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Sarilumab (Kevzara®): A New Treatment for Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that can cause both structural bone and cartilage damage that may potentially lead to disability in the affected joints.[1] Rheumatoid arthritis affects 0.5-1% of adults worldwide.[2] This disease is characterised by synovial inflammation, swelling around the joints, and autoantibody production.[1] Not only does this disease effect the joints, it is also associated with systemic effects including increased rates of cardiovascular illnesses and risk of lymphoma. Inflammatory cytokines are believed to be responsible for the damage caused by RA, resulting from leukocytic infiltration and accumulation in the synovial compartment.[3]

New treatment options for RA involve targeting inflammatory cytokines, specifically interleukin-6 (IL-6), its membrane-bound IL-6 receptors (mIL-6R), and soluble IL-6 receptors (sIL-6R) which play important roles in RA.[3] Increased levels of IL-6 have been linked to increased neutrophil adhesion, which increases neutrophil secretion of proteolytic enzymes and reactive oxygen intermediates, leading to increased joint destruction. The sIl-6Rs are also released from neutrophils, which can increase monocyte proliferation, leading to the shift from acute inflammation to chronic inflammation. IL-6 is also responsible for the characteristic erosion seen in bones and articular cartilage. In both in vitro and in vivo mice studies, IL-6 and sIL-6R appear to induce osteoclastogenesis. Meanwhile in human chondrocyte cultures, the combination of sIL-6R and IL-6 inhibited the synthesis of proteoglycans, the main component of articular cartilage. Consequently, targeting IL-6 and its receptors serve as an effective strategy for RA treatment.

Currently, the primary treatment for RA is the use of a disease-modifying antirheumatic drug (DMARD), preferably methotrexate (MTX).[4] After three months, should that prove to be ineffective, the next step is to add either a tumor necrosis factor (TNF) inhibitor or a non-TNF biologic grouped into a category called biological DMARDs (bDMARD). A new FDA approved treatment option for RA, sarliumab, is an IL-6 receptor antagonist within the medication class of non-TNF biologics. Sarilumab (Kevzara®) has recently been approved by the FDA for the treatment of moderately to severely active RA. The purpose of this article is to review sarilumab and its efficacy in treating rheumatoid arthritis as reported in three phase III clinical trials.

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Mechanism of Action

Sarliumab is a monoclonal antibody that exerts its effects by binding to both membrane-bound and soluble IL-6 receptors.[5] This process stops IL-6 from binding and activating its receptors, which in turn blocks osteoclast and fibroblastic synovial cell activation, neutrophil recruitment, and trans-signaling that leads to proinflammatory activity.[3] Upon sarilumab administration, there is a rapid and dose dependent decrease in C-reactive proteins (CRP) levels, a test marker for inflammation.[5]

Pharmacokinetics

Patients given sarilumab 200 mg had a three-fold increase in maximum plasma concentration and five-fold increase in the area under the curve (AUC) compared to those who received sarilumab 100 mg, suggesting that sarilumab possesses nonlinear pharmacokinetics.[5] The average time to reach maximum plasma concentration did not differ between doses, with average times reported as 3.77 days for sarliumab 100 mg and 3.67 days for sarliumab 200 mg (**Table 1**). The volume of distribution for sarilumab is 7.3 L.[4] Sarilumab follows a biphasic elimination pathway with a predominantly linear, non-saturable pathway at higher concentrations and nonlinear, saturable, target mediated pathway at lower concentrations. The half-life of the drug is dependent on its concentration. At 200 mg every two weeks, the half-life is 10 days at steady state but at a smaller dose of 150 mg, the half-life is 8 days. The exact metabolic pathway of sarilumab is unknown, but it is predicted to follow degradation into peptides and amino acids through catabolic pathways like other similar monoclonal antibodies. Neither hepatic nor renal pathways are involved in the elimination process.

