Arthritis & Rheumatology
Vol. 72, No. 9, September 2020, pp 1456–1466
DOI 10.1002/art.41299

American College of Rheumatology
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Association of High Serum Interleukin-6 Levels With Severe Progression of Rheumatoid Arthritis and Increased Treatment Response Differentiating Sarilumab From Adalimumab or Methotrexate in a Post Hoc Analysis

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Objective. The development of biomarkers to guide treatment decisions is a major research focus in rheumatoid arthritis (RA). Patients with RA have elevated interleukin-6 (IL-6) levels; however, the utility of IL-6 as a predictor of treatment response is unclear. This study was undertaken to investigate, by post hoc analysis, whether baseline IL-6 levels are predictive of sarilumab treatment responses in 2 phase III studies.

Methods. Serum IL-6 concentrations were measured in patients with RA prior to receiving sarilumab 200 mg (n = 148) or adalimumab 40 mg (n = 152) every 2 weeks (in the MONARCH trial; ClinicalTrials.gov identifier: NCT02332590) or sarilumab 150 mg, sarilumab 200 mg, or placebo every 2 weeks plus methotrexate (MTX) (n = 401, n = 396, and n = 397, respectively) (in the MOBILITY trial; ClinicalTrials.gov identifier: NCT01061736). Efficacy and patient-reported outcomes were compared between and within groups according to IL-6 tertile using linear and logistic regression.

Results. In MONARCH, patients with high baseline IL-6 levels (all ≥3 times the upper limit of normal; n = 100) had higher disease activity at baseline than those with low IL-6 levels (n = 100). The magnitude of clinical improvement over 24 weeks with sarilumab versus adalimumab was greater in patients with high compared to those with low baseline IL-6 levels. In MOBILITY, compared to patients with low IL-6 levels (n = 397), patients with high IL-6 levels (n = 398) had higher disease activity and joint damage at baseline, were more likely to have joint progression, and had less clinical improvement over 52 weeks' treatment with placebo plus MTX compared to sarilumab 150 mg or 200 mg plus MTX. Baseline IL-6 and C-reactive protein levels were both predictive of outcomes. Safety profiles were similar between defined IL-6 tertiles.

Conclusion. IL-6 may be a prognostic marker of disease progression and severity, and patients with high IL-6 levels may be likely to benefit from sarilumab compared to adalimumab or MTX. Prospective validation is warranted to confirm the results of these post hoc analyses.

INTRODUCTION

A variety of biologic disease-modifying antirheumatic drugs (DMARDs), conventional synthetic DMARDs, and targeted synthetic DMARDs are available to reduce disease activity, inhibit joint damage progression, and prevent disability in patients with rheumatoid arthritis (RA) (1,2). However, up to 40% of patients will not respond to treatment, and sustained remission will be achieved in only 30% (3–5).

Treatment algorithms recommend initiation of a conventional synthetic DMARD such as methotrexate (MTX), followed by a biologic DMARD or targeted synthetic DMARD for

Presented in part at the 82nd Annual Scientific Meeting of the American College of Rheumatology, Chicago, IL, October 2018.

Supported by Regeneron Pharmaceuticals and Sanofi-Genzyme BioVentures.

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Dr. Boyapati owns stock or stock options in Regeneron Pharmaceuticals. Dr. Schwartzman has received consulting fees, speaking fees, and/or honoraria from Abbott/AbbVie, Genentech, Crescendo, Dermtech, Janssen, Gilead, Eli Lilly, Myriad, Novartis, Regeneron, Samsung, and Sanofi (less than $10,000 each) and owns stock or stock options in Amgen, Boston Scientific,

patients with inadequate control of disease activity (1,2). Biologic DMARD selection is often determined by patient access, physician experience/bias, or consideration of high-risk comorbidities (6).

Treatment decisions could be optimized if diagnostics were available to help identify patients most likely to benefit from a particular therapy. However, currently, there are no validated predictive markers of treatment response. Although biomarkers have been evaluated in clinical trials and real-world cohorts, the ability to predict outcomes before therapy initiation remains elusive (7). For example, C-reactive protein (CRP) level is measured in rheumatology practice, generally correlates with disease activity, and may be elevated during flares. However, CRP testing is not utilized for selecting biologic therapies, as there is insufficient predictive value for response to specific RA treatments (8).

Patients with RA have elevated levels of interleukin-6 (IL-6) in serum and synovial fluid (9,10). IL-6 drives inflammation and promotes articular destruction, is involved in the development of extraarticular manifestations, and correlates with disease activity (10–12). Despite the key role of IL-6 in RA, there are limited and inconclusive data on the potential of serum IL-6 levels to predict treatment response (13).

Two monoclonal antibodies that target IL-6 signaling (sarilumab and tocilizumab) are approved for the treatment of RA (14,15), and patients with elevated IL-6 levels may be more likely to derive benefit from these agents versus others. The objective of this post hoc analysis was to investigate whether baseline IL-6 level could differentially predict clinical efficacy and patient-reported outcomes (PROs) to sarilumab versus adalimumab in the MONARCH trial (ClinicalTrials.gov identifier: NCT02332590) and to sarilumab versus MTX in the MOBILITY trial (ClinicalTrials.gov identifier: NCT01061736) (16,17).

PATIENTS AND METHODS

Study design. Details of the MONARCH and MOBILITY studies have been described previously (16,17) (Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41299/abstract). In the MONARCH study, patients with moderate-to-severe RA who were intolerant of MTX or had an inadequate response to MTX were randomized to receive monotherapy with sarilumab 200 mg every 2 weeks (n = 184) or adalimumab 40 mg every 2 weeks (n = 185) for 24 weeks. In the MOBILITY study, patients with moderate-to-severe RA and an inadequate response to MTX were randomized to receive sarilumab 150 mg (n = 400), sarilumab 200 mg (n = 399), or placebo (n = 398) every 2 weeks along with weekly MTX for 52 weeks. Patient randomization was stratified by region (in both studies) and by prior biologic use (in the MOBILITY study only).

Both trials were conducted in accordance with the Declaration of Helsinki and approved by the appropriate ethics committees/institutional review boards, and each patient provided written informed consent before participation.

