PHARMACEUTICAL APPROACHES OF IL-6 INHIBITORS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS, FOCUS ON NEW FDA APPROVED DRUG: SARILUMAB

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ABSTRACT
Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology and the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability. RA is characterized by synovial inflammation and hyperplasia, autoantibody production, cartilage and bone destruction, and systemic features, including cardiovascular, pulmonary, psychological, and skeletal disorders. Interleukin-6 (IL-6) is a potent pro-inflammatory agent which plays a crucial role in the pathogenesis of systemic inflammatory disease. During acute inflammation in RA, monocytes, macrophages and endothelial cells release IL-6, accompanied by an increase in neutrophils in synovial fluids. As disease progresses, IL-6 is thought to influence the shift from acute to chronic inflammation. Recently, the agents targeting the IL-6 (classes of biologic therapies) and/or its receptor attracted significant attention as a promising arthritics drug. RA patients with inadequate response to TNF inhibitor and non-biologic disease modifying anti-rheumatic drugs (DMARDs), demonstrated a therapeutic response to IL-6 receptor blockers. This article attempts to review the new FDA approved IL-6 inhibitor drug Sarilumab for RA from pharmaceutical aspects.

KEYWORDS: Sarilumab, Rheumatoid Arthritis, IL-6 inhibitor, IL-6 receptor blockers.

1. INTRODUCTION
Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology and the most common form of chronic inflammatory arthritis and often results in joint damage and
physical disability (Kasper et al., 2015; Alam et al., 2017). RA is characterized by synovial inflammation and hyperplasia (“swelling”), autoantibody production (rheumatoid factor and anti-citrullinated protein antibody [ACPA]), cartilage and bone destruction, and systemic features, including cardiovascular, pulmonary, psychological, and skeletal disorders (McInnes & Schett, 2011; Firestein & McInnes, 2017). Genetic factors may explain up to 60% of the occurrence of RA in twin studies, with concordance rates of 15 to 30% among monozygotic twins and 5% among dizygotic twins (McInnes & Schett, 2011; Kasper et al., 2015).

RA affects approximately 0.5-1% of the adult population worldwide. Like other autoimmune diseases, RA occurs commonly in females than in males, with a 2:3 : 1 ratio. RA can begin at any age, but the peak onset is in the fourth or fifth decade for women and the sixth to eighth decades for men (Papadakis & McPhee, 2017; Kasper et al., 2015). RA is associated with long-term disability, with 28% of RA patients less than age 65 considering themselves disabled after 15 years of disease. Furthermore, as a systemic disease, RA patients have increased mortality, which in male RA patients is estimated as 7 years less than expected (June & Olsen, 2016).

Pathogenesis RA involves complex humoral and cellular reactions including IC formation, vascular reactions and infiltration of lymphocytes and monocytes into the synovium. These infiltrating cells and synoviocytes release proinflammatory mediators, including including tumor necrosis factor a (TNF-a), interleukin (IL)-1, and IL-6, which perpetuate inflammation and destruction through effects on other cell types in the synovium and peri-articular structures (Dayer & Choy, 2010; Kim et al., 2015).

Treatment of RA revolves around three classes of medications: non-biologic disease modifying anti-rheumatic drugs (DMARDs), synthetic small molecule inhibitors, and biologic therapies (June & Olsen, 2016). There are five classes of bDMARDs namely TNF-a inhibitors, anti-CD80/86, anti-CD20, anti-IL-1 receptor (IL-1R), and anti- IL-6 receptor (IL-6R) and they are used in the RA patients with inadequate response to conventional DMARDs (Kim et al., 2015). Recently, the agents targeting the IL-6 and/or its receptor attracted significant attention as a promising arthritics drug. Starting with the approval of tocilizumab (TCZ) in the treatment of moderate to severe RA, many other investigational IL-6 blockers are currently undergoing clinical trials, and the latest is the new fda approved drug Sarilumab (Kim et al., 2015; Smolen et al., 2016).
2. Role of IL-6 Inhibitor in pathogenesis of RA

Interleukin 6 (IL-6) is an important cytokine in the pathogenesis of RA. IL-6 contributes to the systematic inflammatory and bone destructive cascade that give rise to the clinical picture of RA (Aly & Furst, 2017; Hussar & Lee, 2017). IL-6 is also a pleiotropic cytokine with diverse activities by contributing to T cell activation, B cell activation, synoviocyte stimulation, endothelial activation, osteoclast maturation, production of acute-phase proteins, inducing intracellular adhesion molecules (Tanaka & Mola, 2014; Kim et al., 2015; Venuturupalli, 2017). During acute inflammation in RA, monocytes, macrophages and endothelial cells release IL-6, accompanied by an increase in neutrophils in synovial fluids. As disease progresses, IL-6 is thought to influence the shift from acute to chronic inflammation (Kaplanski et al., 2003). In the serum of RA patients, elevated levels of IL-6 and sIL-6R are detected with positive correlation to RA disease severity and radiological joint damage. Moreover, over production of IL-6 has been found in the synovial cell and macrophage of the joint of RA patients. These functions of IL-6 in the pathogenesis of RA make IL-6 as a remarkable target for the RA therapy (Kim et al., 2015; Alam et al., 2017).