Clinical Trials

Three phase III clinical trials evaluated the efficacy of sarilumab for the treatment of RA. Data from these clinical trials is summarized in **Table 2**. All three of these trials used the 28-joint disease activity score with erythrocyte sedimentation rate (DAS28-ESR) and high-sensitivity C reactivity protein (DAS28-CRP) to

Table 1 | Pharmacokinetics of Sarilumab[4,5]

Absorption	
C_{max}	12.9 mg/mL
T_{max}	10 days
AUC	102 day*mg/L
Distribution	
V_d	7.3 L
Metabolism	
(unknown) via linear proteolytic pathway and target-mediated elimination	
Elimination	
$T_{1/2}$	10 days

AUC: area under the curve; **C_{max}:** maximum concentration; **L:** liter; **mg:** milligram; **mL:** milliliter; **$T_{1/2}$:** elimination half-life; **Vd:** volume of distribution

assess sarilumab's therapeutic effects in RA.[9] These measures look at the number of both tender and swollen joint count as well as a general health assessment and a laboratory count of ESR or CRP, both are indicators of inflammation, and calculate a score from 0-9. In both measures, a higher score indicates a more developed disease state. A score higher than 5.2 is considered as high disease activity, a score of 3.2-5.2 indicates moderate disease activity, a score of 2.6-3.2 indicates low disease activity, and a score of < 2.6 indicates remission. This measure is among the six measures recommended by the American College of Rheumatology to be used in clinical practices.

Another disease activity measure shared by the three trials is the Health Assessment Questionnaire-Disability Index (HAQ-DI).[10] This questionnaire seeks to assess the magnitude of debilitation a RA patient feels by examining their ability to perform specific activities under nine categories. Each of the nine categories are individually scored, and a score between 0-4 is given based on the patient's ability to perform an activity. A zero means the patient is able to perform the task independently without difficulty and four means the patient is unable to perform the activity at all. The nine individual scores are then added and divided by the number of categories answered to produce the index.

The American College of Rheumatology (ACR) developed a criterion of its own as a means to define improvement or remission in RA that was also used by the studies. At its most basic level, the ACR20 is considered as >20% improvement in both tender and swollen joint count as well as >20% improvement in at least three of the following categories: patient pain assessment, patient global assessment, patient self-assessed disability, and acute-phase reactant (ESR or CRP). The criteria can be taken further to explore patients who saw >50% (ACR50) or >70% (ACR70) improvement in those categories.

MOBILITY

Part B of the MOBILITY trial was a multi-centered, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of different sarilumab doses as compared with placebo in conjunction with weekly MTX.[6] Patients were followed for 52 weeks and divided into one of two cohorts. The first cohort was randomized to receive placebo or a subcutaneous sarilumab dose (100 mg weekly, 150 mg weekly, 100 mg every 2 weeks, 150 mg every 2 weeks, or 200 mg every 2 weeks).[10] After 12 weeks of treatment, sarliumab 150 mg every 2 weeks and 200 mg every 2 weeks were determined to have the most ideal dosing regimens. After this initial 12 week period, these participants were then randomized in the second cohort to receive either placebo, sarilumab 150 mg every two weeks, or sarilumab 200 mg every two weeks in addition to weekly MTX. There were three co-primary endpoints associated with the MOBILITY trials: proportion of patients achieving an ACR20 improvement response at week 24, change from baseline in physical function assessed with HAQ-DI at week 16, and change from baseline in the modified Sharp/van der Heijde scoring (SHS) score of radiographic progression of structural damage. Secondary endpoints included proportion of patients achieving ACR70 improvement response and maintaining it for >6 consecutive months, proportion of patients with DAS28-CRP <3.2 at 24 weeks and <2.6 after the completion of the 52 week treatment course. Of the original 1,369 total participants, only 172 patients were enrolled in cohort 1 for dose selection and 1,197 patients were in cohort 2 for the intent-to-treat population. There was a fairly good retention rate among participants as 79% of those randomized in cohort 2 completed the 52-week treatment period.

The study was composed of patients aged 18–75 years who fulfilled the ACR 1987 revised classification criteria for RA.[11] Patients were included if they had active RA as defined as a swollen joint count ≥6 [of 66 joints assessed], tender joint count (TJC) ≥8 [of 68 joints assessed], and high-sensitivity CRP level ≥0.6 mg/dl [upper limit of normal <0.6 mg/dl], with a disease lasting more than 3 months despite treatment with MTX for a minimum of 12 weeks at a stable dosage (10–25 mg/week). Additionally, patients were included if they had at least one documented bone erosion, were positive for anti–cyclic citrullinated peptide (anti-CCP) antibodies, or seropositive for rheumatoid factor on screening laboratory tests at baseline. Exclusion criteria included uncontrolled concomitant diseases, significant extraarticular manifestations of RA, functional class IV RA, other inflammatory joint diseases, current/recurrent infections, or prior nonresponse to bDMARDs.

