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Concise report

Sarilumab monotherapy vs sarilumab and methotrexate combination therapy in patients with rheumatoid arthritis

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Abstract

Objective. Sarilumab, as monotherapy or in combination with conventional synthetic DMARDs, such as MTX, has demonstrated improvement in clinical outcomes in patients with RA. The primary objective of this *post hoc* analysis was to compare the efficacy of sarilumab (200 mg every 2 weeks) monotherapy (MONARCH study) with that of sarilumab and MTX combination therapy (MOBILITY study) at week 24.

Methods. The endpoints assessed were mean change from baseline in the Clinical Disease Activity Index (CDAI), 28-joint Disease Activity using CRP (DAS28-CRP), CRP, haemoglobin (Hb), pain visual analogue scale (VAS) and Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue. Least square (LS) mean change from baseline (95% CI) at week 24 for all endpoints was compared between the treatment arms for adjusted comparisons.

Results. This analysis included 184 patients on sarilumab monotherapy and 399 patients on sarilumab plus MTX. Differences ($P < 0.05$) were observed in ethnicity, region, body mass index group, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, swollen joint count, CRP, CDAI and oral glucocorticoid use between these treatment groups. After adjusting for these differences in a mixed-effect model repeated measure, LS mean change from baseline for all assessments was similar between the treatment groups with overlapping CIs: CDAI, -28.79 vs -26.21 ; DAS28-CRP, -2.95 vs -2.81 ; CRP, -18.31 vs -16.46 ; Hb, 6.59 vs 8.09 ; Pain VAS, -33.62 vs -31.66 ; FACIT–Fatigue, 9.90 vs 10.24 .

Conclusion. This analysis demonstrated that the efficacy of sarilumab monotherapy was similar to that of sarilumab and MTX combination therapy.

Key words: rheumatoid arthritis, sarilumab, IL-6Ri, MONARCH, MOBILITY, monotherapy, combination with MTX

Rheumatology key messages

- Sarilumab, monotherapy or in combination with methotrexate, demonstrated clinical improvements in patients with rheumatoid arthritis.
- The efficacy of sarilumab monotherapy was similar to its combination with methotrexate.
- Sarilumab monotherapy may be a valuable treatment strategy in patients with a contraindication/intolerance to methotrexate.

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Introduction

Treatment guidelines recommend combining biologic and targeted synthetic DMARDs (tsDMARDs) with conventional synthetic DMARDs (csDMARDs), which primarily consists of MTX [1, 2]. A recent real-world study in patients with RA reported suboptimal adherence to MTX citing adverse events as the main reason, which ultimately resulted in poor persistence of MTX [3]. Another systematic review also showed high variability in MTX adherence and persistence in patients with RA [4]. Therefore, there is a need for alternative treatment strategies in patients who are non-adherent to MTX.

IL-6 plays a predominant role in the pathogenesis of RA by regulating a diverse range of activities that drive chronic inflammation associated with RA. IL-6 also mediates various activities that underlie both local and systemic clinical symptoms of RA via cell signalling modulated by membrane-bound and soluble forms of its receptor [5, 6]. IL-6 receptor inhibitors, namely tocilizumab and sarilumab, have shown improvement in clinical outcomes in clinical studies and are approved for use as combination with csDMARDs or as monotherapy in patients with RA [5, 7, 8]. Recent EULAR guidelines recommend that IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other, biologic DMARDs (bDMARDs) in patients who cannot use csDMARDs as comedication [2].

Sarilumab, an IL-6 receptor- α (IL-6R α) inhibitor, is a fully human monoclonal antibody which binds soluble and membrane-bound IL-6R α to inhibit IL-6-mediated signalling [9–11]. In the MONARCH and MOBILITY trials, sarilumab as monotherapy and in combination with MTX, respectively, has demonstrated symptomatic and functional improvements in RA patients with inadequate responses/intolerance to MTX (MTX-IR/INT) [12, 13]. There are no studies that have directly compared the efficacy of sarilumab monotherapy with that of its combination with MTX. In this *post hoc* analysis, we compared the efficacy of sarilumab monotherapy with sarilumab in combination with MTX using mixed-effect model repeated measure (MMRM) models.