Biomarker assessments. In the MOBILITY study, serum IL-6 and CRP levels were prespecified to be measured in the intent-to-treat (ITT) population at baseline and at multiple time points postbaseline. In the MONARCH study, serum IL-6 levels were measured retrospectively in samples from randomized patients who provided consent for future use of samples and who had at least 1 serum sample drawn at baseline. This cohort included patients who had baseline IL-6 or CRP measurements available and is referred to as the biomarker population. It consisted of 307 of 369 patients in the ITT population in the MONARCH study (300 of whom had baseline IL-6 values available; 148 treated with sarilumab 200 mg and 152 treated with adalimumab 40 mg) and 1,194 of 1,197 patients in the ITT population in the MOBILITY study who had baseline IL-6 or CRP values available (401 patients treated with sarilumab 150 mg, 396 patients treated with sarilumab 200 mg, and 397 patients treated with placebo). Due to the differences in design between the 2 clinical studies in terms of duration, comparator arms, and study end points, biomarker populations were analyzed separately for each study. Analyses were performed using continuous and categorical biomarker variables, with patients grouped into tertiles according to baseline IL-6 or CRP level (high, medium, or low) (Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41299/abstract). Additional biomarkers were assessed in both studies (18,19).

Serum IL-6 levels were measured using a validated enzyme-linked immunosorbent assay (ELISA) (Quantikine; R&D Systems)

Gilead, Medtronic, and Pfizer. Mr. Msihid owns stock or stock options in Sanofi. Dr. Choy has received consulting fees, speaking fees, and/or honoraria from AbbVie, Amgen, AstraZeneca, Biogen, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Chelsea Therapeutics, Chugai Pharma, Daiichi Sankyo, Eli Lilly, Ferring Pharmaceutical, GlaxoSmithKline, Hospira, Ionis, Jazz Pharmaceuticals, Janssen, MedImmune, Merrimack Pharmaceutical, Merck Sharp & Dohme, Napp, Novimmune, Novartis, ObsEva, Pfizer, Regeneron, Roche, R-Pharm, SynAct Pharma, Sanofi-Genzyme, Tonix, Union Chimique Belge, and Sanofi-Aventis (less than $10,000 each) and research support from Amgen, Bio-Cancer, Chugai Pharma, Ferring Pharmaceuticals, Novimmune, Pfizer, Roche, and Union Chimique Belge. Dr. Genovese has received consulting fees from Sanofi/Genzyme, Genentech/Roche, and R-Pharm (less than $10,000 each) and research support from those companies. Dr. Burmester has received consulting fees, speaking fees, and/or honoraria from AbbVie, Eli Lilly, Merck Sharp & Dohme, Pfizer, Sanofi, Roche, and Union Chimique Belge (less than $10,000 each) and research support from AbbVie, Pfizer, Union Chimique Belge, and Roche. Dr. Lam has received consulting fees, speaking fees, and/or honoraria from Sanofi Genzyme, Regeneron, Bristol Myers Squibb, Janssen, AbbVie, and UCB (less than $10,000 each). Dr. Kimura owns stock or stock options in Regeneron Pharmaceuticals. Dr. Sadeh owns stock or stock options in Sanofi and Bristol Myers Squibb. Drs. Weinreich, Yancopoulos, and Graham own stock or stock options in Regeneron Pharmaceuticals.

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Submitted for publication April 21, 2019; accepted in revised form April 23, 2020.

at Covance Central Labs. The intraassay precision was ≤9.1%, and the interassay precision was ≤12%. The reportable range was 3.1–153,600 pg/ml. The normal value for IL-6 identified by the laboratory was <12.5 pg/ml (20), and this value was used as the definition of normal for these analyses. For both studies, ~90% of serum samples were collected in the morning. No separate assessment of the biologic activity of serum IL-6 was performed.

CRP level was measured using a high-sensitivity CRP assay (Siemens) at Covance Central Labs. The intraassay precision was <3%, the interassay precision was <5.4%, and the reference range for healthy controls was ≤2.87 mg/liter. Inclusion criteria specified a minimum CRP value required at study entry (>6 mg/liter for the MOBILITY study; ≥8 mg/liter or erythrocyte sedimentation rate [ESR] ≥28 mm/hour, assessed between screening and randomization, for the MONARCH study).

Correlation analyses were performed using continuous and categorical biomarker variables, with patients grouped into tertiles according to baseline IL-6 or CRP level (high, medium, or low) (Supplementary Table 1). Values below the lower limit of quantification were replaced by a value equal to half of the lower limit of quantification to retain these values for the analysis.

Efficacy and PRO end points. Efficacy was evaluated as either continuous end points using change from baseline, binary end points using a minimal clinically important difference threshold for change from baseline, or using a clinical threshold, such as low disease activity or remission. Primary, a subset of secondary, and exploratory end points were evaluated.

The following end points were assessed in the MOBILITY and MONARCH studies: the proportion of patients achieving a response according to the American College of Rheumatology criteria for 20% improvement (ACR20) (21), 50% improvement (ACR50), and 70% improvement (ACR70); remission according to the Clinical Disease Activity Index (CDAI) (≤2.8) (22); low disease activity according to the CDAI (≤10); remission according to the Disease Activity Score in 28 joints (DAS28) using the CRP level (DAS28-CRP) (23) or DAS28 using the ESR (DAS28-ESR) (<2.6); low disease activity according to the DAS28-CRP or DAS28-ESR (<3.2); and improvement in Health Assessment Questionnaire (HAQ) disability index (DI) (24) (improvement of ≥0.22 and change from baseline, assessed at week 16 in the MOBILITY study and week 24 in the MONARCH study). Due to low patient numbers, remission according to the DAS28-ESR and remission according to the CDAI were not assessed in the MOBILITY study and the MONARCH study, respectively.

Additional PRO end points evaluated at week 24 in both studies and at week 52 in the MOBILITY study included continuous change from baseline in patient global assessment of disease activity on a visual analog scale (VAS) and pain on a VAS. Coprimary end points in the MOBILITY study were ACR20, modified total Sharp score, and HAQ DI; secondary end points included ACR70, DAS28-CRP, and CDAI. The primary end point in the MONARCH study was DAS28-ESR; secondary end points included remission according to the DAS28-ESR, HAQ DI, and ACR20/50/70.

