Article:
Curtis, J.R., Emery, P. orcid.org/0000-0002-7429-8482, Kricorian, G. et al. (4 more authors) (Cover date: September 2023) Factors Associated With Maintenance of Remission Following Change From Combination Therapy to Monotherapy in Patients With Rheumatoid Arthritis. Journal of Rheumatology, 50 (9). pp. 1114-1120. ISSN 0315-162X

https://doi.org/10.3899/jrheum.2022-1008

The Journal of Rheumatology 2023;50:1114–20
doi:10.3899/jrheum.2022-1008
First Release June 1 2023

The Journal of Rheumatology

Factors Associated With Maintenance of Remission Following Change From Combination Therapy to Monotherapy in Patients With Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Some patients with rheumatoid arthritis (RA) who persist in remission may decide to stop their therapy. We evaluated baseline characteristics associated with remaining in remission or low disease activity (LDA) following medication withdrawal.

Methods. The Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects With Rheumatoid Arthritis (SEAM-RA) was a phase III, multicenter, randomized withdrawal, double-blind, controlled study in patients with RA on methotrexate (MTX) + etanercept (ETN). If remission (Simplified Disease Activity Index [SDAI] ≤ 3.3) was sustained through a 24-week run-in period, patients then entered a 48-week double-blind period and were randomized 2:2:1 to receive MTX monotherapy, ETN monotherapy, or continue combination therapy. Multivariate logistic regression analysis was performed to identify baseline factors associated with remission or LDA at the end of both periods.

Results. Of 371 patients enrolled, 253 entered the double-blind period. After adjusting for other factors, covariates associated with achieving SDAI remission at the end of the run-in period included younger age, longer duration of MTX treatment, and less severe clinical disease variables. Covariates associated with maintaining remission/LDA at the end of the 48-week double-blind period included lower patient global assessment of disease activity (PtGA), lower C-reactive protein, rheumatoid factor (RF) negativity, longer RA duration in the MTX arm, shorter duration of ETN treatment, and lower magnesium.

Conclusion. These findings indicate patients with overall lower disease activity are more likely to remain in SDAI remission/LDA after switching from combination therapy to monotherapy. RF-negative status and lower PtGA scores were strongly associated with increased likelihood of remaining in remission/LDA with MTX or ETN monotherapy. (SEAM-RA; ClinicalTrials.gov: NCT02373813)

Key Indexing Terms: etanercept, induction of remission, methotrexate, rheumatoid arthritis

A treat-to-target approach has been recommended for the treatment of rheumatoid arthritis (RA), with low disease activity (LDA) or remission as treatment targets.[1,2] Remission is achieved more frequently with combination therapy with biologics and conventional disease-modifying antirheumatic drugs (DMARDs) than either treatment alone.[3] However, once remission is achieved, patients may not need to continue both therapies. Reducing therapy may be preferable to patients because of cost, medication burden, and tolerability.

According to the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology recommendations, continuation of all DMARDs at their current dose is conditionally recommended over a dose reduction of a DMARD. However, patients with RA who persist in remission

This study was funded by Immunex, a wholly owned subsidiary of Amgen Inc.

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JRC received grants and consultant fees from AbbVie, Amgen, BMS, Corrona, Eli Lilly, Gilead, Janssen, Myriad, Novartis, Pfizer, Sanofi, and Scipher Medicine; and speaker bureau fees from AbbVie, Amgen, BMS, Corrona, Eli Lilly, Gilead, Janssen, Myriad, Novartis, Pfizer, Sanofi, and Scipher Medicine. PE received consultant fees from AbbVie, BMS, Celltrion, Gilead, Eli Lilly, Novartis, Pfizer, Roche, Samsung, and Sandoz; and received grants from AbbVie, BMS, Eli Lilly, Novartis, Roche, and Samsung. GK, PKY, and DHC are employees and stockholders of Amgen Inc. VB received consultant fees from Amgen, BMS, Gilead, Pfizer, Sanofi-Genzyme/Regeneron, Scipher Medicine, and UCB; and received grant/research support from Amgen and Novartis. BH received speaker bureau fees from AbbVie, Celgene, Janssen, Pfizer, and UCB; received consultant fees from AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Merck, Pfizer, Roche, Sandoz, Sanofi-Genzyme, and UCB; and received grant/research support from Roche, AbbVie, Amgen, Merck, and Pfizer.