Methods

Patients and study design

This *post hoc* analysis was performed using data from the MONARCH (NCT02332590 [14]) and MOBILITY (NCT01061736 [15]) phase III trials of sarilumab in patients with active RA. Details of the study design, patient population and outcomes of these trials have been published previously [12, 13]. In the MONARCH trial, MTX-IR/INT patients with RA (enrolled based on the 2010 ACR/EULAR criteria) were randomized to receive subcutaneous (s.c.) sarilumab 200 mg every 2 weeks (q2w) or adalimumab 40 mg q2w in combination with placebo for 24 weeks [12]. In the MOBILITY trial, MTX-IR patients with RA (enrolled based on 1987 ACR revised

classification criteria) were randomized to receive s.c. sarilumab 150 mg or 200 mg q2w or placebo in combination with weekly MTX for 52 weeks [13]. Detailed inclusion and exclusion criteria for both the trials were published previously [12, 14–16].

The present *post hoc* analysis is based on the data collected from MONARCH and MOBILITY studies. Both MONARCH and MOBILITY studies were performed in accordance with the Declaration of Helsinki and the protocols for both the studies were approved by the appropriate ethics committees/institutional review boards for the respective studies and patients gave written consent before participation [12, 13, 17].

Treatment arms

This analysis included all patients who received sarilumab 200 mg q2w in the MONARCH and MOBILITY trials, based on treatment assigned. In the MOBILITY trial, patients received a stable dose of MTX (10–25 mg/week) for a minimum of 6 weeks prior to the screening visit, except patients within the Asia-Pacific region (Taiwan, South Korea, Malaysia, Philippines, Thailand and India) who were allowed to use a stable dose of MTX between 6 and 25 mg/week for a minimum of 6 weeks prior to the screening visit. Patients were to continue the stable dose of MTX for the duration of the study [16].

Endpoints

The endpoints assessed in this analysis included mean change from baseline in Clinical Disease Activity Index (CDAI), 28-joint Disease Activity using CRP (DAS28-CRP), CRP, haemoglobin (Hb), pain visual analogue scale (VAS) and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue. Percentage of responders was analysed for categorical endpoints including CDAI low disease activity (CDAI LDA; CDAI ≤ 10), DAS28-CRP LDA (DAS28-CRP score < 3.2), CRP (mg/l) < 10 , and minimal clinically important difference (MCID) in Hb (percentage change from baseline in Hb [g/l] > 7), pain VAS (change from baseline in pain VAS (mm) ≤ -10) and FACIT-Fatigue (change from baseline in FACIT-fatigue ≥ 4), using observed cases (OC) and intent-to-treat (ITT) population, and was compared between the treatment arms.

Statistical analysis

For adjusted comparisons, continuous changes in endpoints from baseline were set as dependent variables and patient baseline characteristics that differed ($P < 0.05$) between the two trials were set as covariates in MMRM models; least squares (LS) mean change in endpoints from baseline (95% CI) at week 24 was compared between the treatment arms. Patients with non-missing endpoint values were considered for these comparisons. For unadjusted comparisons of efficacy between monotherapy and combination therapy treatment arms, mean change in endpoints from baseline (95% CI) at week 24 was compared between the treatment arms.

Responder analysis was performed using both ITT (patients with missing data imputed as non-responders) and OC (patients with missing data excluded) populations.

Results

Patient baseline characteristics

This analysis included 184 patients in the sarilumab 200 mg q2w monotherapy arm from MONARCH and 399 patients in the sarilumab 200 mg q2w plus MTX combination therapy arm from MOBILITY. Baseline demographic and disease characteristics for patients included in both trials are shown in Table 1. Comparing the baseline characteristics of patients in these two trials, differences ($P < 0.05$) were observed in ethnicity, region, body mass index group, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, swollen joint count, CRP, CDAI and oral glucocorticoid use between the treatment arms and

were selected to be included in the MMRMs (Table 1). Details on the regional distribution of the study patients are provided in Supplementary Data S1, available at *Rheumatology* online.