Statistical analysis. For all end points, baseline was defined as the last value before the first dose of study drug. In all analyses, patients were analyzed according to the treatment received. Baseline disease characteristics by IL-6 tertile were summarized for each study and compared using the Kruskal-Wallis test.

The predictive value of serum IL-6 level for binary efficacy outcomes was tested using a logistic regression, with treatment, study randomization stratification factors (region in both studies and prior biologic use in the MOBILITY study), baseline IL-6 tertile, and IL-6 tertile at baseline–by-treatment interaction

Table 1. Baseline disease activity according to baseline IL-6 tertile in the MONARCH study*

	Low IL-6 tertile (n = 100)	Medium IL-6 tertile (n = 100)	High IL-6 tertile (n = 100)
No. receiving adalimumab/no. receiving sarilumab	45/55	53/47	54/46
IL-6, median (range) pg/ml†	2.4 (1.6–7.1)	16.2 (7.2–39.5)	64.7 (39.6–692.3)
CRP, mg/liter‡	5.6 ± 9.2	15.2 ± 17.1	41.5 ± 34.1§
HAQ DI	1.5 ± 0.6	1.6 ± 0.6	1.8 ± 0.6§
DAS28-CRP	5.5 ± 0.8	6.0 ± 0.7	6.5 ± 0.8§
DAS28-ESR	6.5 ± 0.7	6.8 ± 0.7	7.1 ± 0.9§
CDAI	40.6 ± 11.7	42.9 ± 11.4	46.0 ± 12.2§
TJC	26.3 ± 13.1	28.2 ± 14.0	27.8 ± 13.9
SJC	15.9 ± 10.1	18.6 ± 10.0	18.8 ± 10.7§
Pain (VAS, 0–100 mm)	66.2 ± 18.8	70.1 ± 17.4	77.5 ± 18.9§
Patient global assessment of disease activity (VAS, 0–100 mm)	63.4 ± 18.8	67.1 ± 17.0	73.6 ± 16.9§

* Except where indicated otherwise, values are the mean ± SD. CRP = C-reactive protein; HAQ DI = Health Assessment Questionnaire disability index; DAS28-CRP = Disease Activity Score in 28 joints using the CRP level; DAS28-ESR = DAS28 using the erythrocyte sedimentation rate; CDAI = Clinical Disease Activity Index; TJC = tender joint count; SJC = swollen joint count; VAS = visual analog scale.
† Normal <12.5.
‡ Normal <2.87.
§ Nominal $P < 0.05$ by Kruskal-Wallis test, for difference between at least 2 interleukin-6 (IL-6) tertiles.

as fixed effects; the interaction *P* value was used to perform this assessment. Pairwise comparisons of efficacy end points were then performed separately between each sarilumab and comparator arm in each IL-6 tertile, and the Mantel-Haenszel estimate (stratified by randomization factors) of odds ratio (OR) and corresponding 95% confidence interval (95% CI) were derived. Pairwise comparisons between IL-6 tertiles within each treatment group were similarly computed. For continuous end points, an analysis of covariance was performed with treatment, study randomization stratification factors, baseline value, IL-6 tertile at baseline, and IL-6 tertile at baseline–by-treatment interaction as fixed effects. Pairwise comparisons of efficacy end points between sarilumab and comparator arms were performed separately for each IL-6 tertile, and the least squares mean and corresponding 95% CI were derived. The predictive value of serum IL-6 level for change from baseline in PROs was tested using an analysis of covariance using the same fixed effects as described for efficacy outcomes. Similar regressions were performed using baseline IL-6 as a continuous measure. The incidence of treatment-emergent adverse events (AEs) in each IL-6 tertile was analyzed descriptively. Since all predictive analyses were post hoc, all *P* values should be considered nominal. Analyses were performed using SAS version 9.2 or higher.

RESULTS

IL-6 distribution and baseline disease activity. Serum IL-6 levels were measured at baseline in 1,193 of 1,197 patients in the MOBILITY ITT population and in 300 of 369 patients in the MONARCH ITT population (Table 1). In both studies, all patients in

