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: SEAM-RA was a phase 3, multicenter, randomized withdrawal, double-blind, controlled study in patients with RA on methotrexate + etanercept. 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 methotrexate monotherapy, etanercept 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 methotrexate treatment, and less severe clinical disease parameters. 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 methotrexate arm, shorter duration of etanercept treatment, and lower magnesium.

Conclusions: 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 likelihood of remaining in remission/LDA with methotrexate or etanercept monotherapy.
INTRODUCTION

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.\textsuperscript{1, 2} Remission is achieved more frequently with combination therapy with biologics and conventional disease-modifying antirheumatic drugs (cDMARDs) than either treatment alone.\textsuperscript{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 League Against Rheumatism (EULAR) 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 may consider tapering their therapy, provided that a therapeutic dose of at least one DMARD is maintained.\textsuperscript{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 while others experience disease-worsening.\textsuperscript{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
investigate the effect of withdrawing either methotrexate or etanercept on the maintenance of remission.\textsuperscript{5} SEAM-RA showed that significantly more patients receiving etanercept monotherapy maintained remission defined by the Simple Disease Activity Index (SDAI) than those receiving methotrexate monotherapy at 48 weeks (49.5\% vs 28.7\%; \( P < 0.004 \)). This is consistent with ACR guidelines, which note that discontinuation of methotrexate is conditionally recommended over discontinuation of a biological DMARD or target-specific DMARD in patients taking methotrexate 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.\textsuperscript{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 (NCT02373813) was a phase 3, 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 (Supplemental Figure 1). During the run-in period, patients received
open-label etanercept and methotrexate 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 etanercept 50 mg weekly by subcutaneous (SC) injection plus oral placebo, oral methotrexate 10 to 25 mg weekly plus SC placebo, or etanercept 50 mg weekly SC plus oral methotrexate 10 to 25 mg weekly (combo). After randomization, if a patient experienced disease-worsening, they received rescue treatment with etanercept 50 mg weekly plus methotrexate 10 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 or more separate visits, or SDAI >11 at any time.

This study was conducted in accordance with 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. Patients with RA were ≥18 years of age taking etanercept and methotrexate 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 or more separate visits, or SDAI >11 at any time during the run-in period (ie, disease-worsening).

**Statistical Analysis**

We evaluated more than 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 \( \leq 0.25 \) was required to enter the regression model, and covariates remained in the multivariate model if the \( P \) value was \( \leq 0.15 \) 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 treatment arm were also assessed during variable selection to consider varying magnitudes of association by treatment arm. Score selection with best subset was used to confirm the model.

Patients with missing SDAI value at week 48 and patients who disease-worsened were considered non-responders. \( P \) values for odds ratios were calculated using the Wald test. \( P \)-values were not adjusted for multiplicity and thus are all nominal.

The Receiver Operating Characteristic (ROC) curve 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 two 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. 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 methotrexate at baseline than those who did not. Additionally, patients who achieved remission had lower baseline Patient Global Assessment (PtGA) and clinical parameters, including swollen joint count (SJC), tender joint count (TJC), SDAI, and Disease Activity Score-28 with C-reactive protein (DAS28-CRP).

Multivariate logistic regression analysis

Methotrexate and etanercept 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 methotrexate duration prior to enrollment was associated with 1.10 times the odds of remission ($P=0.004$). An increase in age, PtGA, and etanercept duration prior to enrollment were all associated with decreased odds of remission ($P=0.010$, 0.002, 0.035, respectively). Higher SJC and TJC were associated with lower odds of
maintaining remission, and higher methotrexate dose was associated with increased odds.

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). The group of patients who remained in remission or LDA (n=118) had fewer women and fewer patients with BMI >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 methotrexate duration prior to enrollment and shorter duration of RA. SDAI, PtGA, and Physician Global Assessment (PhGA) were lower and fewer patients were anti-CCP positive or RF positive in those who maintained remission.