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Accepted for publication February 16, 2023.

may consider tapering their therapy, provided that a therapeutic dose of at least 1 DMARD is maintained.[2,4] Dose reduction is recommended over discontinuation, but if a DMARD is discontinued, it is recommended that patients do so gradually. After withdrawing therapy, some patients persist in remission whereas others experience disease-worsening.[5] Identification of clinical markers associated with a patient remaining in remission or LDA following tapering would be of value to guide clinicians in their decision to taper therapy. Further, being able to accurately predict which patients may remain in remission would be helpful for clinicians and to facilitate shared decision-making.

Although a number of studies have examined treatment withdrawal among patients with RA in LDA, the Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects With Rheumatoid Arthritis (SEAM-RA) was the first trial, to our knowledge, to investigate the effect of withdrawing either methotrexate (MTX) or etanercept (ETN) on the maintenance of remission.[5] SEAM-RA showed that significantly more patients receiving ETN monotherapy maintained remission defined by the Simplified Disease Activity Index (SDAI) than those receiving MTX monotherapy at 48 weeks (49.5% vs 28.7%; $P < 0.004$). This is consistent with ACR guidelines, which note that discontinuation of MTX is conditionally recommended over discontinuation of a biological DMARD or target-specific DMARD in patients taking MTX in combination with a DMARD.

We have previously conducted a univariate logistic regression analysis to identify baseline factors associated with persisting in remission following medication withdrawal in SEAM-RA.[5] Here we conducted a more rigorous assessment using multivariate logistic regression analysis to identify factors associated with maintaining remission both on combination therapy and after switching to monotherapy. To our knowledge, this is the first study to identify factors associated with remission upon therapy withdrawal, and then use those factors to develop a model evaluating the likelihood of remaining in remission at the end of the trial.

METHODS

Study design. SEAM-RA (ClinicalTrials.gov: NCT02373813) was a phase III, multicenter, randomized withdrawal, double-blind, controlled study. The study consisted of a 30-day screening period, a 24-week open-label run-in period, a 48-week double-blind treatment period, and a 30-day safety follow-up period (Supplementary Figure S1, available with the online version of this article). During the run-in period, patients received open-label ETN and MTX at the same dose they were receiving during screening. If remission (SDAI ≤ 3.3) was sustained through the run-in period, patients were randomized 2:2:1 to receive ETN 50 mg weekly by subcutaneous (SC) injection + oral placebo, oral MTX 10 mg to 25 mg weekly + SC placebo, or ETN 50 mg weekly SC + oral MTX 10 mg to 25 mg weekly (combo). After randomization, if a patient experienced disease-worsening, they received rescue treatment with ETN 50 mg weekly + MTX 10 mg to 25 mg, regardless of their assigned treatment. Disease-worsening was defined as SDAI > 3.3 and ≤ 11 on 2 consecutive visits at least 2 weeks apart, SDAI > 3.3 and ≤ 11 on ≥ 3 separate visits, or SDAI > 11 at any time.

This study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines. 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.

Patients. A detailed account of eligibility criteria has been previously reported.[5] Patients with RA were ≥ 18 years of age taking ETN and MTX for at least 6 months prior to study entry. Key eligibility criteria for the run-in period included very good disease control for 6 months prior to study entry and SDAI ≤ 3.3 at screening. Eligibility criteria for entering the double-blind period included SDAI ≤ 3.3 at run-in visit 3. Exclusion criteria included any clinically significant change in eligibility criteria during the run-in period, SDAI > 3.3 and ≤ 11 on 2 consecutive visits at least 2 weeks apart, SDAI > 3.3 and ≤ 11 on ≥ 2 separate visits, or SDAI > 11 at any time during the run-in period (ie, disease-worsening).