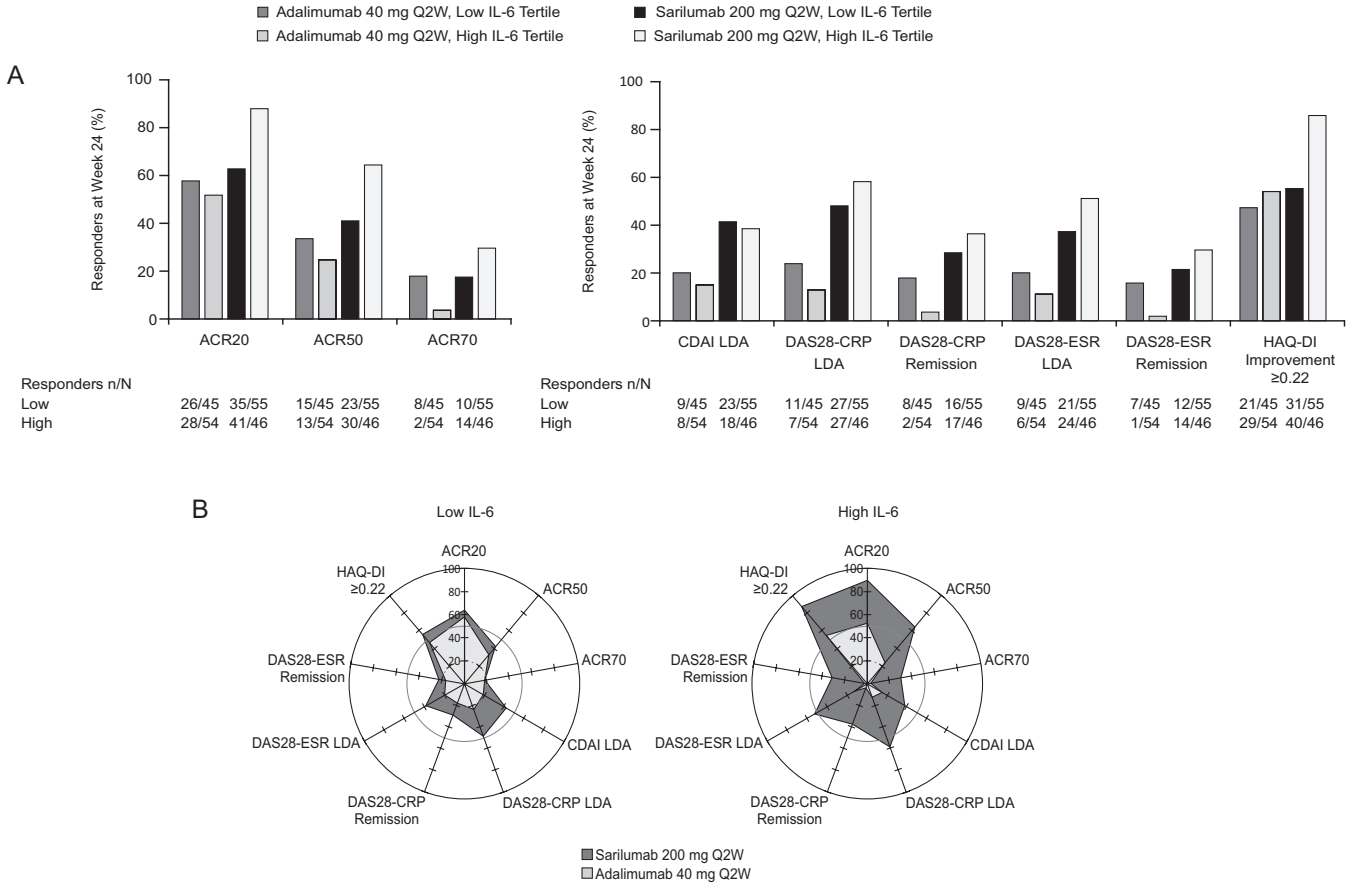


Figure 1. Proportion of responders at week 24 according to baseline interleukin-6 (IL-6) tertile in the MONARCH study. **A**, Left, Proportion of patients treated with adalimumab 40 mg every 2 weeks (QW2) or sarilumab 200 mg every 2 weeks who met American College of Rheumatology criteria for 20% improvement (ACR20), 50% improvement (ACR50), and 70% improvement (ACR70) in the low IL-6 tertile versus the high IL-6 tertile. Right, Proportion of patients treated as indicated who had low disease activity (LDA) according to the Clinical Disease Activity Index (CDAI), low disease activity according to the Disease Activity Score in 28 joints (DAS28) using the C-reactive protein (CRP) level, disease in remission according to the DAS28-CRP, low disease activity according to the DAS28 using the erythrocyte sedimentation rate (ESR), disease in remission according to the DAS28-ESR, and an improvement of ≥0.22 in the Health Assessment Questionnaire (HAQ) disability index (DI) in the low IL-6 tertile versus the high IL-6 tertile. Values are the number of responders/total number of patients in the low IL-6 tertile and high IL-6 tertile. **B**, Proportion of patients in the low IL-6 tertile and patients in the high IL-6 tertile who met the indicated end points after treatment with sarilumab versus adalimumab. Due to the low number of patients in the intent-to-treat population in whom remission according to the CDAI was achieved, this measure was not analyzed by IL-6 tertile.

the low baseline IL-6 tertile had normal IL-6 levels (<12.5 pg/ml). Of the patients in the high baseline IL-6 tertile, 85% in the MOBILITY study and all in the MONARCH study had IL-6 levels ≥3 times the upper limit of normal (ULN). The distribution of IL-6 levels among tertiles was consistent in both studies (Supplementary Table 1).

Given the moderate-to-high correlation between IL-6 and CRP levels (Spearman's coefficient 0.71 in the MONARCH study and 0.58 in the MOBILITY study), CRP level was elevated in patients in the high IL-6 tertile compared to those in the low IL-6 tertile. Compared to patients in the low IL-6 tertile, those in the high IL-6 tertile had moderately greater disease activity at baseline in both studies and more joint damage (Table 1 and Supplementary Table 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41299/abstract). HAQ DI and patient global assessments of disease activity and pain were also elevated in the high IL-6 tertile relative to the low IL-6 tertile (Table 1 and Supplementary Table 2). Baseline disease activity was well balanced across treatment arms for both studies. (The mean ± SD DAS28-CRP in the MONARCH study was 6.0 ± 0.9 in patients receiving adalimumab and 6.0 ± 0.9 in patients receiving sarilumab; the mean ± SD DAS28-CRP in the MOBILITY study was 5.9 ± 0.9 in patients receiving placebo, 6.0 ± 0.9 in patients receiving sarilumab 150 mg every 2 weeks, and 6.0 ± 0.9 in patients receiving sarilumab 200 mg every 2 weeks.)

Predictive value of baseline serum IL-6 levels for the magnitude of difference in efficacy between sarilumab and adalimumab in the MONARCH study. In the overall ITT population in the MONARCH study, sarilumab efficacy was significantly greater than adalimumab efficacy (16). Patients treated with sarilumab with high baseline IL-6 levels had numerically greater responses compared to patients with low baseline IL-6 levels across all end points except low disease activity according to the CDAI (Figure 1). Patients treated with adalimumab with high IL-6 levels had lower response rates at week 24 compared to those with low IL-6 levels for most end points, except HAQ DI.

An interaction test demonstrated that the greatest difference in ACR 20/50/70 criteria, remission according to DAS28-ESR, remission according to DAS28-CRP, and improvement in the HAQ DI in response to sarilumab versus adalimumab was in the high versus low IL-6 tertiles. These differences in the high IL-6 tertile resulted in high ORs for achieving a response across many clinical parameters (Table 2). In the high IL-6 tertile, sarilumab-treated patients were >10 times more likely to achieve ACR70 versus adalimumab-treated patients (Table 2). In addition, a larger reduction in disease activity (remission according to the DAS28-ESR or DAS-CRP) was observed in sarilumab-treated patients versus adalimumab-treated patients in the high IL-6 tertile (Table 2). Sarilumab treatment improved multiple PROs compared to adalimumab in the overall ITT population (25). An interaction test for continuous changes over the 24-week treatment period demonstrated that the treatment effect of sarilumab on DAS28-CRP and PROs was also greater in the high IL-6 tertile than in the low IL-6 tertile (Table 3, Supplementary Figures 2B and C, and Supplementary Table 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41299/abstract). Similar conclusions were drawn when IL-6 was considered as a continuous measure, although the effect on disease activity and PROs appeared to be driven by high IL-6 values (data not shown).