Efficacy assessments

After adjusting for the selected baseline characteristics in MMRM, LS mean change from baseline at week 24 for all assessments was similar between the treatment arms with overlapping CIs (Fig. 1). Results of unadjusted comparisons were similar to adjusted comparisons (data not shown).

Responder analysis

At week 24, there were no discernible differences in the percentage of responders, for all outcomes between the treatment arms. In the ITT population, there were 42% responders in the monotherapy arm vs 43% responders in the combination treatment arm for CDAI LDA; 52% vs

TABLE 1 Differences in baseline characteristics of patients in the MONARCH and MOBILITY studies

Parameter	Sarilumab 200 mg q2w (MONARCH; $n = 184$)	Sarilumab 200 mg q2w + MTX (MOBILITY B; $n = 399$)	<i>P</i> -value
Age ^a , mean (s.d.), years	50.9 (12.6)	50.8 (11.8)	0.9608
Age group (years) ^b , n (%)			
<65	158 (85.9)	348 (87.2)	0.6772
≥65 and <75	25 (13.6)	50 (12.5)	
≥75	1 (0.5)	1 (0.3)	
Sex ^b , n (%)			
Male	27 (14.7)	62 (15.5)	0.7873
Female	157 (85.3)	337 (84.5)	
Race ^b , n (%)			
Caucasian/White	171 (92.9)	343 (86.0)	0.0007
Black	1 (0.5)	8 (2.0)	
Asian/Oriental	2 (1.1)	33 (8.3)	
Other	10 (5.4)	15 (3.8)	
Ethnicity ^b , n (%)			
Hispanic	46 (25.0)	151 (37.8)	0.0023
Non-Hispanic	138 (75.0)	248 (62.2)	
Region ^b , n (%)			
Region 1	61 (33.2)	75 (18.8)	<0.0001
Region 2	36 (19.6)	155 (38.9)	
Region 3	87 (47.3)	169 (42.4)	
Weight ^{a,c} , mean (s.d.), kg	72.3 (16.5)	74.7 (19.7)	0.1303
Height ^{a,c} , mean (s.d.), cm	163.3 (9.1)	161.4 (9.0)	0.0203
BMI ^{a,c} , mean (s.d.), kg/m ²	27.1 (5.6)	28.6 (6.7)	0.0059
BMI group (kg/m ²) ^{b,c} , n (%)			
<25	71 (38.6)	129 (32.4)	0.0123
≥25 and <30	70 (38.0)	127 (31.9)	
≥30	43 (23.4)	142 (35.7)	
Duration of RA since diagnosis, mean (s.d.), years ^a	8.1 (8.1)	8.6 (7.0)	0.5051
RA functional class ^b , n (%)			
I	29 (15.8)	42 (10.5)	0.1488
II	125 (67.9)	277 (69.4)	
III	30 (16.3)	80 (20.1)	
IV	0	0	

(continued)