Patients who received either sarilumab doses showed significant improvements in both the co-primary endpoints and the secondary clinical efficacy endpoints. The ACR20 response rates in patients with sarilumab 150 mg (58.0%) and sarilumab 200 mg (66.4%) were significantly higher than that compared with patients on placebo (33.4%, p<0.0001). Similarly, the percentage of patients who achieved a DAS28-CRP score <2.6 at week 24 was higher among those who received the sarilumab 150 mg (27.8%) and sarilumab 200 mg (34.1%) compared to those who received the placebo (10.1%, p <0.0001). Data is not available to show the percentage of patients who achieved a DAS28-CRP score <2.6 at the conclusion of the trial. The least squares means (LSM) change from baseline in the HAQ-DI score at week 16 was -0.53 in patients receiving 150 mg every two weeks and -0.55 in patients receiving 200 mg every two weeks, respectively, compared to a LSM change of -0.29 seen in patients with the placebo (p<0.0001). Finally, when looking at the progression of structural damage, patients on sarilumab 150 mg showed a mean change of 0.9 from baseline while patients on sarilumab 200 mg had a mean change of 0.25. Both of which showed a slower progression when compared to patient on placebo which had a mean change of 2.78 (P < 0.0001 for each dose group versus placebo). In conclusion, sarilumab demonstrated significant improvements in signs and symptoms of RA compared to placebo.

MONARCH

The MONARCH study was a multi-centered, randomized, double-blind, and active-controlled study that compared the efficacy and safety of sarilumab monotherapy to that of adalimumab monotherapy over the course of 24 weeks.[7] Patients were randomized to receive subcutaneous sarilumab 200 mg every two weeks plus placebo or adalimumab 40 mg every two weeks plus placebo. Intent-to-treat (ITT) population consisted of 369 patients, of which 184 patients were in the sarilumab group. The primary efficacy endpoint was change from baseline in DAS28-ESR at the conclusion of the treatment period. Secondary efficacy endpoints included the following: DAS28-ESR remission (defined as a score of <2.6); the Health Assessment Questionnaire-Disability Index (HAQ-DI); ACR20, ACR50, and ACR70 improvement from baseline measures; among others.

Patients aged >18 years were eligible for the study if they fulfilled the 2010 ACR or the European League Against Rheumatism (EULAR) Classification Criteria for RA.[9] Patients were included if they had active RA, defined as ≥6 of 66 swollen and ≥8 of 68 tender joints and high-sensitivity C reactive protein (CRP) ≥8 mg/L or erythrocyte sedimentation rate (ESR) ≥28 mm/hours and (DAS28-ESR) >5.1 assessed between screening and randomization, with disease duration ≥3 months, and did not respond well to MTX therapy. Patients were excluded if they had prior experience with bDMARDs or if they previously had tuberculosis.

At the conclusion of the trial, the primary efficacy endpoint with sarilumab 200 mg every two weeks showed a mean change from baseline in the DAS28-ESR score of -3.28 whereas adalimumab 40 mg every two weeks only showed a LSM change of -2.20 (difference: −1.08; 95% CI −1.36 to −0.79; p<0.0001). The odds of achieving DAS28-ESR remission with sarilumab compared to adalimumab were greater at both week 12 (OR: 2.61; 95% CI 1.31 to 5.20; p=0.0051) and week 24 (OR: 4.88; 95% CI 2.54 to 9.39; p<0.0001). The change in DAS28-ESR from sarilumab was reflected in the change in DAS28-CRP, as the sarilumab group had a LSM change in DAS28-CRP of -2.86 compared to -1.97 in the adalimumab group (95% CI −1.14 to −0.63; nominal p<0.0001). The percentage of patients who achieved an ACR20/50/70 response at week 24 was significantly greater in the sarilumab group (71.7%/45.7%/23.4%) than the adalimumab group (58.4%/29.7%/11.9%; all p≤0.0074), respectively. Sarliumab also demonstrated improvements compared to adalimumab in HAQ-DI score (−0.61 sarilumab vs −0.43 adalimumab; difference: −0.18; 95% CI −0.31 to −0.06; p=0.0037). The authors conclude the data as presented suggests that sarilumab demonstrated

