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Efficacy and safety of sarilumab in patients with active rheumatoid arthritis

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Abstract: The mainstay of rheumatoid arthritis (RA) treatment involves the use of medications that slow disease progression and reduce inflammation. Inadequate treatment responses and intolerances to conventional RA treatment have led to the development of biologic agents for the management of moderate-to-severe disease activity. Interleukin-6 (IL-6) inhibition is one of the targets for biologic activity in RA treatment. IL-6 is found in excess in the synovial fluid and contributes to joint erosion through its action on osteoclast cells. Sarilumab is a new IL-6 inhibitor indicated for the treatment of moderate-to-severe RA as monotherapy or in combination with conventional therapies in patients with an inadequate response to previous RA treatment.

Keywords: Rheumatoid arthritis, interleukin-6, sarilumab, biologic DMARD

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Background

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by erosive joint damage as well as the extra-articular involvement of several organ systems that affects approximately 0.5–1% of the world's adult population, equating to nearly 1.3 million adults in the United States (US).[1] The mainstay of treatment is with conventional and biologic disease-modifying antirheumatic drugs (DMARDs).[2] Biologic DMARDs (bDMARDs) are recommended for use in patients with moderate-to-severe disease progression or patients with incomplete responses or intolerances to conventional DMARDs (cDMARDs).[2] The targets of the bDMARDs include cytokines and cells directly involved in the inflammatory processes of RA. These targets include tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 (IL-1), T lymphocytes, and B lymphocytes.[3] Sarilumab is the second IL-6 inhibitor to gain US Food and Drug Administration (FDA) approval for the treatment of moderate to severe RA as monotherapy or in conjunction with cDMARD therapy.[4]

IL-6 is an inflammatory cytokine with pleiotropic effects on the immune system, some of which includes promoting the differentiation of B lymphocytes into antibody-producing plasma cells, stimulating the release of C-reactive protein (CRP) from hepatocytes, increasing vascular permeability, leading to joint edema, and stimulating receptor activator of nuclear factor kappa-B ligand (RANKL), leading to increased osteoclast formation and subsequent bone resorption.[5]

The goals of therapy for the management of RA are decreased disease activity or remission.[2] The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) treatment guidelines measure disease activity using several validated tools.[2,3] The 28-Joint Disease Activity Score (DAS28) examines 28 joints for the presence of swelling or tenderness and asks the patient to rate their global assessment of health on a scale of 0–10. Blood measurements of CRP or erythrocyte sedimentation rate (ESR) may also be calculated into the DAS28.[6] Remission is defined by a DAS28 score of <2.6 out of a 0–9.4 range.[2] Another scoring instrument utilized by the guidelines is the Clinical Disease Activity Index (CDAI), which includes tender and swollen joint counts in addition to patient and provider global activity scores.[6] A CDAI score of 2.8 or less out of a possible 76 indicates remission.[2] The ACR improvement criteria calculates the percent reduction in seven RA variables (tender joint count, swollen joint count,

acute phase reactant, patient rating of pain, patient global assessment of disease activity, observer global assessment of disease activity, and physical disability) to assess a patient's response to therapy and is utilized as a common endpoint in clinical trials.[6] A patient is defined as a responder to drug therapy if they experience at least a 20% reduction in the number of both swollen and tender joints in addition to a 20% reduction in three or more of the remaining five RA variables.[6]

Tocilizumab *versus* sarilumab

The FDA approved the first IL-6 inhibitor, tocilizumab, in 2010 for adult patients with moderate-to-severe RA who had an incomplete response to one or more DMARDs.[7] Tocilizumab is dosed either as intravenous (IV) 4 mg/kg every 4 weeks (q4w) or subcutaneous (SC) 162 mg every 2 weeks (q2w) for patients weighing less than 100 kg or 162 mg weekly for patients weighing 100 kg or more. Dosage increases to IV 8 mg/kg q4w or SC 162 mg weekly may be made based on clinical response.[7] Sarilumab received approval from the FDA in May 2017 following approval by the European Medicine Agency (EMA) in April 2017 and Canadian approval in January 2017.[3] Sarilumab is dosed subcutaneously at a dose of 200 mg q2w with an optional dose decrease to 150 mg q2w for patients who experience neutropenia, thrombocytopenia, or elevated transaminases.[8]