Predictive value of baseline serum IL-6 levels for radiographic progression in the MOBILITY study. Overall, patients who received placebo plus MTX had significantly more radiographic progression than patients in the sarilumab 150 mg

Table 2. Odds ratios for efficacy parameters at week 24 in patients treated with sarilumab versus patients treated with adalimumab, according to baseline IL-6 tertile in the MONARCH study*

	Low IL-6 tertile (n = 100)	Medium IL-6 tertile (n = 100)	High IL-6 tertile (n = 100)	All (biomarker population) (n = 307)†
No. receiving adalimumab/no. receiving sarilumab	45/55	53/47	54/46	154/153
ACR20	1.4 (0.6, 3.1)	1.2 (0.5, 3.0)	6.6 (2.3, 18.6)‡	2.0 (1.2, 3.2)
ACR50	1.6 (0.7, 3.7)	1.5 (0.6, 3.5)	5.5 (2.3, 13.2)‡	2.4 (1.5, 3.8)
ACR70	1.1 (0.4, 3.2)	1.7 (0.6, 4.6)	10.5 (2.3, 48.4)‡	2.4 (1.3, 4.5)
Remission according to DAS28-ESR	1.5 (0.5, 4.4)	5.6 (1.6, 19.4)	33.9 (3.5, 328.7)‡	4.1 (2.1, 8.1)
LDA according to DAS28-ESR	2.6 (1.0, 6.7)	5.1 (1.8, 14.1)	10.5 (3.5, 31.4)	4.2 (2.5, 7.3)
Remission according to DAS28-CRP	2.0 (0.8, 5.3)	4.0 (1.5, 10.9)	18.4 (3.8, 90.0)‡	3.5 (2.0, 6.3)
LDA according to DAS28-CRP	3.2 (1.3, 7.6)	2.2 (1.0, 5.1)	9.2 (3.4, 24.8)	3.4 (2.1, 5.6)
LDA according to CDAI	3.1 (1.2, 7.7)	1.6 (0.7, 3.7)	3.6 (1.4, 9.0)	2.3 (1.4, 3.7)
Improvement in HAQ DI of ≥0.22	1.5 (0.7, 3.2)	1.2 (0.5, 2.8)	5.0 (1.9, 13.2)‡	2.0 (1.2, 3.2)

* Values are the Mantel-Haenszel estimate of the odds ratio (95% confidence interval) for sarilumab versus adalimumab at week 24, stratified by study randomization stratification factors. ACR20 = American College of Rheumatology criteria for 20% improvement; LDA = low disease activity (see Table 1 for other definitions).
† Includes the overall biomarker population, regardless of whether patients had baseline IL-6 values available.
‡ Nominal $P < 0.05$ versus low and medium tertiles, by IL-6 tertile–by-treatment interaction (logistic regression with treatment, study randomization stratification factors [region], IL-6 tertile at baseline, and IL-6 tertile at baseline–by-treatment interaction as fixed effects).

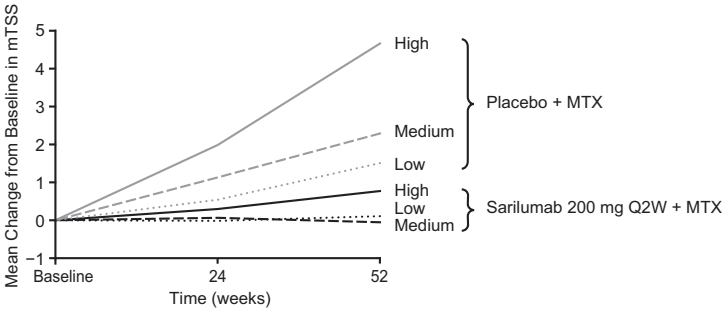
Table 3. LSM change from baseline for efficacy parameters according to baseline IL-6 tertile in the MONARCH study (week 24)*

Treatment group	Low IL-6 (n = 100)	Medium IL-6 (n = 100)	High IL-6 (n = 100)	All (biomarker population) (n = 307)†
Change in TJC				
Sarilumab 200 mg every 2 weeks	−18.7 (−20.9, −16.5)	−18.6 (−21.8, −15.4)	−18.6 (−21.2, −16.0)	−18.9 (−20.4, −17.4)
Adalimumab 40 mg every 2 weeks	−16.8 (−19.5, −14.1)	−18.8 (−21.6, −15.9)	−15.9 (−18.5, −13.4)	−17.2 (−18.7, −15.6)
Change in SJC				
Sarilumab 200 mg every 2 weeks	−12.8 (−13.9, −11.8)	−13.2 (−15.1, −11.3)	−15.1 (−16.8, −13.4)‡	−13.8 (−14.7, −12.9)
Adalimumab 40 mg every 2 weeks	−12.7 (−14.0, −11.5)	−14.0 (−15.7, −12.3)	−11.5 (−13.2, −9.9)	−12.9 (−13.8, −11.9)
Change in DAS28-CRP§				
Sarilumab 200 mg every 2 weeks	−2.5 (−2.8, −2.2)‡	−2.8 (−3.2, −2.4)‡	−3.5 (−3.8, −3.2)‡	−3.0 (−3.2, −2.8)‡
Adalimumab 40 mg every 2 weeks	−1.8 (−2.2, −1.5)	−2.2 (−2.6, −1.8)	−2.1 (−2.4, −1.8)	−2.1 (−2.3, −1.9)
Change in CDAI				
Sarilumab 200 mg every 2 weeks	−27.1 (−29.6, −24.7)	−28.0 (−31.6, −24.4)	−33.1 (−35.9, −30.3)‡	−29.7 (−31.3, −28.1)‡
Adalimumab 40 mg every 2 weeks	−25.0 (−27.9, −22.1)	−27.4 (−30.7, −24.2)	−25.9 (−28.6, −23.2)	−26.4 (−28.0, −24.7)

* Values are the least squares mean (LSM) change from baseline (95% confidence interval). The LSM was derived from a linear regression performed on the change from baseline in efficacy measures, with baseline efficacy value, treatment, and study randomization stratification factors (region) as fixed effects, in each biomarker tertile. See Table 1 for other definitions.
† Includes the overall biomarker population, regardless of whether patients had baseline IL-6 values available.
‡ Nominal $P < 0.05$ versus adalimumab.
§ For IL-6 tertile–by-treatment group interaction, nominal $P < 0.05$ for high or medium tertile versus low tertile, by linear regression with treatment, study randomization stratification factors (region), baseline efficacy value, IL-6 tertile at baseline, and IL-6 tertile at baseline–by-treatment interaction as fixed effects.

and 200 mg plus MTX treatment groups, as assessed by modified total Sharp score at week 52 (17).