Statistical analysis. We evaluated > 60 covariates in a stepwise approach to identify baseline factors (measured respectively at time of enrollment and randomization) associated with persisting in SDAI remission at the end of the run-in period, as well as a separate model for maintaining SDAI remission or LDA at the end of 48 weeks without disease-worsening during the double-blind treatment period. A P value of ≤ 0.25 was required to enter the regression model, and covariates remained in the multivariate model if the P value was ≤ 0.15 or if they were of clinical interest based on prior reports in the literature. For the double-blind treatment period, interactions between all covariates and the treatment arm were also assessed during variable selection to consider varying magnitudes of association by treatment arm. Score selection with the best subset was used to confirm the model.

Patients with missing SDAI values at week 48 and patients whose disease worsened were considered nonresponders. P values for odds ratios (ORs) were calculated using the Wald test. P values were not adjusted for multiplicity and thus are all nominal.

The receiver-operating characteristic curve (ROC) was used to assess discrimination of the logistic regression model. Additionally, a decile-based calibration curve comparing the predicted probability of SDAI remission to the observed probability of SDAI remission was generated to assess the agreement between the 2 probabilities by testing for lack of fit.

RESULTS

Run-in period: patient characteristics. A total of 371 patients were enrolled. Baseline demographics and disease characteristics for the run-in period have been published previously.[6] At the end of the run-in period, 253 patients were in remission and 118 were not. There were some differences in baseline characteristics between those who achieved remission and those who did not (Table 1). Patients who achieved remission at the end of the run-in period were younger and receiving a higher dose of MTX at baseline than those who did not. Additionally, patients who achieved remission had lower baseline patient global assessment (PtGA) and clinical variables, including swollen joint count (SJC), tender joint count (TJC), SDAI, and Disease Activity Score in 28 joints with C-reactive Protein (DAS28-CRP).

Run-in period: multivariate logistic regression analysis. MTX and ETN duration prior to enrollment, age, and PtGA at baseline (measured at time of enrollment) were all found to be significantly associated with sustaining remission at the end of the run-in period (Figure 1). Each 1-year increase in MTX duration prior to enrollment was associated with 1.10 times the odds of remission ($P = 0.004$). An increase in age, PtGA, and ETN duration prior to enrollment were all associated with decreased odds of remission ($P = 0.01$, 0.002, and 0.04, respectively). Higher SJC and TJC were associated with lower odds of maintaining remission, and higher MTX dose was associated with increased odds.

Table 1. Demographics and disease characteristics at enrollment for run-in period.

	Not in SDAI Remission at End of Run-In, n = 118	In SDAI Remission at End of Run-In, n = 253	Overall, N = 371
Age, yrs	59.6 (11.4)	55.6 (12.2)	56.8 (12.1)
MTX dose, mg/wk	14.9 (4.4)	16.3 (4.7)	15.9 (4.6)
MTX duration prior to enrollment, yrs	5.4 (4.6)	6.3 (5.4)	6.0 (5.2)
ETN duration prior to enrollment, yrs	4.6 (3.7)	3.8 (3.6)	4.1 (3.6)
Duration of RA, yrs	11.9 (9.6)	10.3 (7.8)	10.8 (8.4)
TJC (0-68)	0.6 (1.1)	0.2 (0.5)	0.3 (0.8)
SJC (0-66)	0.4 (0.8)	0.1 (0.5)	0.2 (0.6)
PtGA (0-100)	10.2 (14.1)	5.3 (7.4)	6.8 (10.3)
PGA (0-100)	3.4 (5.5)	2.5 (3.0)	2.8 (4.0)
CRP, mg/L	4.7 (7.7)	4.4 (9.2)	4.5 (8.7)
SDAI (0-86)	2.4 (2.1)	1.4 (1.3)	1.8 (1.7)
DAS28-CRP	1.8 (0.5)	1.6 (0.4)	1.6 (0.4)

Values represent mean (SD). CRP: C-reactive protein; DAS28-CRP: Disease Activity Score in 28 joints with C-reactive protein; ETN: etanercept; MTX: methotrexate; PGA: physician global assessment of disease activity; PtGA: patient global assessment of disease activity; RA: rheumatoid arthritis; SDAI: Simplified Disease Activity Index; SJC: swollen joint count; TJC: tender joint count.