Table 2 | Summary of Clinical Trials for Sarilumab

Trial	MOBILITY[6]	MONARCH[7]	TARGET[8]
Primary Outcome	Co-primary outcomes of proportion of patients achieving ACR20 improvement at 12 weeks, change in HAQ-DI score at 16 weeks, and change in SHS score at 52 weeks	Change from baseline DAS28-ESR score at 24 weeks	Co-primary outcomes of proportion of patients achieving ACR20 after 24 weeks and change from baseline HAQ-DI after 12 weeks
Treatment	sarilumab 200 mg q2w (n=399) vs placebo (n=398)	sarilumab 200 mg q2w (n=165) vs adalimumab 40 mg q2w (n=156)	sarilumab 150 mg q2w (n=125); sarilumab 200 mg q2w (n=133) vs placebo (n=101)
Proportion of patients achieving ACR20	66.4% vs 33.4% (p<0.0001)	—	sarilumab 150 mg: 55.8%, sarilumab 200 mg: 60.9% vs placebo: 33.7% (p<0.0001)
LSM change from baseline HAQ-DI	-0.55 vs -0.29 (p<0.0001)	—	sarilumab 150 mg: -0.46, sarilumab 200 mg: -0.47, vs placebo: -0.26 (p<0.001)
Change from baseline DAS28 -CRP <2.6	—	-3.28 vs -2.20 (difference = -1.08; 95% CI, -1.36 to -0.79)	—
Mean change in SHS	0.25 vs 2.78 (p<0.0001)	—	—

95% CI: 95% confidence interval; **mg =** milligram; **n =** number of patients; **CS =** topical corticosteroid **LSM:** least squares mean; **q2w:** every 2 weeks. **ACR 20:** American College of Rheumatology Criteria with > 20% improvement (20% improvement in both tender and swollen joint count and three of the following categories: patient pain assessment, patient global assessment, patient self-assessed disability). **DAS28-CRP:** disease activity score using C reactive protein (>5.1: high disease activity; 3.2-5.1: moderate disease activity, 2.6-3.2: low disease activity, < 2.6: remission). **HAQ-DI:** Health Assessment Questionnaire-Disability Index (nine categories examining ability to perform activities with a score between 0-4, with 0 having no problem performing activities and 4 being unable to perform), **SHS:** modified Sharp/van der Heijde scoring (SHS) system. A composite score obtained by rating joint space narrowing and erosions at 15 sites in each hand and wrist and six in each foot. Each site is rated on a scale of 0 to 4: 0 indicates no narrowing, 1 represents minimal narrowing, 2 indicates loss of 50% of the joint space, 3 indicates lass of 75% of the joint space, and 4 represents complete loss of joint space.

superior therapeutic benefit in the treatment of RA compared to monotherapy with adalimumab.

TARGET

The TARGET trial was another multi-centered, randomized, double-blind, placebo-controlled trial that looked at the efficacy and safety of sarilumab with synthetic DMARD in patients who either had an inadequate response to or intolerance to anti-TNF therapies.[8] The two co-primary endpoints investigated were the proportion of patients achieving an ACR20 improvement response at week 24 and a change from baseline in physical function assessed with HAQ-DI at week 12. Secondary endpoints included change from baseline in the DAS28-CRP at week 24, ACR50 and ACR70 response rates at week 24, DAS28-CRP level of <2.6 at week 24, and change from baseline in the HAQ-DI at week 24. A total of 546 patients were randomly allocated to treatment groups in this study. For 24 weeks, patients received either subcutaneous sarliumab 150 mg every two weeks, sarilumab 200 mg every two weeks, or placebo.