Immunologic activity and pharmacokinetics of sarilumab

Sarilumab is a human monoclonal antibody that binds and inhibits IL-6-facilitated signaling, resulting in reduced inflammation.[8,9] The activity of sarilumab is independent of complement or antibody cell-mediated cytotoxicity.[9] Sarilumab is administered as a SC injection every two weeks.[8] It has a t_{max} of 2 to 4 days and reaches steady state within 14 to 16 weeks. The metabolism of sarilumab is by catabolic pathways and not cytochrome-p (CYP) 450 enzymatic process. At high concentrations, the elimination is by linear, nonsaturable proteolytic pathway but low concentrations follow nonlinear saturable target-mediated elimination. The half-life is concentration dependent and is up to 8 days for the 150 mg dose and up to 10 days for the 200 mg dose. Once sarilumab has reached steady state, discontinuation of the drug results in nondetectable levels at 28 and 43 days for the 150 mg and 200 mg doses, respectively. Sarilumab in not excreted by the renal or hepatic systems, therefore, no dose adjustments for impairment in either system is required.[8]

Sarilumab has a direct effect on IL-6, which has an important role in inflammation and joint damage but also affects CYP3A4.[8,10] Patients with elevated IL-6 activity have decreased CYP3A4 enzymes, which lead to increased exposure to CYP3A4 substrates. Sarilumab's inhibition of IL-6 therefore increases CYP3A4 activity and decreases the exposure of substrates such as simvastatin. In a phase I study of the interaction of simvastatin and sarilumab, simvastatin plasma exposure was decreased by 45% and β-hydroxy-simvastatin (a primary active metabolite) was decreased by 36% after receiving one dose of both agents.[10] No change was seen in C_{max} or half-life of simvastatin or its metabolite after exposure to sarilumab. Currently, this drug interaction has not led to a recommendation to avoid the concomitant use of these agents in sarilumab's prescribing information.[8]

Phase II clinical trials

Sarilumab was studied in the Monoclonal antibody to IL-6Rα IN RA patients: a pivotal Trial with X-raY (MOBILITY) clinical trial series which included a part A phase II clinical trial and a part B phase III clinical trial.[9,11] Participants in the dose-finding part A study had continued RA symptoms despite current methotrexate treatment.[9] A total of 306 subjects were randomized to placebo or a sarilumab-dosing regimen in addition to concurrent methotrexate. The following subcutaneous sarilumab dosing strategies were evaluated over 12 weeks: 100 mg every q2w, 150 mg q2w, 200 mg q2w, 100 mg weekly, and 150 mg weekly.[9] The primary endpoint of ACR20 response rate was 46% for placebo compared with 49%, 67%, 65%, 62%, and 72% for the 100 mg q2w, 150 mg q2w, 200 mg q2w, 100 mg weekly, and 150 mg weekly sarilumab arms, respectively. All of the sarilumab dosing strategies had statistically significant results when compared with placebo, with the exception of the sarilumab 100 mg q2w.[9] Additionally, a greater percentage participants achieved the secondary endpoint of remission as defined by a DAS28 disease activity score of <2.6 in the sarilumab 150 mg q2w, 200 mg q2w, 100 mg weekly, and 150 mg weekly compared to placebo with a statistical significance of $p = 0.0152$, $p = 0.0018$, $p = 0.0107$, and $p = 0.0005$, respectively.[9] Of the four efficacious

sarilumab dosing strategies, similar efficacy and safety profiles were observed between the weekly and q2w dosing regimens, which led investigators to consider q2w dosing for future phase III studies.[9]

Phase III clinical trials

Sarilumab has been studied against placebo in patients with an inadequate response to methotrexate or TNF-α inhibitors, and head-to-head against the TNF-α inhibitor, adalimumab, in three separate phase III clinical trials.[11–13] Trial results for the primary and secondary endpoints of the phase III clinical trials are listed in Table 1.

