decision-making for patients and physicians when withdrawal of therapy is being considered to reduce treatment burden in the setting of well-controlled RA.

ACKNOWLEDGMENT

We thank Linda Rice, PhD, of Amgen Inc. for providing assistance with the drafting of the manuscript and for preparing the tables and figures.

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. Curtis 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.

Study conception and design. Curtis, Haraoui, Kricorian, Chung.
Acquisition of data. Curtis, Haraoui, Bykerk, Karis, Yen, Kricorian, Chung.
Analysis and interpretation of data. Curtis, Emery, Karis, Haraoui, Bykerk, Yen, Kricorian, Chung.

ROLE OF THE STUDY SPONSOR

Amgen Inc., the sponsor of the SEAM-RA trial, designed the trial in collaboration with academic investigators, oversaw data collection, performed the data analyses, and supported the development of this manuscript. Data interpretation and writing of the manuscript were performed by both the Amgen and non-Amgen authors. The corresponding author had full access to all of the data in the study. The sponsor and the corresponding author had the final responsibility for the decision to submit this report for publication. Publication of this article was contingent upon approval by Amgen Inc. and all of the authors.

REFERENCES

1. Hamann P, Holland R, Hyrich K, Pauling JD, Shaddick G, Nightingale A, et al. Factors associated with sustained remission in rheumatoid arthritis in patients treated with anti–tumor necrosis factor. Arthritis Care Res (Hoboken) 2017;69:783–93.
2. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. JAMA 2018;320:1360–72.
3. Edwards CJ, Galeazzi M, Bellinvia S, Ringer A, Dimitroulas T, Kitas G. Can we wean patients with inflammatory arthritis from biological therapies? [review]. Autoimmun Rev 2019;18:102399.
4. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675–81.
5. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26–37.
6. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al, on behalf of the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594–602.
7. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016; 68:1–26.
8. Smolen JS, Landewe RB, Bijlsma JW, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:685–99.
9. Treharne GJ, Douglas KM, Iwaszko J, Panoulas VF, Hale ED, Mitton DL, et al. Polypharmacy among people with rheumatoid arthritis: the role of age, disease duration and comorbidity. Musculoskeletal Care 2007;5:175–90.
10. Wang W, Zhou H, Liu L. Side effects of methotrexate therapy for rheumatoid arthritis: a systematic review. Eur J Med Chem 2018;158:502–16.
11. Pope JE, Haraoui B, Thorne JC, Vieira A, Poulin-Costello M, Keystone EC. The Canadian Methotrexate and Etanercept Outcome Study: a randomised trial of discontinuing versus continuing methotrexate after 6 months of etanercept and methotrexate therapy in rheumatoid arthritis. Ann Rheum Dis 2014;73:2144–51.
12. Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazoque-Palazuelos F, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. Lancet 2013;381:918–29.
13. Van Vollenhoven RF, Ostergaard M, Leirisalo-Repo M, Uhlig T, Jansson M, Larsson E, et al. Full dose, reduced dose or discontinuation of etanercept in rheumatoid arthritis. Ann Rheum Dis 2016; 75:52–8.
14. Emery P, Hammoudeh M, FitzGerald O, Combe B, Martin-Mola E, Buch MH, et al. Sustained remission with etanercept tapering in early rheumatoid arthritis. N Engl J Med 2014;371: 1781–92.
15. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008;372:375–82.
16. Emery P, Breedveld F, van der Heijde D, Ferraccioli G, Dougados M, Robertson D, et al. Two-year clinical and radiographic results with combination etanercept–methotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. Arthritis Rheum 2010;62:674–82.
17. Prince FH, Bykerk VP, Shadick NA, Lu B, Cui J, Frits M, et al. Sustained rheumatoid arthritis remission is uncommon in clinical practice. Arthritis Res Ther 2012;14:R68.
18. Ajeganova S, Huizinga T. Sustained remission in rheumatoid arthritis: latest evidence and clinical considerations. Ther Adv Musculoskelet Dis 2017;9:249–62.
19. Curtis JR, Trivedi M, Haraoui B, Emery P, Park GS, Collier DH, et al. Defining and characterizing sustained remission in patients with rheumatoid arthritis. Clin Rheumatol 2018;37:885–93.
20. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford) 2003;42: 244–57.
21. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573–86.
22. Enbrel (etanercept) prescribing information. Thousand Oaks (CA): Immunex; 2017.
23. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62: 2569–81.
24. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
25. Van der Heijde D. Radiographic progression in rheumatoid arthritis: does it reflect outcome? Does it reflect treatment? Ann Rheum Dis 2001;60 Suppl 3:iii47–50.
26. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum 2002;46:1443–50.
27. Van der Heijde D, Klareskog L, Landewé R, Bruyn GA, Cantagrel A, Durez P, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 2007;56: 3928–39.
28. US Food and Drug Administration. Guidance document: rheumatoid arthritis–developing drug products for treatment. May 2013. URL: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rheumatoid-arthritis-developing-drug-products-treatment.
29. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, et al. Low-dose methotrexate for the prevention of atherosclerotic events. N Engl J Med 2019;380:752–62.
30. Jani M, Barton A, Warren RB, Griffiths CE, Chinoy H. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. Rheumatology (Oxford) 2014; 53: 213–22.
31. Fagerli KM, Lie E, van der Heijde D, Heiberg MS, Lexberg AS, Rodevand E, et al. The role of methotrexate co-medication in TNF-inhibitor treatment in patients with psoriatic arthritis: results from 440 patients included in the NOR-DMARD study. Ann Rheum Dis 2014;73:132–7.

32. Favalli EG, Pregnolato F, Biggioggero M, Becciolini A, Penatti AE, Marchesoni A, et al. Twelve-year retention rate of first-line tumor necrosis factor inhibitors in rheumatoid arthritis: real-life data from a local registry. Arthritis Care Res (Hoboken) 2016; 68:432–9.
33. Emery P, Vlahos B, Szczypa P, Thakur M, Jones HE, Woolcott J, et al. Longterm drug survival of tumor necrosis factor inhibitors in patients with rheumatoid arthritis. J Rheumatol 2020;47: 493–501.
34. Pappas DA, Litman HJ, Lesperance T, Kricorian G, Karis E, Rebello S, et al. Persistence on biologic DMARD monotherapy after achieving rheumatoid arthritis disease control on combination therapy: retrospective analysis of CORRONA registry data. Rheumatol Int 2021;41: 381–90.