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Drug Evaluation:

Room for more IL-6 blockade? Sarilumab for the treatment of rheumatoid arthritis

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Abstract

Introduction—Rheumatoid arthritis (RA) treatment has been revolutionized by the development of highly efficacious biotherapeutics. However, a significant subset of RA patients has persistently active disease and ongoing erosive joint damage despite the available therapies. Sarilumab targets interleukin-6, one of the main cytokines mediating inflammation in RA. Positive results with sarilumab in RA clinical trials support the licensing application currently under review with the US Food and Drug Administration.

Areas covered—The rationale for IL-6 targeting in RA, the pharmacologic properties of sarilumab, and the clinical trial results are reviewed focusing on the pending application for the RA indication. Comparisons with other IL-6 targeting biologics as well as additional potential therapeutic directions are discussed.

Expert opinion—Sarilumab is a highly active therapeutic in patients with RA. While pharmacologic data demonstrate that sarilumab has a higher affinity than tocilizumab for the target receptor, available clinical results suggest that efficacy and adverse event profiles are similar to this other IL-6 blocker, which is currently approved for the treatment of RA. Whether there are other distinct differences or advantages of sarilumab that will support the approval and successful marketing of this drug, over existing therapies, remains to be determined.

Keywords

Rheumatoid arthritis; Interleukin-6; Monoclonal antibody; Sarilumab; Tocilizumab

1.Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized by synovial inflammation causing a symmetrical, polyarticular arthritis[1]. RA has a worldwide

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prevalence of approximately 1%, incidence rises with age, women are disproportionately affected and the most common age of onset is between 35–50 years[2]. RA is associated with long term disability, with 28% of RA patients less than age 65 considering themselves disabled after 15 years of disease[3]. Furthermore, as a systemic disease, RA patients have increased mortality, which in male RA patients is estimated as 7 years less than expected[4].

Treatment of RA revolves around three classes of medications: non-biologic disease modifying anti-rheumatic drugs (DMARDs), synthetic small molecule inhibitors, and biologic therapies[5]. Cornerstone DMARD therapy is low dose methotrexate (MTX), with efficacy reported initially in 1985, and increased use has been associated with improved functional outcomes[6–8]. While MTX can be effective as monotherapy[9], up to 50% of patients discontinue MTX at one year[10]. Targeted inhibition of Tumor Necrosis Factor-α (TNF) was shown in combination therapy with MTX to be effective in 1999[11] and soon became standard of care in MTX incomplete responders (MTX-IR)[5]. However, TNF-inhibition is only effective in 20–50% of RA patients at 6 months of therapy[12]. Inhibition of other cytokines, IL-1[13] and IL-6[14], proved effective in combination with MTX and now 9 biologic therapies plus one small molecule inhibitor (Table 1) are available[5, 15].

Despite these advances[7], only 5–10% of RA patients are in remission and remission is rarely sustained[16]. Serum IL-6 levels are the most predominant cytokine in RA and correlate with disease activity[12]. It is therefore an attractive therapeutic target. Sarilumab (SAR) is a fully human monoclonal antibody directed against the IL-6 receptor-α and has higher affinity for the target molecule than the only approved and available inhibitor of IL-6, tocilizumab(TCZ)[17]. Based on favorable clinical trial results (Table 2), SAR is currently awaiting FDA approval for use in RA. This review focuses on the pharmacology, clinical efficacy, and expected uses of SAR in RA.

2.Market Overview

In the United States, RA has an economic burden of up to 41.6 billion dollars[18]. Specialty drugs account for over 50% of the cost of care in RA and the medico-economics landscape is changing with biosimilar development[19]. Despite the availability of these new therapeutics, a large unmet need remains in the treatment of RA, with about half of patients still failing to achieve minimal disease activity scores[18].

RA drug development focuses on four populations of RA patients: MTX IR, monotherapy in patients who are either MTX naïve, MTX-intolerant or in whom it is contraindicated, non-MTX DMARD incomplete responders, and finally, the most difficult treatment group, TNF-inhibitor non-responders. While combination non-biologic DMARD therapy, coined “triple therapy” (MTX, hydroxychloroquine and sulfasalazine), has been shown equivalent to MTX with added TNF inhibition[11, 20, 21], clinical practice has not seen a significantly increased use of triple therapy[22]. Practical application of therapies such as payer mix, out of pocket costs and route of administration all affect clinical use and market share[18, 23]. Pharmaceutical companies aim to meet patient preferences, as seen by the further development of abatacept and TCZ, originally approved for IV administration, into subcutaneous formulations[5].