The part B MOBILITY study evaluated the use of sarilumab 150 mg q2w and 200 mg q2w *versus* placebo in 1369 subjects with active RA disease activity despite current methotrexate use.[11] Additionally, approximately 20% of the study population had a history of previous biologic DMARD use. Subjects received placebo, sarilumab 150 mg q2w, or sarilumab 200 mg q2w in a 1:1:1 ratio. The coprimary endpoints were percentage of patients with an ACR20 at week 24, change in the Health Assessment Questionnaire Disability Index (HAQ-DI) at week 16, and the change in the Sharp/van der Heijde score (SHS) at week 52. Pertinent secondary endpoints included sustained ACR70 improvement for ⩾6 months, disease activity scores, and clinical disease activity index scores.[11] Both doses of sarilumab performed statistically better than placebo for all three coprimary endpoints, with a level of significance of $p < 0.0001$, and the results were sustained at week 52. The sarilumab treatment arms also showed statistically significant improvements over the placebo arm for all of the secondary endpoints, including a higher number of sarilumab participants achieving remission at week 24, based on the DAS28-CRP and CDAI scores compared with placebo.[11] Prior use of a biologic DMARD did not affect the response rate to sarilumab.[11]

Strand and colleagues explored the patient-reported outcomes of the phase III MOBILITY study.[14] Studied outcomes included the patient global assessment of disease activity (PtGA), pain visual analog scale (VAS), HAQ-DI, Short Form-36 Health Survey (SF-36), and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F). Greater improvements in the PtGA, VAS, HAQ-DI, and FACIT-F scores were seen in both sarilumab arms compared with the placebo arm, $p < 0.0001$, with improvements noted as early as 2 weeks following treatment with sarilumab.[14] The results of this analysis support the clinical efficacy and safety demonstrated in the MOBILITY study.[14]

Boyapati and colleagues evaluated sarilumab's effects on biomarkers associated with bone resorption in a separate analysis of the MOBILITY study.[15] Studied biomarkers included RANKL, CRP, matrix metalloproteinases (MMP), and collagen types I, II, and III (C1, C2, and C3, respectively), all of which are typically seen in elevated concentrations in RA, resulting in synovial inflammation and joint erosion.[15] Of note, CRP was significantly lowered in the sarilumab arms compared with placebo, with peak reductions observed at week 12 ($p < 0.0001$ for both sarilumab doses), as well as RANKL, with significant reductions seen at week 2, with continued reduction through week 24 ($p < 0.05$ at week 2 and $p < 0.01$ at week 24).[15]

Fleischmann and colleagues, in the TARGET clinical trial, evaluated patients with an inadequate response or intolerance to previous treatment with at least one TNF-α over the 24-week study.[12] Participants were randomized in a 1:1:1 fashion to placebo, sarilumab 150 mg q2w, or sarilumab 200 mg q2w. Participants were also continued on their nonbiologic DMARD therapy, which could include methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine. Similar to other studies of sarilumab, participants who had not achieved at least a 20% improvement from baseline in swollen joint count or tender joint count were given the opportunity to switch to open-label sarilumab for the duration of the study.[12] Subjects in the sarilumab treatment arms had significantly higher rates of ACR20 compared with placebo ($p < 0.0001$ for both doses).[12] Although not powered to detect a difference, more participants in the sarilumab 200 mg q2w met the ACR20 criteria than participants in the 150 mg q2w arm. Statistically significant improvements were also seen in the coprimary endpoint of change from baseline to week 12 in HAQ-DI scores.[12] It is important to note that approximately 60% of the participants in this trial were on low-dose chronic corticosteroid therapy; however, concurrent steroid use did not alter the statistical significance and the rates of the reported primary endpoints were similar

Table 1. Summary of phase III clinical trials of sarilumab in rheumatoid arthritis.