The area under the curve for the ROC was 0.71, which indicated fair efficiency of the model in prediction of SDAI remission. A calibration plot using deciles confirmed the model was well-calibrated, as the predicted values were closely distributed around the straight line (Figure 2).

Double-blind treatment period: patient characteristics. In total, 253 patients with RA were included in the analysis of the double-blind treatment period. Demographics and clinical characteristics at time of randomization were well-balanced across treatment groups (previously published).[5] The group of patients who remained in remission or LDA (n = 118) had fewer women and fewer patients with BMI (calculated as weight in kilograms divided by height in meters squared) > 30 at time of randomization compared to the group that did not maintain remission or LDA at the end of the double-blind period (n = 135; Table 2). The group that maintained remission or LDA also had shorter MTX duration prior to enrollment and shorter duration of RA. SDAI, PtGA, and physician global assessment (PGA) were lower and fewer patients were anticyclic citrullinated peptide (CCP) positive or rheumatoid factor (RF) positive in those who maintained remission.

Double-blind treatment period: multivariate logistic regression analysis. We first evaluated baseline factors (measured at time of randomization) associated with remaining in persistent remission or LDA at the end of the treatment period in the overall population. After adjusting for other factors, each 1-point higher PtGA at baseline was associated with a 0.93 lower likelihood to maintain SDAI remission/LDA at week 48 ($P = 0.01$; Figure 3A). Patients who were RF positive were less than half as likely as patients who were RF negative to remain in remission/LDA at week 48. Each 1-unit increase in CRP also was associated with 0.93 times the odds of remaining in remission/LDA at week 48 ($P = 0.03$). Longer duration of ETN treatment slightly increased the odds of SDAI remission/LDA at week 48 (OR 1.12). Although not significant, higher BMI at baseline decreased the odds of remaining in remission/LDA at week 48, and anti-CCP positivity increased the odds. A sensitivity analysis excluding patients without an SDAI value at week 48 and who did not disease-worsen found consistent results. No predictors of lack of follow-up were identified.

We have previously shown that ETN monotherapy showed benefit in maintaining remission over MTX monotherapy in this study.[5] Here we assessed this further by analyzing factors that had an interaction with the treatment arm. The joint Wald test for an interaction effect between treatment arm and magnesium concentration yielded a P value of 0.05. Patients on MTX monotherapy and ETN monotherapy and with higher magnesium concentrations at baseline had lower odds of maintaining

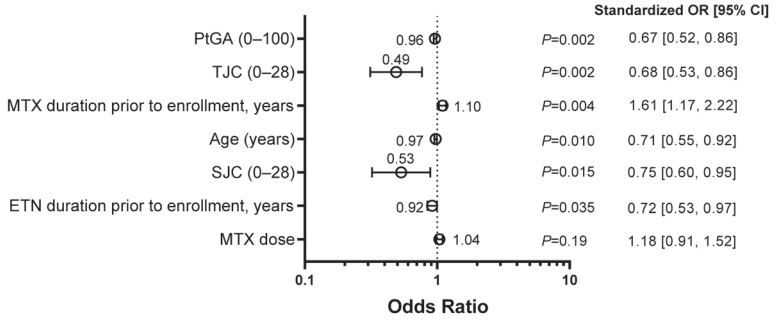

Figure 1. Odds of remaining in SDAI remission/LDA at the end of the run-in period by baseline clinical variable (measured at time of enrollment). OR < 1 indicates decreased odds of remaining in remission; OR > 1 indicates increased odds of remaining in remission. Error bars indicate 95% CI. For continuous variables, ORs were calculated for a 1-unit increase. *P* values are nominal. ETN: etanercept; LDA: low disease activity; MTX: methotrexate; OR: odds ratio; PtGA: patient global assessment of disease activity; SDAI: Simplified Disease Activity Index; SJC: swollen joint count; TJC: tender joint count.