The signaling pathway of IL-6 includes two molecules, a specific receptor for IL-6 and a cell-surface glycoprotein called gp130 as a signal transducer (Hibi et al. 1990). IL-6 transmits its signal through binding to membrane-bound IL-6R (mIL-6R) or soluble IL-6R (sIL-6R) that are respectively called classic signaling and trans-signaling (Tanaka & Mola, 2014; Yusof & Emery, 2013). Trans-signalling, where IL-6 binds to the sIL-6R, homodimerizes with glycoprotein 130 subunits and induces signal transduction, has been found to play a key role in acute and chronic inflammation (Dayer & Choy, 2010). Soluble IL-6R (sIL-6R) has the same affinity for IL-6 as the membrane receptor. (Aly & Furst, 2017). Serum levels of IL-6 and soluble IL-6 receptor (IL-6R) are elevated and correlate with disease activity in RA patients and so blocking IL-6/IL-6R has been considered beneficial for the treatment of RA (Tanaka & Mola, 2014; van Vollenhoven, 2016).

RA patients with inadequate response to TNF inhibitor and DMARDs demonstrated a therapeutic response to IL-6 receptor blockers such as tocilizumab (Aly & Furst, 2017). In accordance with this, accumulated evidence has shown the clinical efficacy as well as the adequate safety of tocilizumab, a humanised anti-IL-6R monoclonal antibody (mAb), as monotherapy or in combination with sDMARDs such as MTX in patients who are sDMARD naive and have an inadequate response to TNF inhibitors. The successful treatment of RA by
tocilizumab has encouraged the development of novel bDMARDs targeting IL-6 or IL-6R. In addition to tocilizumab, the phase II clinical trials of olokizumab, sarilumab and sirukumab, three new bDMARDs targeting IL-6, are reported (Tanaka & Mola, 2014; Schoels et al., 2013; Fleischmann et al., 2017). Though sarilumab is similar to tocilizumab, as both bind to membrane bound IL-6 and soluble IL-6 receptors, they differ in affinity and structure and sarilumab has a higher affinity for the receptor than does tocilizumab (Aly & Furst, 2017; Tanaka & Mola, 2014).

3. Pharmacodynamic of sarilumab
Following single-dose subcutaneous administration of sarilumab 200 mg and 150 mg in patient with RA, rapid reduction of C-Reaktif Protein (CRP) levels was observed. Levels were reduced to normal within 2 weeks after treatment initiation. Following single-dose sarilumab administration, in patients with RA, absolute neutrophil counts decreased to the nadir between 3 to 4 days and thereafter recovered towards baseline. Treatment with sarilumab resulted in decreases in fibrinogen and serum amyloid A, and increases in hemoglobin and serum albumin (FDA, 2017; Chaplin, 2017).

Sarilumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6Rα), and inhibits IL-6 mediated signaling. IL-6 is a pleiotropic pro-inflammatory cytokine that is widely involved in diverse physiological processes such as migration and activation of T-cells, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of haematopoietic precursor cell proliferation and differentiation. Local production of IL-6 by synovial and endothelial cells in joints affected by chronic inflammatory disease, such as RA, may play an important role in development of the inflammatory processes (Scott, 2017; Chaplin, 2017).

4. Pharmacokinetic sarilumab
The affinity of SAR for the human IL-6 receptor is approximately 20-fold greater than Tocilizumab (TCZ). Consistent with the higher binding affinity, the dissociation constant (Kd) of SAR for the target receptor is 12.8 pM, which is about 55 times lower than that of TCZ. Clearance of SAR is biphasic and target-mediated with a dose dependent effect and non-linear clearance. Trough serum levels of functional and bound SAR are measurable throughout a 2 week dosing interval. Serum drug levels show dose-related increases in treated patients through at least 12 weeks (June & Olsen, 2016).
In 1770 patients with RA treated with sarilumab for 52 weeks (631 with 150mg SC q2w and 682 with 200mg SC q2w), the median tmax was observed in 2 to 4 days. Steady state was reached in 14-16 weeks with a 2- to 3-fold accumulation compared to a single dose. For the 150 mg every two weeks dose regimen, the estimated mean (±SD) steady state area under the curve (AUC), Cmin and Cmax of sarilumab were 202 ± 120 mg.day/L, 6.35 ± 7.54 mg/L , and 20.0 ± 9.20 mg/L, respectively. For the 200mg every two weeks dose regimen, the estimated mean (±SD) steadystate area under the curve (AUC), Cmin and Cmax of sarilumab were 395 ± 207, mg.day/L, 16.5 ± 14.1 mg/L , and 35.6 ± 15.2 mg/L, respectively (Aly & Furst, 2017).