Patient inclusion criteria were similar to that of the MONARCH trial. In addition, the inclusion criteria required patients to have had: 1) an inadequate response or intolerance ≥1 anti-TNF therapy and 2) received continuous treatment with a synthetic DMARD either as a monotherapy or in a combination with other therapies. Patients were excluded from the study if they had uncontrolled concomitant disease, significant extraarticular manifestations of RA, functional class IV RA, other inflammatory diseases, current/recurrent infections, tuberculosis, or were receiving prednisone >10 mg/day or equivalent.

Both co-primary endpoints had statistically significant changes for each of the sarilumab doses. The proportion of patients achieving ACR20 was 55.8% in the sarilumab 150 mg group and 60.9% in the sarilumab 200 mg every two weeks at 24 weeks compared to only 33.7% of patients on placebo (p<0.0001 compared to both active treatment groups). Similar results were seen in the proportion of patients achieving ACR50 on sarilumab 150 mg every two weeks (37.0 %) and sarilumab 200 mg every two weeks (40.8%) compared to those on placebo (18.2%; P < 0.0001). The ACR70 responses were also significantly improved in the sarilumab 150 mg (19.9%; P = 0.0002) and sarilumab 200 mg (16.3%; P = 0.0056) vs placebo (7.2%). At week 12 the placebo mean change in HAQ-DI was –0.26 compared to –0.46 in the sarilumab 150 mg group (p=0.007 compared to placebo) and −0.47 in the sarilumab 200 mg group (p=0.0004 compared to placebo). Improvements in both symptom relief and physical function occurred regardless of the number of prior anti-TNF treatment.

Adverse Reactions

In both the MOBILITY and the TARGET studies, the most common reported adverse reaction associated with sarilumab was infection (**Table 3**).[8,9] This was seen in 40.1% of patients taking sarilumab 150 mg every two weeks and 39.6% of patients on sarilumab 200 mg every two weeks during the MOBILITY trial. In the TARGET trial, the prevalence of infection was smaller but still present at 22.1% of patients taking sarilumab 150 mg every two weeks and 30.4% of patients on sarilumab 200 mg every two weeks. Infections were also reported in the MONARCH study with 28.8% of patients on sarliumab 200 mg every two weeks compared to 27.7% of patients on adalimumab 40 mg every two weeks.[7] Additional adverse reactions seen across the three studies include injection-site reactions, reduced absolute neutrophil count, increase in alanine aminotransferase count, and increased total cholesterol.[7-9]

Dosing and Administration

Sarilumab is available as a subcutaneous injection and is recommended to be given 200 mg once every two weeks.[4] Based on management of neutropenia, thrombocytopenia, and elevated liver enzymes, the dose can be reduced to 150 mg once every two weeks. Sarilumab should be used with caution in patients with active infection or with biological DMARDs due to increased risk of immunosuppression and infection. There is limited information regarding the efficacy and safety of sarliumab in paediatric patients. For geriatric patients, caution should be exercised because of the increased incidence of infection in that population. The wholesale acquisition cost (WAC) of sarilumab is $36,000 a year which is 30% less than the WACs of its competitors.[15] However, pricing will vary significantly between patients and suppliers.

Conclusion

Sarilumab is a monoclonal antibody that targets the IL-6 receptors, allowing it to effectively and safely treat rheumatoid arthritis. While more studies are required to assess its use among special populations such as those with hepatic problems, it appears that sarilumab may be an appropriate second line treatment option for the treatment of RA should synthetic DMARDs like methotrexate fail to elicit an appropriate therapeutic response in

Table 3 | Select Adverse Effects of Sarilumab 200 mg from Clinical Trials

Trial	MOBILITY (n=399)[6]	MONARCH (n=165)[7]	TARGET (n=133)[8]
Infections (%)	39.6	64.1	65.2
Upper Respiratory Tract Infection (%)	8.7	1.6	3.3
Bronchitis (%)	5.7	6.5	-
Urinary Tract Infections (%)	5.4	-	7.1
Neutropenia (%)	14.4	13.6	12.5
Leukopenia (%)	4.2	-	1.6
Elevated ALT (%)	7.5	3.8	5.4

Data represent the percent of trial subjects that received sarilumab 200 mg every 2 weeks and experienced the adverse event

patients.

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