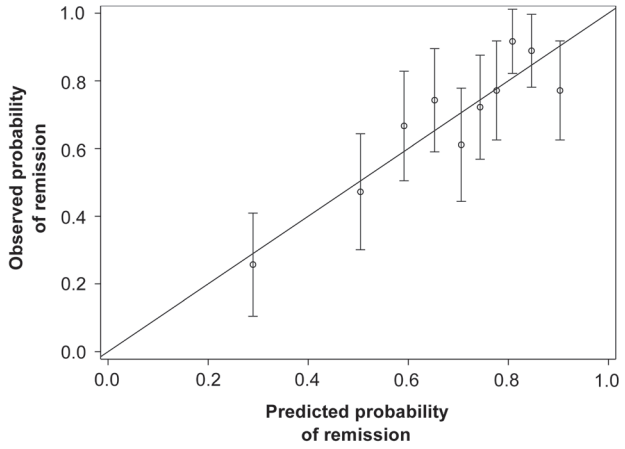

Figure 2. Decile calibration plot for run-in period multivariate model estimating the likelihood of remaining in remission. Values below the line indicate overestimation; values above the line indicate underestimation.

Table 2. Patient demographics and clinical characteristics at randomization for the double-blind period.

	Not in SDAI Remission or LDA at End of Double-Blind Period, n = 135	In SDAI Remission or LDA at End of Double-Blind Period, n = 118	Overall, N = 253
Age, yrs	56.0 (12.0)	55.0 (12.5)	55.6 (12.2)
Women, n (%)	107 (79.3)	86 (72.9)	193 (76.3)
White, n (%)	118 (87.4)	102 (86.4)	220 (87.0)
BMI[a] > 30, n (%)	55 (40.7)	37 (31.4)	92 (36.4)
ETN duration prior to enrollment, yrs	3.8 (3.4)	3.9 (3.7)	3.8 (3.6)
MTX duration prior to enrollment, yrs	6.6 (5.8)	5.8 (5.0)	6.2 (5.4)
Duration of RA, yrs	10.9 (7.2)	9.7 (8.4)	10.3 (7.8)
SDAI (0-86)	1.5 (1.3)	0.9 (1.0)	1.3 (1.2)
SJC (0-66)	0.2 (0.5)	0.1 (0.4)	0.1 (0.5)
TJC (0-68)	0.2 (0.6)	0.2 (0.6)	0.2 (0.6)
PtGA (0-100)	5.4 (7.4)	3.0 (5.1)	4.3 (6.5)
PGA (0-100)	3.5 (8.3)	2.0 (2.5)	2.8 (6.3)
CRP, mg/L	3.6 (5.3)	3.2 (7.1)	3.4 (6.2)
Anti-CCP positive, n (%)	95 (70.4)	73 (61.9)	168 (66.4)
RF positive, n (%)	91 (67.4)	67 (56.8)	158 (62.5)
Magnesium, mg/dL	2.2 (0.2)	2.1 (0.2)	2.1 (0.2)

Values represent mean (SD), unless otherwise specified. [a]BMI calculated as weight in kilograms divided by height in meters squared. CCP: cyclic citrullinated peptide; CRP: C-reactive protein; ETN: etanercept; LDA: low disease activity; MTX: methotrexate; PGA: physician global assessment of disease activity; PtGA: patient global assessment of disease activity; RA: rheumatoid arthritis; RF: rheumatoid factor; SDAI: Simplified Disease Activity Index; SJC: swollen joint count; TJC: tender joint count.

