

Sarilumab: A new arsenal for Rheumatoid ArthritisKumar R¹, Jassal B², Sehgal A³

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ABSTARCT

Rheumatoid arthritis is a debilitating disease that has significant impact on quality of life. Biological and non biological DMARDs improved the outcome in RA patients. New agents are still required in inadequate responders or intolerant patients. FDA has recently approved a new drug Sarilumab, a monoclonal antibody for the treatment of moderate to severe form of RA which acts by binding to Interleukin receptor 6 and interrupts the resultant cytokine-mediated inflammatory signaling.

Key Words: IL-6, monoclonal antibody, sarilumab, cytokine

Introduction

Rheumatoid arthritis is an autoimmune disease in which there is joint inflammation, synovial proliferation and destruction of articular cartilage. It is a debilitating disease that has significant impact on quality of life. Despite the availability of wide range of treatments including DMARDs, new agents are still needed in patients who are inadequate responders or intolerant to available drugs. FDA has recently approved a new drug Sarilumab, a monoclonal antibody for the treatment of moderate to severe active rheumatoid arthritis (RA). It is given to patients who do not respond well or have intolerance to disease-modifying antirheumatic drugs (DMARDs), such as methotrexate. It can be used alone or in combination with methotrexate or another DMARD. Sarilumab's approval comes after two phase 3 trials involving about 2900 adults whose condition did not respond well to existing treatments and who showed positive results with the drug.

Sarilumab is a human monoclonal antibody directed against the IL-6 receptor (IL-6R). It binds with high affinity to both soluble (sIL-6R) and membrane (mIL-6R) bound IL-6 receptor and interrupts the resultant cytokine-mediated inflammatory signaling. IL-6 is the most abundant cytokine in the serum and synovial fluid of

patients with RA and levels correlate with both disease activity and joint destruction. Sarilumab demonstrated statistically significant, clinically meaningful improvements in adult patients with RA by reducing signs and symptoms, radiographic progression of disease & improving physical function in various clinical trials.^[1,2,3]

There was rapid reduction of CRP levels in RA patients following single subcutaneous administration of sarilumab in dose of 200-mg and 150-mg. Levels were reduced to normal within 2 weeks after treatment initiation. ANC (absolute neutrophil counts) decreased to the nadir between 3 to 4 days and thereafter recovered towards baseline. There was decrease in fibrinogen and serum amyloid A, and increase in hemoglobin and serum albumin levels.^[1,2,3,4]

The pharmacokinetics were ascertained in 1770 patients with RA treated with sarilumab, 631 patients were given 150 mg dose and 682 patients treated with 200 mg dose by subcutaneous injection every two weeks for up to 52 weeks. The median t_{max} was observed in 2 to 4 days. At steady state, exposure over the dosing interval measured by area under curve (AUC) increased 2-fold with an increase in dose from 150 to 200 mg every two weeks. Steady state was reached in 14 to 16 weeks with a 2- to 3-fold

accumulation compared to single dose exposure. For the 150 mg every two weeks dose regimen, the estimated mean (\pm SD) steady-state AUC, C_{min} and C_{max} of sarilumab were 202 ± 120 mg day/L, 6.35 ± 7.54 mg/L, and 20.0 ± 9.20 mg/L respectively. For the 200 mg every two weeks dose regimen, the estimated mean (\pm SD) steady-state AUC, C_{min} and C_{max} of sarilumab were 395 ± 207 mg day/L, 16.5 ± 14.1 mg/L, and 35.6 ± 15.2 mg/L respectively. ^[3,4]

The apparent volume of distribution at steady state was 7.3 L and is eliminated by parallel linear and non-linear pathways. At higher concentrations, the elimination is predominantly through the linear, non-saturable proteolytic pathway, while at lower concentrations, non-linear saturable target-mediated elimination predominates. The half-life which is concentration dependent is up to 8 days and 10 days respectively at 150 mg every 2 weeks and 200 mg every 2 weeks doses in patients with RA at steady state. After the last steady state dose of 150 mg and 200 mg sarilumab, the median time to non-detectable concentration are 28 and 43 days, respectively. The metabolic pathway has not been characterized. As a monoclonal antibody it is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. It is not eliminated via renal or hepatic pathways. No formal study of the effect of hepatic impairment and renal impairments on the pharmacokinetics of sarilumab was conducted.