Study	Population	Sarilumab	Comparator	Primary endpoints	*p* value	Pertinent secondary endpoints	*p* value
MOBILITY[11]	MTX-IR	150 mg SC q2w + background weekly MTX 200 mg SC q2w + background weekly MTX	Placebo + background weekly MTX	**ACR20 at week 24**		**ACR70 at week 24**	
				150 mg *versus* placebo: 58% *versus* 33.4%	$p < 0.0001$	150 mg *versus* placebo: 12.8% *versus* 3%	$p < 0.0001$
				200 mg *versus* placebo: 66.4% *versus* 33.4%	$p < 0.0001$	200 mg *versus* placebo: 14.8% *versus* 3%	$p < 0.0001$
				HAQ-DI at week 16		**DAS28-CRP $<$ 2.6 at week 24**	
				150 mg *versus* placebo: −0.53 *versus* −0.29	$p < 0.0001$	150 mg *versus* placebo: 27.8% *versus* 10.1%	$p < 0.0001$
				200 mg *versus* placebo: −0.55 *versus* −0.29	$p < 0.0001$	200 mg *versus* placebo: 34.1% *versus* 10.1%	$p < 0.0001$
				SHS at week 24		**CDAI $\leqslant$ 2.8 at week 24**	
				150 mg *versus* placebo: 0.90 *versus* 2.78	$p < 0.0001$	150 mg *versus* placebo: 10.3% *versus* 5%	$p < 0.0001$
				200 mg *versus* placebo: 0.25 *versus* 2.78	$p < 0.0001$	200 mg *versus* placebo: 13.8% *versus* 5%	$p < 0.0001$
TARGET[12]	anti-TNF- IR	150 mg SC q2w + background cDMARDs 200 mg SC q2w + background cDMARDs	Placebo + background cDMARDs	**ACR20 at week 24**		**ACR50 at week 24**	
				150 mg *versus* placebo: 55.8% *versus* 33.7%	$p < 0.0001$	150 mg *versus* placebo: 37% *versus* 18.2%	$p < 0.0001$
				200 mg *versus* placebo: 60.9% *versus* 33.7%	$p < 0.0001$	200 mg *versus* placebo: 40.8% *versus* 18.2%	$p < 0.0001$
				HAQ-DI at week 12		**ACR70 at week 24**	
				150 mg *versus* placebo: −0.5 *versus* −0.3	$p < 0.01$	150 mg *versus* placebo: 19.9% *versus* 7.2%	$p < 0.001$
				200 mg *versus* placebo: −0.6 *versus* -0.3	$p < 0.001$	200 mg *versus* placebo: 16.3% *versus* 7.2%	$p < 0.01$
						DAS28-CRP $<$ 2.6 at week 24	
						150 mg *versus* placebo: 24.9% *versus* 7.2%	$p < 0.0001$
						200 mg *versus* placebo: 28.8% *versus* 7.2%	$p < 0.0001$

Table 1. (Continued)

Study	Population	Sarilumab	Comparator	Primary endpoints	*p* value	Pertinent secondary endpoints	*p* value
MONARCH[13]	MTX-IR	200 mg SC q2w monotherapy	Adalimumab 40 mg SC q2w	**DAS28-ESR at week 24** Sarilumab *versus* adalimumab: 3.5 *versus* 4.5	$p < 0.0001$	**DAS28-ESR < 2.6 at week 24** Sarilumab *versus* adalimumab: 26.6% *versus* 7% **HAQ-DI at week 24** Sarilumab *versus* adalimumab: 1 *versus* 1.2 **ACR20 at week 24** Sarilumab *versus* adalimumab: 71.4% *versus* 58.4% **ACR50 at week 24** Sarilumab *versus* adalimumab: 45.7% *versus* 29.7% **ACR70 at week 24** Sarilumab *versus* adalimumab: 23.4% *versus* 11.9%	$p < 0.0001$ $p = 0.0037$ $p = 0.0074$ $p = 0.0017$ $p = 0.0036$