remission/LDA, with an especially strong association within ETN monotherapy (Figure 3B). Specifically, a patient with 0.1 mg/dL higher magnesium concentration at baseline in the MTX arm was 16% less likely to be in remission/LDA, and a patient with a 0.1 mg/dL higher magnesium concentration at baseline in the ETN arm was 39% less likely to be in remission/LDA, after adjusting for other covariates in the model. The joint Wald test for an interaction effect between the treatment arm and duration of RA yielded a *P* value of 0.04. Shorter RA duration (≤ 5 yrs) in the MTX arm was associated with 5.28 times the odds of SDAI remission/LDA compared to longer (> 5 yrs) duration (Figure 3B). Among patients with RA duration > 5 years, those receiving ETN monotherapy and combo therapy were more likely to remain in remission/LDA than those receiving MTX monotherapy (Figure 3C). Odds varied depending on baseline levels of magnesium.

Discrimination of the prediction model to maintain remission over 48 weeks was good, with an area under the curve for the ROC of 0.78. The decile calibration plot showed that the overall prediction model was well-calibrated (Figure 4). There was no evidence of poor fit ($P = 0.75$).

DISCUSSION

Understanding factors associated with a patient achieving remission while on therapy for RA is important to predict how well an individual patient will do. Here we found significant differences in baseline characteristics between patients who remained in remission and those who did not after 24 weeks of ETN and MTX combination therapy. Patients who maintained remission at the end of the run-in period were younger, had been receiving a higher dose of MTX, and had lower disease activity. In alignment with this, a multivariate analysis also found increased age and PtGA to be significantly associated with lower odds of maintaining remission at the end of the run-in period. Interestingly, although there was a significant difference in baseline PtGA between those who maintained remission and those who did not, there was no difference in PGA, suggesting a patient's assessment of their own disease may be more sensitive. This difference may reflect the ability of the patient assessment to identify disease aspects not able to be observed by physician assessment such as psychosocial factors. In support of this, patient well-being and disease perception have been found to predict the probability of sustained remission in patients with RA.[7] Whereas a longer duration of MTX treatment prior to enrollment was associated with better odds of maintaining remission during the run-in period, the converse was found for duration of ETN treatment. It is possible this discrepancy may be a result of factors such as age, disease duration, duration of treatment (ie, MTX alone is typically prescribed first in clinical practice and therefore used longer than ETN), and use of MTX and ETN as a monotherapy vs combination therapy.

Drug-free remission is of increasing interest in the treatment paradigm for RA.[8] In order to help achieve this, there is a need to identify patients who are likely to succeed in maintaining remission following treatment tapering. In a multivariate logistic regression analysis, we found that higher PtGA and CRP were significantly associated with decreased likelihood of maintaining persistent remission or LDA following a reduction from combination therapy to monotherapy with ETN or MTX. In contrast to results from the run-in period, longer duration of ETN treatment prior to enrollment, but not MTX, was significantly