*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
($P=0.012$) (Figure 3A). Rheumatoid factor (RF)-positive patients were less than half as
likely as RF-negative patients to remain in remission/LDA at week 48. Each 1-unit
increase in C-reactive protein (CRP) also was associated with 0.93 times the odds of
remaining in remission/LDA at week 48 ($P=0.033$). Longer duration of etanercept
treatment slightly increased the odds of SDAI remission/LDA at week 48 (odds ratio
1.12). Although not significant, higher body mass index (BMI) at baseline decreased
odds of remaining in remission/LDA at week 48, and anti-cyclic citrullinated peptide
(CCP) positivity increased 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 etanercept monotherapy showed benefit in
maintaining remission over methotrexate monotherapy in this study.\(^5\) Here we assessed
this further by analyzing factors that had an interaction with treatment arm. The joint
Wald test for an interaction effect between treatment arm and magnesium concentration
yielded a $P$-value of 0.052. Methotrexate and etanercept patients with higher
magnesium concentrations at baseline had lower odds of maintaining remission/LDA,
with an especially strong association within etanercept monotherapy (Figure 3B).
Specifically, a patient with 0.1-unit mg/dL higher magnesium concentration at baseline
in the methotrexate arm was 16\% less likely to be in remission/LDA, and a patient with
a 0.1-unit mg/dL higher magnesium concentration at baseline in the etanercept 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 treatment arm and duration of RA yielded a \( P \)-value of 0.041. Shorter RA duration (\( \leq 5 \) years) in the methotrexate arm was associated with 5.28 times the odds of SDAI remission/LDA compared to longer (>5 years) duration (Figure 3B). Among patients with RA duration >5 years, those receiving etanercept monotherapy and combo therapy were more likely to remain in remission/LDA than those receiving methotrexate 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 etanercept and methotrexate combination therapy. Patients who maintained remission at the end of the run-in period were younger, had been receiving a higher dose of methotrexate, 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, while there was a significant difference in baseline PtGA between those who maintained remission and those who did not, there...
was no difference in PhGA, suggesting a patient’s assessment of their own disease may be more sensitive. This difference may reflect the ability of the patient assessment to capture 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 methotrexate treatment prior to enrollment was associated with better odds of maintaining remission during the run-in period, the converse was found for duration of etanercept treatment. It is possible this discrepancy may be due to factors such as age, disease duration, duration of treatment (ie, methotrexate alone is typically prescribed first in clinical practice and therefore used longer than etanercept), and use of methotrexate and etanercept 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 etanercept or methotrexate. In contrast to results from the run-in period, longer duration of etanercept treatment prior to enrollment, but not methotrexate, was significantly 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.\textsuperscript{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 confidence intervals, and the forcing of anti-CCP into the model due to 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 etanercept or methotrexate was discontinued. The ability to predict which patients may do well off therapy is important and is likely to encourage patients with a greater likelihood to do well off treatment to attempt discontinuation.

Early treatment of disease has been established as key for achieving optimal treatment outcomes.\textsuperscript{9} Patients who enter remission faster are also more likely to sustain remission.\textsuperscript{10} Patients with shorter duration of RA are better able to achieve remission.\textsuperscript{11} Our findings align with this in that shorter duration of RA (≤5 years) in the methotrexate 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 in younger patients.\textsuperscript{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.\textsuperscript{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. 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 etanercept treatment arm. This connection between magnesium and maintenance of remission has not been reported previously. We have reported previously that overall odds of maintaining remission favor etanercept over methotrexate. That pattern continued here with higher odds of maintaining remission with etanercept versus methotrexate at lower levels of magnesium (1.6 and 2.1 mg/dL) and longer duration of RA.

Limitations
This study 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 methotrexate or etanercept. As such, while some treatment guidelines recommend gradual discontinuation of a DMARD over abrupt discontinuation, 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 likely was 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 post-hoc 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.