Volume of Distribution in RA patients at steady state was 7.3 L (Aly & Furst, 2017). Sarilumab is eliminated by both linear and non-linear pathways depending on the drug concentration. At high concentrations, the elimination is predominantly through the linear, non-saturable proteolytic pathway, while at lower concentrations, the non-linear, saturable targetmediated pathway is predominant (Aly & Furst, 2017). These parallel elimination pathways result in an initial elimination half-life of 8–10 days and a terminal, concentration-dependent half-life of 2–4 days. After the last steady-state dose of 150 or 200 mg, the respective median times to non-detectable concentrations are 28 and 43 days (Scott, 2017). Sarilumab is neither excreted through the hepatic nor renal pathways. There have been no formal studies examining the effect of hepatic or renal impairments on sarilumab metabolism and excretion (Aly & Furst, 2017).

5. Safety data of sarilumab
Sarilumab is generally safe and well tolerated. The most common side effect include neutropenia, increased alanine aminotransferase levels, injection site erythema and upper respiratory tract infections, neutropenia, increased alanine aminotransferase (ALT) levels, injection site erythema and upper respiratory tract infections (URTIs). Use with caution in patient with gastrointestinal (GI) perforation because risk may be increased with concurrent diverticulitis or concomitant use of NSAIDs or corticosteroids, promptly evaluate acute abdominal signs or symptoms. Sarilumab is contraindicated in patients with known hypersensitivity to sarilumab or any of the inactive ingredients (FDA, 2017; Scott, 2017).

6. Drug interaction of sarilumab
Sarilumab, restores CYP3A4 activity, which results in decreased exposure of the sensitive CYP3A4 substrate simvastatin and its active metabolite b-hydroxy-simvastatin acid in
patients with active RA. IL-6Ra blockade with sarilumab decreases IL-6 signaling in patients with RA, leading to restoration of CYP3A4 enzyme activity. The modulation of IL-6 effect on CYP enzymes by sarilumab may be clinically relevant for CYP substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of sarilumab in patients being treated with CYP substrate medicinal products, therapeutic monitoring of effect or drug concentration should be performed, and the individual dose of the medicinal product may need to be adjusted, as needed. Caution should be exercised when sarilumab is coadministered with CYP3A4 substrates (e.g. oral contraceptives or statins) as there may be a reduction in exposure, which may reduce the activity of these CYP3A4 substrates (Lee et al., 2016).

7. Clinical trials of sarilumab

7.1 PHASE 1
Phase I: Three phase I randomized double-blind, placebo controlled trials of SAR in RA were carried out in a total of 83 active treatment and 24 placebo patients using ascending doses of 50 mg, 100mg, 150 mg, and 200 mg. A dose dependent reduction in levels of acute phase reactants was observed, with a greater than 90% reduction in hsCRP and serum amyloid A after a single 200 mg dose of SAR (June & Olsen, 2016).

7.2 PHASE 2 (MOBILITY STUDY PART A)
In this study of 306 patients with active RA dose-related neutropenia was observed. Sarilumab 150 mg and sarilumab 200 mg q2w had the most favourable efficacy, safety and dosing. Infections were the most common adverse event; none were serious. Changes in laboratory values (neutropenia, transaminases and lipids) were consistent with other IL-6Rα inhibitors (ALT increased to 3x upper limit of normal in 4% and mean cholesterol was elevated in 10-20% at 12 weeks) (Huizinga et al., 2014).

7.3 PHASE 3
- Mobility Study Part B
The MOBILITY trial randomised 1197 patients with moderate to severe active RA to receive sarilumab (doses of 150 mg or 200 mg) or placebo every 2 weeks in conjunction with weekly MTX for 52 weeks. The primary endpoints were the proportion of patients achieving American College of Rheumatology 20% (ACR20) improvement responses at week 24, change from baseline in the Health Assessment Questionnaire (HAQ) disability index (DI) at
week 16, and change from baseline in the modified Sharp/van der Heijde score (SHS) of radiographic damage at week 52 (Genovese et al., 2015).

Compared with methotrexate plus placebo, methotrexate plus sarilumab significantly increased the proportion of patients with ACR20 response at 24 weeks (66.4% and 58% with 200mg and 150mg sarilumab vs 33.4% with placebo; p<0.0001). Though responses were slightly diminished after 52 weeks, treatment was associated with a significant improvement in physical activity and a significant reduction in radiographic progression (proportions with no progression at 52 weeks were 56% and 48% with 200mg and 150mg sarilumab vs 39% with placebo) (Genovese et al., 2015).