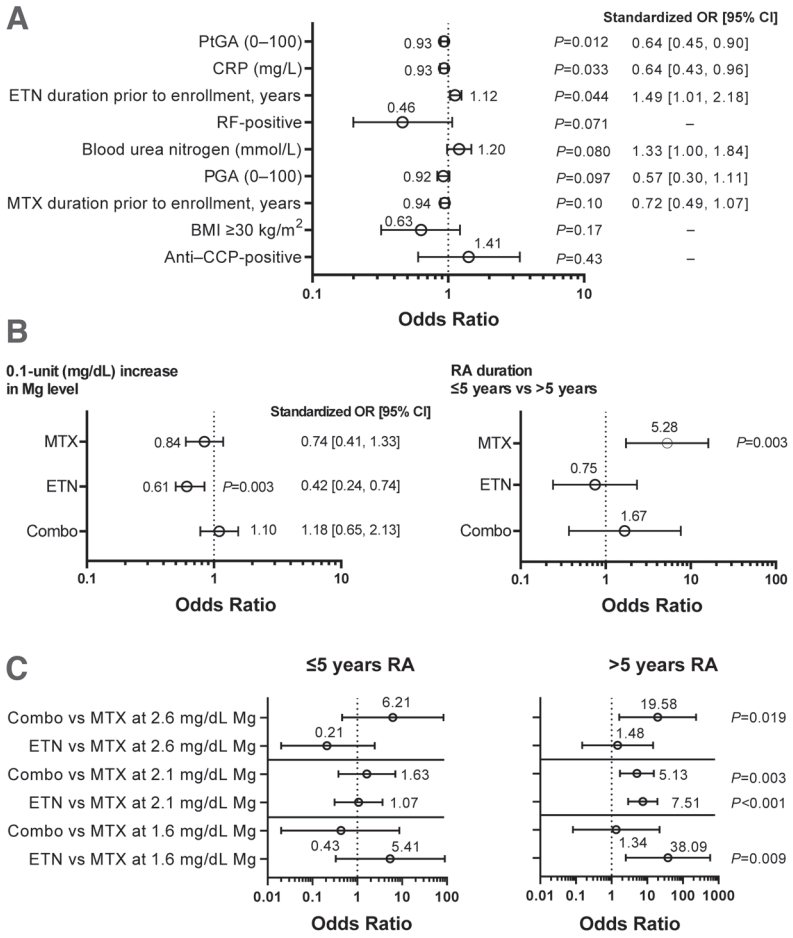

Figure 3. (A) Multivariable-adjusted odds of remaining in SDAI remission/LDA at the end of the double-blind treatment period by baseline clinical variable (measured at time of randomization), (B) factors interacting with treatment arm, and (C) baseline magnesium level. OR < 1 indicates decreased odds of remaining in remission; OR > 1 indicates increased odds of remaining in remission. Error bars indicate 95% CIs. For continuous variables, ORs were calculated for a 1-unit increase. *P* values are nominal. Standardized ORs describing the OR associated with a 1 SD change are shown to the right of the figure for continuous variables. CCP: cyclic citrullinated peptide; CRP: C-reactive protein; ETN: etanercept; LDA: low disease activity; Mg: magnesium; MTX: methotrexate; OR: odds ratio; PGA: physician global assessment of disease activity; PtGA: patient global assessment of disease activity; RA: rheumatoid arthritis; RF: rheumatoid factor; SDAI: simplified disease activity index.

associated with increased likelihood of maintaining persistent remission or LDA during the double-blind period. Although not achieving significance, RF positivity and BMI ≥ 30 were negatively associated with remission/LDA. These results support our earlier findings by univariate logistic regression analysis that higher SDAI, RF positivity, and higher BMI at baseline were associated with decreased likelihood of remaining in remission.[5] Interestingly, RF and anti-CCP positivity appeared to have opposite associations. However, the direction of one must be interpreted in the context of the opposite directionality of the other in the same model, as they are adjusted for one another. Additionally, the wide overlapping CIs, and the forcing of anti-CCP into the model because of clinical interest should limit interpretation. We also found that we were able to accurately estimate who could maintain persistent remission during the run-in period (when no treatment was being modified) as well as during the double-blind period when ETN or MTX was discontinued. The ability to predict which patients may do well off of therapy is important and is likely to encourage patients with a greater likelihood to do well off of treatment to attempt discontinuation.

Early treatment of disease has been established as key for achieving optimal treatment outcomes.[9] Patients who enter remission faster are also more likely to sustain remission.[10] Patients with shorter duration of RA are better able to achieve remission.[11] Our findings align with this in that shorter duration of RA (≤ 5 yrs) in the MTX arm was significantly associated with increased odds of maintaining remission/LDA (P = 0.003). Similarly, age has been reported to be a factor influencing likelihood of achieving remission, with higher rates of remission