Patients who received placebo plus MTX who were in the high IL-6 tertile developed substantially more joint damage at weeks 24 and 52 than those who were in the low IL-6 tertile (mean ± SD modified total Sharp score progression 2.00 ± 4.78 versus 0.54 ± 3.12 at week 24 and 4.67 ± 9.80 versus 1.51 ± 5.25 at week 52; OR for progression in the high tertile versus the low tertile 2.3 [95% CI 1.4, 3.8] and 3.3 [95% CI 1.9, 5.6], respectively; nominal $P < 0.05$) (Figure 2). Increases in erosion score and joint space narrowing (JSN) were observed in patients who received placebo plus MTX in the high tertile versus those in the low tertile. Patients treated with sarilumab 200 mg plus MTX developed the least joint damage, with patients in the low and medium IL-6 tertiles experiencing minimal to no joint damage over 52 weeks. However, in the high IL-6 tertile, patients receiving sarilumab 200 mg plus MTX were ~3 times less likely than patients receiving placebo plus MTX to have joint damage progression (Figure 2 and Supplementary Table 4, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41299/abstract). The difference in joint damage progression between the sarilumab 150 mg plus MTX



Baseline IL-6 Tertile	Mean Change (SD) in mTSS	Week 24	Week 52
Low	··· Placebo + MTX	0.54 (3.12)	1.51 (5.25)
	··· Sarilumab 200 mg Q2W + MTX	−0.01 (2.05)	0.11 (3.49)
Medium	– – Placebo + MTX	1.14 (3.82)	2.29 (7.45)
	– – Sarilumab 200 mg Q2W + MTX	0.06 (2.79)	−0.06 (5.51)
High	— Placebo+MTX	2.00 (4.78)	4.67 (9.8)
	— Sarilumab 200 mg Q2W + MTX	0.39 (2.9)	0.77 (4.48)

Figure 2. Change from baseline in modified total Sharp score (mTSS) according to baseline interleukin-6 (IL-6) tertile in the MOBILITY study. Values are the mean (SD) change from baseline in patients treated with placebo every 2 weeks (Q2W) plus methotrexate (MTX) weekly and patients treated with sarilumab 200 mg every 2 weeks plus MTX weekly in the low, medium, and high IL-6 tertiles.