CONCLUSION

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 likelihood of remaining in remission/LDA with methotrexate or etanercept monotherapy. The role of magnesium in retaining good disease control warrants further exploration. These results may help guide clinicians in deciding whether to discontinue methotrexate or etanercept in a patient with RA in sustained remission on a combination of etanercept and methotrexate.
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Data Sharing Statement

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/
REFERENCES


FIGURE LEGENDS

Figure 1. Odds of remaining in SDAI remission/LDA at the end of the run-in period by baseline clinical parameter (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, odds ratios were calculated for a 1-unit increase. P-values are nominal.

CI, confidence interval; ETN, etanercept; LDA, low disease activity; MTX, methotrexate; OR, odds ratio; PtGA, Patient Global Assessment of Disease Activity; SDAI, simple 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.

CI, confidence interval.

Figure 3. Multivariable-adjusted odds of remaining in SDAI remission/LDA at the end of the double-blind treatment period by baseline clinical parameter (measured at time of randomization) (A), factors interacting with treatment arm (B), and baseline magnesium level (C). 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, odds ratios were calculated for a 1-unit increase. P-values are nominal.

Standardized ORs describing the OR associated with a 1 standard deviation change are shown to the right of the figure for continuous variables.
BMI, body mass index; CCP, cyclic citrullinated peptide; CI, confidence interval; CRP, C-reactive protein; ETN, etanercept; LDA, low disease activity; Mg, magnesium; MTX, methotrexate; OR, odds ratio; PhGA, Physician Global Assessment of Disease Activity; PtGA, Patient Global Assessment of Disease Activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, simple disease activity index.

**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. CI, confidence interval.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Not SDAI Remission at End of Run-in (n=118)</th>
<th>SDAI Remission at End of Run-in (n=253)</th>
<th>Overall (N=371)</th>
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<tbody>
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<td>55.6±12.2</td>
<td>56.8±12.1</td>
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<td>Methotrexate duration prior to enrollment, years</td>
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<td>6.3±5.4</td>
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<td>3.8±3.6</td>
<td>4.1±3.6</td>
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<tr>
<td>Duration of RA, years</td>
<td>11.9±9.6</td>
<td>10.3±7.8</td>
<td>10.8±8.4</td>
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<tr>
<td>TJC (0–68)</td>
<td>0.6±1.1</td>
<td>0.2±0.5</td>
<td>0.3±0.8</td>
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<tr>
<td>SJC (0–66)</td>
<td>0.4±0.8</td>
<td>0.1±0.5</td>
<td>0.2±0.6</td>
</tr>
<tr>
<td>PtGA (0–100)</td>
<td>10.2±14.1</td>
<td>5.3±7.4</td>
<td>6.8±10.3</td>
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<tr>
<td>PhGA (0–100)</td>
<td>3.4±5.5</td>
<td>2.5±3.0</td>
<td>2.8±4.0</td>
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<tr>
<td>CRP, mg/L</td>
<td>4.7±7.7</td>
<td>4.4±9.2</td>
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<tr>
<td>SDAI (0–86)</td>
<td>2.4±2.1</td>
<td>1.4±1.3</td>
<td>1.8±1.7</td>
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<tr>
<td>DAS28-CRP</td>
<td>1.8±0.5</td>
<td>1.6±0.4</td>
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</table>

Values represent mean ± SD.

CRP, C-reactive protein; DAS28-CRP, Disease Activity Score-28 with C-reactive protein; PhGA, Physician Global Assessment of Disease Activity; PtGA, Patient Global Assessment of Disease Activity; RA, rheumatoid arthritis; SDAI, simple disease activity index; SJC, swollen joint count; TJC, tender joint count.
Table 2. Patient Demographics and Clinical Characteristics at Randomization for the Double-blind Period