TABLE 1 Continued

Parameter	Sarilumab 200 mg q2w (MONARCH; n = 184)	Sarilumab 200 mg q2w + MTX (MOBILITY B; n = 399)	P-value
Rheumatoid factor ^{b,d} , n (%)			
Positive	119 (66.9)	328 (82.6)	<0.0001
Negative	59 (33.2)	69 (17.4)	
Anti-CCP antibody ^{b,d} , n (%)			
Positive	134 (75.3)	337 (84.9)	0.0057
Negative	44 (24.7)	60 (15.1)	
Tender joint count (0–68) ^a , mean (s.d.)	28.0 (13.2)	26.5 (14.5)	0.2498
Tender joint count (0–28) ^a , mean (s.d.)	17.0 (6.1)	15.5 (6.6)	0.0102
Swollen joint count (0–66) ^a , mean (s.d.)	18.6 (10.7)	16.8 (9.7)	0.0418
Swollen joint count (0–28) ^a , mean (s.d.)	13.2 (5.7)	11.9 (5.6)	0.0106
CRP ^a , mean (s.d.), mg/l	17.4 (21.3)	22.2 (23.8)	0.0188
HAQ-DI (0–3) ^a , mean (s.d.)	1.6 (0.6)	1.7 (0.6)	0.3159
DAS28-CRP (>5.1: high disease activity) ^a , mean (s.d.)	6.0 (0.9)	6.0 (0.9)	0.7433
CDAI ^a , mean (s.d.)	43.6 (12.1)	40.4 (12.3)	0.0033
Patient's global assessment of disease activity (0–100 mm) ^a , mean (s.d.)	68.0 (17.5)	66.3 (20.8)	0.3007
Physician's global assessment of disease activity (0– 100 mm) ^a , mean (s.d.)	66.3 (15.7)	63.5 (17.6)	0.0643
Pain VAS (0–100 mm) ^a , mean (s.d.)	71.6 (18.7)	66.6 (21.3)	0.0046
Oral glucocorticoid use ^b , n (%)	98 (53.3)	252 (63.2)	0.0234

Region 1: Western countries; region 2: South America; region 3: rest of world. ^aP-value was obtained using *t*-test for equality of variance or Satterthwaite's *t*-test. ^bP-value was obtained using χ^2 test or Fisher's exact test. ^cn = 398 for the 'sarilumab plus MTX' treatment arm. ^dn = 178 for the 'sarilumab' treatment arm and n = 397 for the 'sarilumab plus MTX' treatment arm. CDAI: Clinical Disease Activity Index; DAS28-CRP: 28-joint Disease Activity Score using C reactive protein; HAQ-DI: HAQ-Disability Index; n: number of patients assessed; q2w: every 2 weeks.

49% for DAS28-CRP LDA; 85% vs 73% for CRP (mg/l) <10; 26% vs 38% for MCID in Hb; 73% vs 64% for MCID in pain VAS; and 66% vs 61% for MCID in FACIT-Fatigue (Supplementary Fig. S1, available at *Rheumatology* online). A similar trend was observed in responder analyses based on OC (Supplementary Fig. S1, available at *Rheumatology* online).

Safety

The safety profile of sarilumab has been previously reported, [12, 13] and was not part of this analysis.