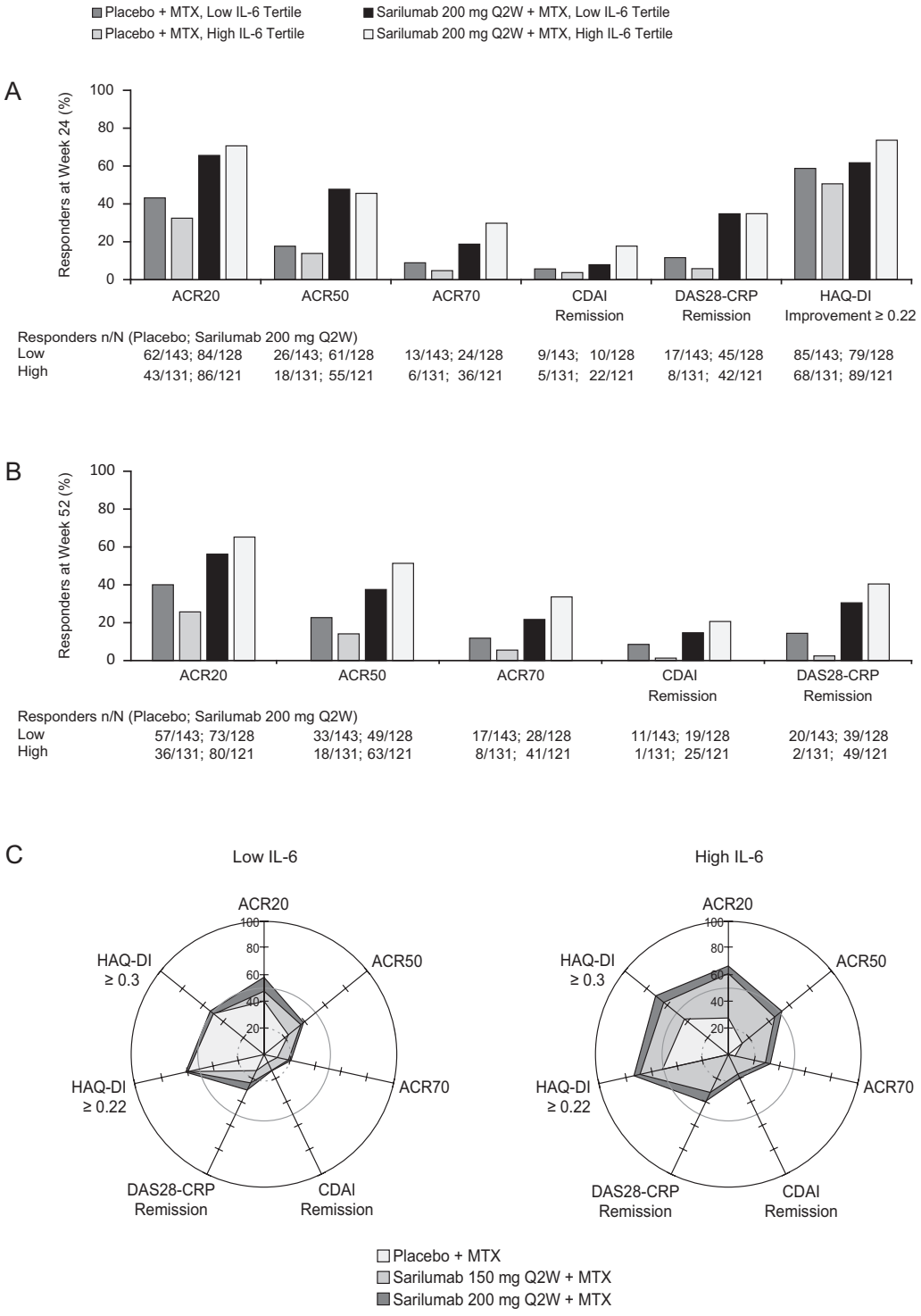


Figure 3. Proportion of responders at weeks 24 and 52 according to baseline IL-6 tertile in the MOBILITY study. **A**, Proportion of patients treated with placebo every 2 weeks plus methotrexate (MTX) or sarilumab 200 mg every 2 weeks plus MTX who met the ACR20, ACR50, and ACR70 criteria, had disease in remission according to the CDAI, had disease in remission according to the DAS28-CRP at week 24, and had an improvement of ≥0.22 in the HAQ DI at week 16 in the in the low IL-6 tertile versus the high IL-6 tertile. **B**, Proportion of patients treated as indicated who met the ACR20, ACR50, and ACR70 criteria, had disease in remission according to the CDAI, and had disease in remission according to the DAS28-CRP at week 52 in the low IL-6 tertile versus the high IL-6 tertile. In **A** and **B**, values are the number of responders/total number of patients in the low IL-6 tertile and high IL-6 tertile. **C**, Proportion of patients in the low IL-6 tertile and patients in the high IL-6 tertile who met the indicated end points at week 52 after treatment with sarilumab 150 mg or sarilumab 200 mg versus placebo. See Figure 1 for other definitions.

group and the placebo plus MTX group at week 52 did not differ between IL-6 tertiles (OR 0.8 in the low IL-6 tertile [95% CI 0.5, 1.4] and 0.5 in the high IL-6 tertile [95% CI 0.3, 0.8]).

Predictive value of baseline serum IL-6 levels for disease activity and PRO response after sarilumab or MTX treatment in the MOBILITY study. Treatment with sarilumab 200 mg plus MTX resulted in numerically greater improvement in disease activity in the high versus low IL-6 tertile for improvement in the HAQ DI, ACR70, and remission according to the CDAI. At week 52, the proportions of patients treated with sarilumab 200 mg plus MTX in whom ACR20, ACR50, and remission according to the DAS28-CRP were achieved were also numerically higher in the high IL-6 tertile than in the low IL-6 tertile. In contrast, there were fewer responders among patients receiving placebo plus MTX in the high IL-6 tertile than in the low IL-6 tertile, particularly for ACR70, remission according to the CDAI, and remission according to the DAS28-CRP (Figure 3).

An interaction test demonstrated that the differences in binary response to sarilumab plus MTX versus placebo plus MTX at week 52 were greater in the high IL-6 tertile versus the low IL-6 tertile (Supplementary Table 4). The test had a nominal $P < 0.05$ for all clinical and joint damage end points at week 52 (ACR20/50/70, remission according to the DAS28-CRP, remission according to the CDAI, and HAQ DI), but not JSN (data not shown). Higher ORs for response to sarilumab plus MTX versus placebo plus MTX were observed in the high IL-6 tertile versus the low IL-6 tertile. Patients receiving sarilumab 200 mg plus MTX were ~40 times more likely than patients receiving placebo plus MTX to achieve remission considering end points with and those without acute-phase reactants (remission according to the DAS28-CRP and remission according to the CDAI, respectively). Patients in the high IL-6 tertile who were treated with sarilumab 150 mg plus MTX were also more likely to achieve remission according to the CDAI or DAS28-CRP than patients who were treated with placebo plus MTX (OR 40.3 [95% CI 4.0, 405.7] and 42.6 [95% CI 8.7, 208.7], respectively).

To explore the disease activity components contributing to differential IL-6 response, tender and swollen joint counts, DAS28-CRP, and CDAI were evaluated by IL-6 tertile for continuous changes over the 52-week treatment period. While patients across all IL-6 tertiles had greater reductions in disease activity with sarilumab plus MTX versus placebo plus MTX, the greatest difference between treatment groups was observed in the high IL-6 tertile compared to the low IL-6 tertile for all measures at week 52 (Supplementary Table 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41299/abstract). The interaction test had a nominal $P < 0.05$ for all end points. Analyses using IL-6 as a continuous measurement were also performed, and results of the interaction tests were very similar (data not shown).

Sarilumab treatment improved PROs compared to placebo plus MTX in the overall ITT population (26). Greater improvements were observed in patients treated with sarilumab plus MTX versus patients treated with placebo plus MTX in each IL-6 tertile for HAQ DI and patient global assessment of disease activity and pain. The magnitude of difference between patients treated with sarilumab plus MTX versus patients treated with placebo plus MTX was larger in the high IL-6 tertile than in the low IL-6 tertile for HAQ DI (with a significant treatment-by–IL-6 tertile interaction), but not for patient global assessment of disease activity and pain (Supplementary Table 6 and Supplementary Figures 2A and C, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41299/abstract). Similar conclusions were drawn when IL-6 was considered as a continuous measurement (data not shown). Differences in efficacy between sarilumab and comparators in patients with high baseline IL-6 were consistent between the MONARCH and MOBILITY studies across multiple end points, including ACR20, ACR70, and low disease activity according to the DAS28-CRP (Supplementary Table 6).

Baseline IL-6 and CRP levels as predictors of outcomes. The predictive value of CRP was analyzed similarly to that of IL-6. In both studies, baseline IL-6 levels and baseline CRP levels were predictive of outcomes, including those for end points without acute-phase reactant measurements, such as remission according to the CDAI (in the MOBILITY study) (Supplementary Table 7, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41299/abstract).

Safety. Safety profiles were similar among patients in the low, medium, and high IL-6 tertiles in each study (Supplementary Table 8, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41299/abstract), and the incidence of individual AEs with sarilumab was consistent with the safety profile of IL-6 blockade. Incidences of infection and neutropenia were similar across IL-6 tertiles in each treatment group (Supplementary Table 8). Patients in the high IL-6 tertile who were treated with sarilumab had a comparable rate of infections to those treated with adalimumab (34.8% versus 31.5%).