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Not SDAI Remission or LDA at End of Double-Blind Period (n=135)</th>
<th>SDAI Remission or LDA at End of Double-Blind Period (n=118)</th>
<th>Overall (N=253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56.0±12.0</td>
<td>55.0±12.5</td>
<td>55.6±12.2</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>107 (79.3)</td>
<td>86 (72.9)</td>
<td>193 (76.3)</td>
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<tr>
<td>White, n (%)</td>
<td>118 (87.4)</td>
<td>102 (86.4)</td>
<td>220 (87.0)</td>
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<tr>
<td>BMI &gt;30 kg/m², n (%)</td>
<td>55 (40.7)</td>
<td>37 (31.4)</td>
<td>92 (36.4)</td>
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<tr>
<td>Etanercept duration prior to enrollment, years</td>
<td>3.8±3.4</td>
<td>3.9±3.7</td>
<td>3.8±3.6</td>
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<td>Methotrexate duration prior to enrollment, years</td>
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<td>Duration of RA, years</td>
<td>10.9±7.2</td>
<td>9.7±8.4</td>
<td>10.3±7.8</td>
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<tr>
<td>SDAI (0–86)</td>
<td>1.5±1.3</td>
<td>0.9±1.0</td>
<td>1.3±1.2</td>
</tr>
<tr>
<td>SJC (0–66)</td>
<td>0.2±0.5</td>
<td>0.1±0.4</td>
<td>0.1±0.5</td>
</tr>
<tr>
<td>TJC (0–68)</td>
<td>0.2±0.6</td>
<td>0.2±0.6</td>
<td>0.2±0.6</td>
</tr>
<tr>
<td>PtGA (0–100)</td>
<td>5.4±7.4</td>
<td>3.0±5.1</td>
<td>4.3±6.5</td>
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<tr>
<td>PhGA (0–100)</td>
<td>3.5±8.3</td>
<td>2.0±2.5</td>
<td>2.8±6.3</td>
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<tr>
<td>CRP, mg/L</td>
<td>3.6±5.3</td>
<td>3.2±7.1</td>
<td>3.4±6.2</td>
</tr>
<tr>
<td>Anti-CCP positive, n (%)</td>
<td>95 (70.4)</td>
<td>73 (61.9)</td>
<td>168 (66.4)</td>
</tr>
<tr>
<td>RF positive, n (%)</td>
<td>91 (67.4)</td>
<td>67 (56.8)</td>
<td>158 (62.5)</td>
</tr>
<tr>
<td>Magnesium, mg/dL</td>
<td>2.2±0.2</td>
<td>2.1±0.2</td>
<td>2.1±0.2</td>
</tr>
</tbody>
</table>

Values represent mean ± SD, unless otherwise specified.

BMI, body mass index; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; PhGA, Physician Global Assessment of Disease Activity; PtGA, Patient Global Assessment of Disease Activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SDAI, simple disease activity index; SJC, swollen joint count; TJC, tender joint count.
Figure 1. Odds of remaining in SDAI remission/LDA at the end of the run-in period by baseline clinical parameter (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, odds ratios were calculated for a 1-unit increase. *P*-values are nominal.

CI, confidence interval; ETN, etanercept; LDA, low disease activity; MTX, methotrexate; OR, odds ratio; PtGA, Patient Global Assessment of Disease Activity; SDAI, simple 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. CI, confidence interval.
Figure 3. Multivariable-adjusted odds of remaining in SDAI remission/LDA at the end of the double-blind treatment period by baseline clinical parameter (measured at time of randomization) (A)

148x64mm (600 x 600 DPI)
Figure 3. factors interacting with treatment arm (B)

148x51mm (600 x 600 DPI)
Figure 3. and baseline magnesium level (C). 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, odds ratios were calculated for a 1-unit increase. P-values are nominal. Standardized ORs describing the OR associated with a 1 standard deviation change are shown to the right of the figure for continuous variables. BMI, body mass index; CCP, cyclic citrullinated peptide; CI, confidence interval; CRP, C-reactive protein; ETN, etanercept; LDA, low disease activity; Mg, magnesium; MTX, methotrexate; OR, odds ratio; PhGA, Physician Global Assessment of Disease Activity; PtGA, Patient Global Assessment of Disease Activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, simple disease activity index.
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. CI, confidence interval.