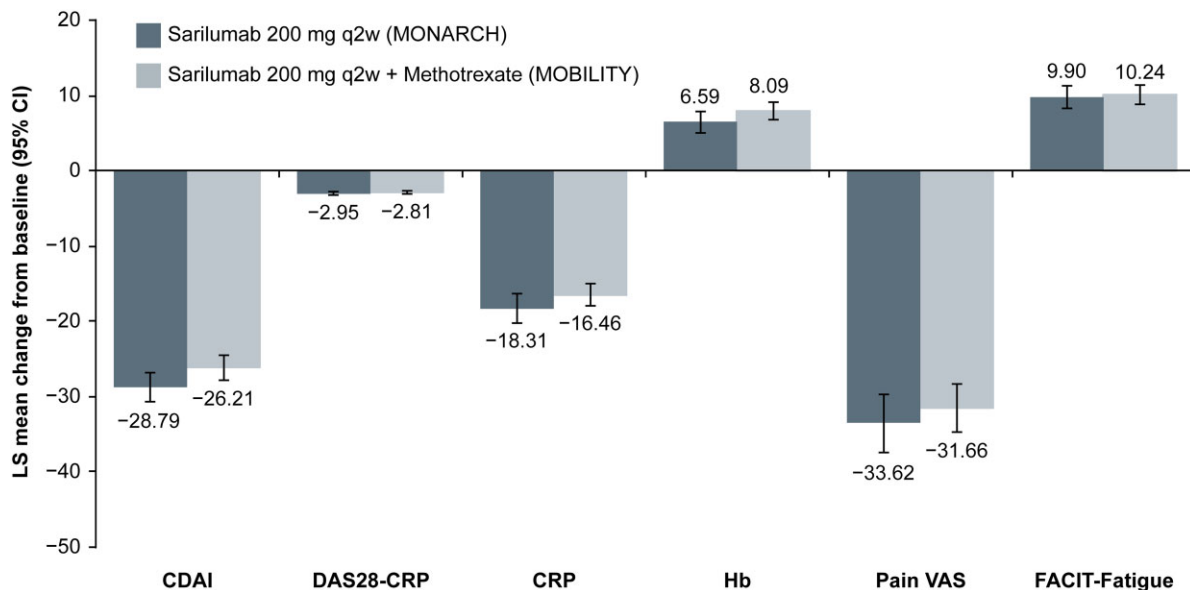
Discussion

After 24 weeks of treatment with sarilumab, both monotherapy and combination therapy showed greater clinical improvement in MTX-IR/INT patients with RA in the respective clinical trials. This *post hoc* analysis showed that for all efficacy assessments, no differences were observed between monotherapy and combination

therapy treatment arms suggesting similar effectiveness of these therapies in patients with RA.

Results of the current analysis are in line with the previous findings observed with another IL-6 receptor inhibitor, tocilizumab [18, 19]. In a study that compared two different tocilizumab-based treatment strategies in patients with active RA (ACT-RAY), no clinically relevant superiority was demonstrated with MTX plus tocilizumab add-on strategy compared with tocilizumab monotherapy [18]. Another study that compared tocilizumab monotherapy with its combination with DMARDs in patients with RA and inadequate responses to previous treatments also showed that the monotherapy and combination therapy were similarly effective [19]. However, a recent study reported that TNF inhibitors require comedication with csDMARDs to achieve optimal clinical efficacy [20, 21].

The results of this analysis suggest that sarilumab monotherapy may be a valuable treatment strategy when monotherapy with bDMARDs is recommended in certain patients with RA, specifically those who are

Fig. 1 Adjusted comparisons of LS mean change from baseline at week 24 using MMRM^a

All values are LS mean change from baseline (95% CI) at week 24. Patients with non-missing endpoint values were considered. ^aMMRM assuming an unstructured covariance structure with endpoint value at baseline, sarilumab group, visit, sarilumab group-by-visit interaction and selected baseline characteristics (see Results section) as covariates. Anti-CCP: anti-cyclic citrullinated peptide; CDAI: Clinical Disease Activity Index; DAS28-CRP: 28-joint Disease Activity using C reactive protein; FACIT: Functional Assessment of Chronic Illness Therapy; Hb: haemoglobin; LS: least square; MMRM: mixed-effect model repeated measure; q2w: every 2 weeks; SJC: swollen joint count; VAS: visual analogue scale.

MTX-IR/INT, and is in line with the EULAR recommendations for the management of RA [2]. This analysis provides preliminary evidence on similar effectiveness of sarilumab vs its combination with MTX, which might help rheumatologists in making informed treatment decisions, particularly, in MTX-IR/INT patients.

One limitation of this analysis is that the data analysed were obtained from two different study populations. To overcome these differences, adjusted comparisons were made between the treatment arms. Difference in the eligibility criteria did not allow the analyses to be adjusted for prior medication including comparison of the background MTX treatment between monotherapy and combination therapy treatment arms. Another limitation is that radiographic data were not obtained during the MONARCH study due to which it was not possible to account for potential differences in radiographic damage at baseline in this analysis. Moreover, the data included in this analysis were from a relatively short duration (24 weeks), which may not be sufficient to derive longer-term conclusions.

Conclusion

This *post hoc* analysis in patients with RA, based on the aggregate data from two clinical studies, demonstrated similar efficacy of sarilumab when administered as either monotherapy or in combination with MTX. These data

suggest that sarilumab monotherapy may be considered as a potential treatment alternative for patients in whom combination therapy with MTX is not appropriate.

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Data availability statement

Qualified researchers may request access to patient-level data and related documents (including, e.g. the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications). Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at <https://www.clinicalstudydatarequest.com>.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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