MTX, methothrexate; IR, inadequate response; SC, subcutaneous; q2w, every 2 weeks; ACR20/50/70, American College of Rheumatology 20%/50%/70% response rate; HAQ-DI, Health Assessment Questionnaire Disability Index; DAS28-CRP, 28-Joint Disease Activity Score using C-reactive protein; SHS, modified Sharp/van der Heijde Score; CDAI, Clinical Disease Activity Index; anti-TNF, antitumor necrosis factor; cDMARDs, conventional disease-modifying antirheumatic drugs; DAS28-ESR, 28-Joint Disease Activity Score using erythrocyte sedimentation rate.

among subjects with or without baseline treatment with corticosteroids.[12]

Sarilumab was studied against the active competitor, adalimumab, in the MONARCH clinical trial.[13] A total of 369 subjects with a reported treatment failure or intolerance to methotrexate were evenly randomized to monotherapy with SC sarilumab 200 mg q2w or adalimumab 40 mg q2w.[13] The primary endpoint of DAS28-ESR was measured at 24 weeks in addition to the secondary endpoints of remission rates, ACR response rates, HAQ-DI scores, SF-36, and FACIT-F. Superiority of sarilumab to adalimumab required at least a 0.6-unit difference in the DAS28-ESR score.[13] A large percentage of each group completed the treatment phase of the study, 90% in the sarilumab arm *versus* 84% in the adalimumab arm. The change in DAS28-ESR was significantly greater in the sarilumab treatment group compared with the adalimumab treatment group, –3.28 *versus* –2.20 respectively ($p < 0.0001$).[13] Superiority of sarilumab over adalimumab was met, as evidenced by a between-group treatment difference of –1.08. Additionally, a greater percentage of subjects in the sarilumab arm achieved remission as defined by the DAS28-ESR than adalimumab at 24 weeks, 26.6% and 7%, respectively ($p < 0.0001$). The between-group difference in ACR20/50/70 was >10% in favor of sarilumab.[13]

Safety

Common adverse drug reactions seen in the clinical trials for sarilumab include infections (such as nasopharyngitis, upper respiratory tract infections, and urinary tract infections), neutropenia, injection-site erythema, increased low-density lipoprotein (LDL) cholesterol, and increased liver enzymes which are consistent with the common adverse drug reactions seen with other biologic immunosuppressive agents.[9,11–13] Treatment-emergent adverse events (TEAEs) varied among the clinical trials. For example, in the MOBILITY phase II trial, TEAEs leading to discontinuation of sarilumab were 3.8% in the 150 mg dose and 7.8% in the 200 mg dose.[9] However, in the MOBILITY phase III trial, adverse events leading to discontinuation were 12.5% for the 150 mg dose and 13.9% for the 200 mg dose.[11] The clinical impact on the occurrence of major adverse cardiovascular events (MACEs) secondary to the increase in LDL cholesterol was reviewed by both the EMA and FDA.[16,17] In the clinical trials, increases in LDL cholesterol resulted in a higher percentage of patients in the sarilumab arms that were initiated on statin therapy compared with subjects in the placebo and active comparator arms; however, the number of MACEs was too low in the trials to make a definitive correlation between MACE and sarilumab-related increases in LDL cholesterol.[11–13,15,16] The prescribing information for sarilumab does contain a black box warning for risk of infections and recommends patients be tested for tuberculosis prior to initiation.[8] Additionally, patients taking sarilumab must avoid live vaccinations because of the risk of infection.[8]

Conclusion

Sarilumab therapy offers another option for patients who cannot tolerate or have an inadequate response to cDMARDs in the management of their moderate-to-severe RA disease. Clinical trial data show that sarilumab is effective at improving several aspects of the disease process, including decreasing acute phase reactants, decreasing the number of tender and swollen joints, and reducing radiographic evidence of progressive joint erosion. Sarilumab, an IL-6 inhibitor, was also found to be superior to adalimumab, a TNF-α inhibitor using the DAS28-ESR as an assessment tool for disease activity. Results from additional studies evaluating sarilumab as monotherapy and in combination with cDMARDs other than methotrexate have not yet been published.

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Conflict of interest statement

Delilah McCarty is currently employed by Novo Nordisk, Inc as an obesity medical liaison. There is no conflict of interest to declare between employment and this manuscript. Author April Robinson declares no conflict of interest.

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