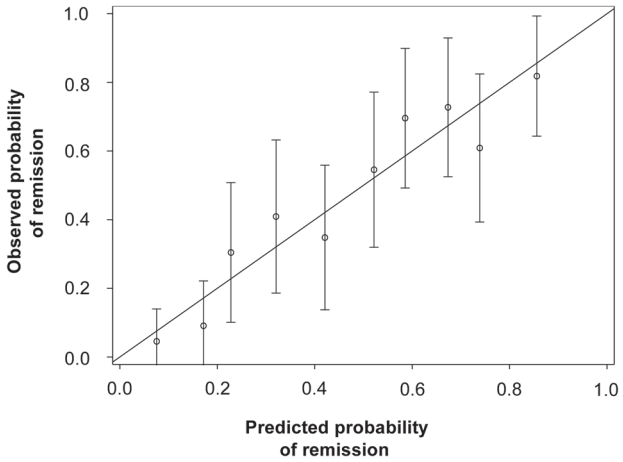

Figure 4. Decile calibration plot for double-blind period multivariate model estimating the likelihood of remaining in remission at the end of the trial. Values below the line indicate overestimation; values above the line indicate underestimation.

in younger patients.[11] Our analysis of the run-in period showed similar results.

Serum magnesium level is emerging as a potential risk factor in RA, though this connection is not yet understood. It is unclear whether magnesium levels influence the disease or vice versa. Magnesium decreases inflammatory cytokine production.[12] A threshold effect has been reported for dietary magnesium intake and risk of RA whereby moderate doses of magnesium (184-446 mg/day) were associated with the lowest prevalence of RA but lower or higher levels had higher prevalence.[13] Similarly, we find here variable odds of remaining in remission according to baseline magnesium levels. Additionally, the association of magnesium levels with remission varied by treatment arm. Higher levels of magnesium were associated with decreased odds of remission in the ETN treatment arm. This connection between magnesium and maintenance of remission has not, to our knowledge, been reported previously. We have reported previously that overall odds of maintaining remission favor ETN over MTX.[5] That pattern continued here with higher odds of maintaining remission with ETN vs MTX at lower levels of magnesium (1.6 and 2.1 mg/dL) and longer duration of RA.

A limitation of this study is that it was not designed prospectively to yield a predictive model to determine which patients could discontinue therapy. The study is influenced by the immediate withdrawal of MTX or ETN. As such, since some treatment guidelines recommend gradual discontinuation of a DMARD over abrupt discontinuation,[4] the model used here may not be directly generalizable to clinical practice. For example, the factors associated with successful discontinuation described herein may be accurate, although the time course may be more prolonged in a real-world setting in which treatment withdrawal is more gradual. Our model, which used baseline factors to evaluate which patients have the greatest chance of success to do well off treatment, was likely influenced by the sequential nature of the study design, in which patients had to successfully maintain remission (or close to it) during the 24-week run-in period in order to remain eligible for the 48-week interventional phase of the study. Additionally, our sample size was limited to create a model using a random split sample or other methods appropriate to select variables and avoid overfitting of the model. Since this was a posthoc analysis, the lack of adjustment for multiplicity should be taken into consideration as well. Considering all these factors, the results from our models may be optimistic. Further study validating this or other predictive models for successful treatment discontinuation in other RA cohorts is needed, and this may be an important component of some value-based care reimbursement strategies.

Even within the significant constraints that patients had to meet to qualify for SEAM-RA, patients with overall lower disease activity are more likely to achieve and remain in SDAI remission/LDA. RF-negative status and lower PtGA scores in particular were associated with increased likelihood of remaining in remission/LDA with MTX or ETN monotherapy. The role of magnesium in retaining good disease control warrants further exploration. These results may help guide clinicians in deciding whether to discontinue MTX or ETN in a patient with RA in sustained remission on a combination of ETN and MTX.

ACKNOWLEDGMENT

Medical writing support was funded by Amgen Inc. and provided by Rebecca Lane, PhD, of Peloton Advantage, an OPEN Health company, and Julie Wang, DPM, of Amgen Inc.

DATA AVAILABILITY

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

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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