In the sarilumab 150 mg, sarilumab 200 mg, and placebo groups, the incidence of serious infections was 2.6%, 4.0%, and 2.3%, respectively. Elevations in ALT levels >3-fold the upper limit of normal occurred in 9.5%, 8.0%, and 2.1% of patients, respectively; in 24 patients, this led to discontinuation of treatment. Elevated total cholesterol levels were observed in 36.8%, 43.0%, and 18.3% of patients, respectively. In patients receiving 150 mg and 200 mg sarilumab, neutrophil counts of 0.5 to <1.0 3 10^9/liter were observed in 5.1% and 7.8% of patients, respectively, while neutrophil counts of <0.5 3 10^9/liter were observed in 0.9% and 0.7% of patients, respectively; none of the patients receiving placebo experienced changes in neutrophil counts (Genovese et al., 2015).

- **Monarch Trial**
This trial compare efficacy and safety of sarilumab 200 mg monotherapy with adalimumab 40 mg monotherapy both given every two weeks in 369 patients with moderate to severe active RA for whom methotrexate was discontinued due to intolerance or inadequate response. The primary end point was change from baseline in 28-joint disease activity score using erythrocyte sedimentation rate (DAS28-ESR) at week 24 (Burmester et al., 2016).

After 24 weeks, the reduction in DAS28-ESR was significantly greater with sarilumab than adalimumab (-3.28 vs -2.20; p<0.0001) and more patients receiving sarilumab compared with adalimumab achieved Clinical Disease Activity Index remission (7.1% vs 2.7%; nominal p=0.0468) and low disease activity (41.8% vs 24.9%; nominal p=0.0005) (Burmester et al., 2016).
• Target Trial

In this trial 546 patients with moderate to severe active RA after inadequate response or intolerance to TNF inhibitor therapy were randomised to receive sarilumab 150mg, sarilumab 200mg or placebo combined with conventional DMARD therapy. The primary endpoints were ACR20 response at 24 weeks and change in disability index after 12 weeks. The ACR20 response rate at week 24 was significantly higher with sarilumab 150 mg and sarilumab 200 mg every 2 weeks compared with placebo (55.8%, 60.9%, and 33.7%, respectively; P< 0.0001). The mean change from baseline in the HAQ DI score at week 12 was significantly greater for sarilumab (least squares mean change: for 150 mg, 20.46 [P< 0.0007]; for 200 mg, 20.47 [P< 0.0004]) versus placebo (20.26). Infections were the most frequently reported treatment-emergent adverse events. Serious infections occurred in 1.1%, 0.6%, and 1.1% of patients receiving placebo, sarilumab 150 mg, and sarilumab 200 mg, respectively (Fleischmann et al., 2017).

8. CONCLUSION

Interleukin-6 (IL-6) is a potent pro-inflammatory agent which plays a crucial role in the pathogenesis of systemic inflammatory disease. Targeting this pathway in RA seems an attractive option as IL-6 is important for both joint destruction and systemic manifestations. According to these findings, IL-6 may be considered as a more specific target for treating RA compared with the broad and unspecific effect of TNF blockade.

Sarilumab is a human monoclonal antibody directed against IL-6 receptor-α. Phase II and three Phase III clinical trials, have showed that sarilumab is clinically effective and safe in active RA patients with either inadequate response to MTX or TNF inhibitors. The efficacy and safety profiles are very similar to the available IL6 targeting drug tocilizumab. In addition, from a pharmacodynamic point of view sarilumab showed a significantly higher affinity compared with tocilizumab with a longer half-life, allowing a lower frequency of administration. The adverse effects and various toxicities do not differ significantly among studies. Sarilumab safety profile seemed to be consistent with what expected with IL-6 inhibitor and previously observed in patients treated with tocilizumab. Infections were relatively common, as is usual in most studies of biologics, but serious infections were rare. Significant LFT abnormalities (>3x upper limit normal) occurred in about 3-8%, were not dose related and hyperlipidemia was similar to that seen with TCZ. In future, observational
data coming from post-marketing real-life studies may provide crucial additional information for better understanding the role of sarilumab in the management of the disease.

REFERENCES
8. Fleischmann, R. et al., Sarilumab and Nonbiologic Disease-Modifying Antirheumatic Drugs in Patients With Active Rheumatoid Arthritis and Inadequate Response or Intolerance to Tumor Necrosis Factor Inhibitors. ARTHRITIS & RHEUMATOLOGY, 2017; 69(2).


13. Kaplanski, G. et al., IL-6: a regulator of the transition from neutrophil to monocyte recruitment during inflammation. *TRENDS in Immunology*, 2003; 24(1).