The recommended dosage is 200 mg once every two weeks, administered as a subcutaneous injection. It is not recommended in patients with ANC (Absolute neutrophil count) less than 2000/mm³, platelets less than 150,000/mm³ or liver transaminases above 1.5 times upper limit of normal (ULN). Dose can be reduced to 150 mg once every 2 weeks to help manage complications of neutropenia, thrombocytopenia, and elevated liver enzyme levels. Available in form of injection of 150 mg/1.14 mL or 200 mg/1.14 mL solution in a single-dose pre-filled syringe.

Adverse reactions

The most common adverse reaction (greater than 1%) that resulted in discontinuation of therapy was neutropenia. The most commonly reported infections (2% to 4% of patients) were upper respiratory tract infections, urinary tract infections, and nasopharyngitis. The most frequently observed serious infections included pneumonia and cellulitis. Cases of opportunistic infection have also been reported. Reports of GI perforation were primarily reported as complications of diverticulitis including lower GI perforation and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs) or corticosteroids. The injection site reactions (including erythema and pruritus) were mild in severity for the majority of patients and necessitated drug discontinuation in 2 (0.2%) patients. Decreases in neutrophil counts less than 500 per mm³ occurred in 0.7% of patients in 200 mg sarilumab + DMARD and 150 mg sarilumab + DMARD groups. Decrease in ANC was not associated with the occurrence of infections, including serious infections. In the long-term safety population, the observations on neutrophil counts, platelet count, hypersensitivity were consistent with what was seen in the placebo-controlled clinical studies. Decreased platelet count was observed without associated bleeding events. Liver enzymes elevation was observed which was not associated with clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic impairment. ^[3,4,5]

Precaution and contraindications

It is contraindicated in patients with known hypersensitivity to sarilumab or any of the inactive ingredients. It should be avoided in serious and active infections and in patients immunized with live vaccines. Dose modification is required in patients with neutropenia, thrombocytopenia, elevated liver enzymes and lipid abnormalities. The concurrent use of sarilumab with biological DMARDs such as TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators has not been studied.

Possibility of increased immunosuppression and increased risk of infection cannot be ruled out when combined with biological DMARDs.

Clinical Trials Experience

The study, SARIL-RA-TARGET, evaluated the efficacy and safety of two subcutaneous sarilumab doses versus placebo, given along with non-biologic disease modifying anti-rheumatic drug (DMARD) in RA patients who were inadequate responders to or intolerant of TNF-alpha inhibitors (TNF-IR). The SARIL-RA-TARGET^[4] trial enrolled 546 TNF-IR patients who were randomized to one of three treatment groups self-administered subcutaneously (SC) every other week -Sarilumab 200 mg, sarilumab 150 mg, or placebo, in addition to DMARD therapy. Both sarilumab groups showed clinically relevant and statistically significant improvements compared to the placebo group in signs and symptoms of RA at 24 weeks and Improvement in physical function, as measured by change from baseline in the Health Assessment Question-Disability Index (HAQ-DI) at 12 weeks.

The safety of sarilumab in combination with conventional DMARDs was evaluated based on data from seven studies, of which two were placebo-controlled, consisting of 2887 patients (long-term safety population). Of these, 2170 patients received sarilumab for at least 24 weeks, 1546 for at least 48 weeks, 1020 for at least 96 weeks, and 624 for at least 144 weeks. The pre-rescue placebo-controlled population included patients from two Phase 3 efficacy studies from weeks 0 to 16 for Study 1 and weeks 0 to 12 for Study 2, and was used to assess common adverse reactions and laboratory abnormalities prior to patients being permitted to switch from placebo to sarilumab.^[5]

Conclusion

Sarilumab is a human monoclonal antibody directed against the IL-6 receptor. The recommended dosage is 150 mg or 200 mg once every two weeks, administered as a subcutaneous injection. It is given to patients who do not respond well or have intolerance to disease-modifying antirheumatic drugs. It can be

used alone or in combination with methotrexate or another non biological DMARD.

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