DISCUSSION

This analysis of patients with RA who were intolerant of or had an inadequate response to MTX demonstrated that patients with the highest baseline IL-6 levels had moderately increased disease activity at baseline, but more baseline joint damage, compared to patients with IL-6 levels in the low or normal range. Moreover, patients with higher baseline IL-6 levels also had faster joint damage progression as well as poorer clinical outcomes whether they were treated with MTX or not, suggesting that elevated IL-6 level is an important marker of faster progression in this disease.

Patients with high IL-6 levels had a greater response to sarilumab compared to adalimumab or placebo plus MTX.

Differences in efficacy between sarilumab and these comparators in patients with RA who had high baseline IL-6 levels were consistent between studies across multiple end points. It should be noted that the large ORs were driven by low levels of response in patients with high IL-6 levels who received comparators. Patients with high IL-6 levels who were treated with sarilumab were more likely to achieve remission according to the DAS28-ESR or DAS28-CRP and ACR responses than those who were treated with adalimumab and were more likely to achieve ACR responses, remission according to the DAS28-CRP or CDAI, and improvement in the HAQ DI than those who were treated with placebo plus MTX.

Our analysis found that high rather than low baseline IL-6 levels had predictive value for differentiating response to sarilumab versus comparators. MTX has been shown to decrease levels of serum IL-6 in several studies (27–29). However, in the patients with an inadequate response to MTX enrolled in the MOBILITY trial, MTX treatment alone was not effective at reducing IL-6 levels over 52 weeks (mean ± SD change in IL-6 level from baseline to week 52 –5.0 ± 43.2 pg/ml) (Boyapati A, et al: unpublished observations). In both studies, baseline IL-6 levels and baseline CRP levels were predictive of outcomes, including radiographic disease progression and end points that did not include acute-phase reactant measurements. This finding suggests that baseline IL-6 levels may be a useful predictive tool when deciding on optimal treatments, and could aid clinicians in their selection of appropriate therapies for individual patients. Given that IL-6 levels are not measured routinely in clinical practice, measurement of CRP levels may also be useful to guide clinicians. Levels of soluble IL-6 receptor were not associated with differential response with sarilumab versus placebo or adalimumab (data not shown). Changes in other biomarkers that were assessed in these studies have been discussed previously (18,19).

Studies of circulating IL-6 concentrations in patients with RA treated with tocilizumab have reported conflicting findings. Some found that responses to treatment improved in patients with low IL-6 levels (30,31), while others identified patients with high IL-6 levels as better responders (13,32,33). A comprehensive study conducted by Wang et al (13) evaluated the impact on change in DAS28-ESR with tocilizumab for every 3-fold increase in baseline IL-6 level. That analysis did not directly compare the patients with the highest IL-6 levels to the patients with the lowest IL-6 levels. It is unclear why baseline IL-6 level was not predictive of a significant change in DAS28-ESR; one possibility is that the analysis combined 2 doses of tocilizumab (4 mg/kg and 8 mg/kg) with different efficacy profiles. For our analysis, we used tertiles to compare efficacy in patients with normal levels of IL-6 (low tertile) and patients with baseline IL-6 levels >3 times the ULN (high tertile). These thresholds are arbitrary, as there are currently no established IL-6 thresholds available from clinical trials or real-world practice. Although overall median IL-6 levels in our study were similar to those in the study by Wang et al, it is possible that the distribution of IL-6 levels was different. Wang et al used the same IL-6 ELISA as was used in this study, and they compared this with other IL-6 tests (13).

There were some potential limitations in this post hoc analysis. Although IL-6 has substantial diurnal variability, ~90% of serum samples were drawn before noon; however, this analysis did not evaluate intrasubject variability (34). Also, historically, some biomarker subgroup analyses have been confounded by a "regression-to-the-mean" effect; the consistency of results across 2 studies and multiple end points provides strong evidence against this. It is also important to note that the overall ITT population has already demonstrated a differential treatment effect. The analyses performed with the high IL-6 tertile showed greater efficacy beyond the effects observed in the overall ITT population, and the treatment-by–baseline IL-6 subgroup interaction test showed a differential treatment effect between the high and low IL-6 tertiles. The observed effects are quantitative effects (further enhancement of efficacy in the same direction) rather than a qualitative effect (change in direction of effect). In the MONARCH study, patients with high baseline IL-6 levels had a better response to sarilumab than adalimumab across all end points; however, some patients with low IL-6 levels in the adalimumab treatment group had improved responses, reducing concerns about regression to the mean. Another limitation of this study is that it did not evaluate levels of tumor necrosis factor (TNF), soluble TNF receptor, or other markers associated with TNF signaling, which may be associated with differentiating response between biologics targeting TNF and those targeting other mechanisms of action.

Since this was a post hoc analysis, findings must be interpreted with caution; neither trial was designed to prospectively evaluate the predictive value of IL-6 as a biomarker in RA. The number of patients in each IL-6 tertile was modest, particularly in the MONARCH study biomarker cohort. Although superior radiographic outcomes for sarilumab versus placebo were demonstrated in the MOBILITY study, the MONARCH study did not evaluate radiographic end points for sarilumab versus adalimumab treatment (16). Further studies are ongoing to conduct a similar analysis in patients who are intolerant of or have an inadequate response to anti-TNF agents.

In patients with an inadequate response to MTX, high baseline IL-6 levels were predictive of more joint damage in patients who continued to receive MTX over time. These analyses suggest that serum IL-6 level could be a useful marker to guide treatment choices for patients with RA, if validated prospectively in an independent clinical study. High baseline IL-6 levels were predictive of a better response to sarilumab compared to adalimumab monotherapy in patients who were intolerant of or had an inadequate response to MTX.

ACKNOWLEDGMENTS

We thank Xin Zhang (Sanofi employee at the time of the study) and Alexis Etienne (IT&M Stats; contractor for Sanofi) for

programming support and Dr. Jennifer Hamilton for critical review of the article. We would also like to thank Julie Frisolone and Prudence Roaf for publication support.

ROLE OF THE STUDY SPONSORS

Regeneron Pharmaceuticals and Sanofi-Genzyme facilitated the study design, provided writing assistance for the manuscript, and reviewed and approved the manuscript prior to submission. The authors independently collected the data, interpreted the results, and had the final decision to submit the manuscript for publication. Writing assistance was provided by Helen Johns of Adelphi Communications (Macclesfield, UK). Publication of this article was not contingent upon approval by Regeneron Pharmaceuticals or Sanofi-Genzyme.

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