Large comparative effectiveness trials between the many biologic therapies are not been available to guide many therapy choices, but recent randomized and pragmatic clinical trials have begun to clarify the picture. The tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA) trial was a randomized controlled double-blind design in 326 severe RA patients, comparing monotherapy of IL-6 versus TNF inhibition[24]. TCZ monotherapy compared to adalimumab showed improved 24 week DAS28 scores. The AMPLE trial, abatacept versus adalimumab comparison in biologic-naïve RA subjects with background methotrexate, compared T cell costimulation blockade with abatacept versus TNF inhibition with adalimumab in 646 RA subjects and showed similar outcomes between the two biologics[25]. Similarly, in an open-label, randomized non-inferiority designed trial in 295 RA patients with inadequate response to DMARDs, TNF inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT), rituximab was non-inferior to TNF inhibition for 12 month outcome measures[26]. Recommendations for first biologics therapies suggest equivalence between TNF and non-TNF biologics[5, 15]. However, despite guidelines and recommendations, TNF inhibitors still remain first line biologics in DMARD failure, which is largely driven in the United States by the reimbursement system. However, even TNF inhibitors have inadequate responses in 20–40% of patients[27, 28]. Fortunately, additional therapies have been developed, increasing the options (Table 1). Biomarkers predictive of responses to available drugs will be needed to improve efficient matching of the most appropriate therapy to an individual patient.

2.1 IL-6 Inhibition with Tocilizumab

Tocilizumab (TCZ) is a recombinant humanized anti-IL-6R monoclonal antibody that prevents IL-6 from binding soluble and membrane bound forms of the IL-6R[29]. TCZ was FDA approved in 2010 for the treatment of moderate to severe RA with inadequate response to one or more DMARDs[30]. It is available for intravenous administration every 4 weeks and also as a subcutaneous dosing once weekly. In the CHARISMA study, intravenous TCZ demonstrated efficacy in MTX-IR RA patients, with 61% and 68% ACR 20 responses at 4 and 8 mg/kg, respectively[14]. The phase III TCZ trials showed efficacy in multiple RA patient populations: for MTX-IRs[31, 32](Table 3), as monotherapy versus MTX[33], in traditional DMARD inadequate responders[34], and in patients refractory to TNF inhibitors[27]. Side effect profiles showed increases in total and LDL cholesterol, transaminitis, thrombocytopenia, neutropenia, intestinal perforation and infections.

3. Introduction to the compound

Many therapies derived from biologic molecules are now available for the treatment of RA. Most of these block the actions of tumor necrosis factor (TNF) alpha, and TCZ is directed at the IL-6 receptor[29]. Sarilumab (SAR), highlighted in this review, is one of at least five biologic therapies in development targeting IL-6 (Table 4)[3517]. It has been co-developed by Sanofi and Regeneron for the treatment of RA. The United States FDA has accepted for review a licensing application for use of SAR in the treatment of moderate to severe RA. A decision is expected in the last quarter of 2016.

4.Pharmacologic properties

4.1. Pharmacodynamic properties

SAR binds to both the membrane-bound and soluble forms of the IL-6 receptor (CD126). This receptor is expressed on mature T cells, activated B cells, neutrophils, macrophage lineage cells, hepatocytes and myeloma cells. Activation occurs when IL-6 is first bound by IL-6Rα, and this complex is then presented to the gp130 molecule that is present on many cell types[36]. Internalization of the activation complex initiates signaling through the Jak/STAT pathway[35]. Soluble forms of IL-6Ralpha that lack the transmembrane domain are formed through cell surface cleavage or alternative splicing. These circulating molecules can also activate gp130-bearing cells through a trans-signaling mechanism, so successful IL-6 receptor therapeutics need to block both membrane and soluble forms[35]. IL-6 is a major driver of C-reactive protein synthesis, and levels were decreased by up to 90% in Phase I and II studies[37, 3839]. Blockade of the IL-6R with TCZ has been shown to reduce numbers of memory B cell subsets in treated patients, and to increase regulatory T cells while not changing Th17 T cell subset frequency[4041]; comparable data with SAR have not been reported. Concentrations of IL-6 were transiently increased after initiation of SAR in Phase I studies and in the first 12 weeks of treatment in Phase II[39]; TCZ has a similar effect, which is thought to be secondary to blockade of the sIL-6R causing decreased consumption of IL-6[42].

4.2 Pharmacokinetic properties

SAR is a fully human monoclonal IgG1 antibody that was developed in mice engineered to produce human antibodies[43]. The affinity of SAR for the human IL-6 receptor is approximately 20-fold greater than TCZ, and it is about 4-fold more potent than TCZ in a luciferase reporter assay[17]. The dissociation constant (Kd) of SAR for the target receptor is 12.8 pM, which is about 55 times lower than that of TCZ, consistent with the higher binding affinity[35]. Clearance of SAR is biphasic and target-mediated with a dose dependent effect and non-linear clearance[38]. 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[39]. Metabolism likely follows the same pathways as other fully human monoclonal IgG1 antibodies such as secukinumab, which has a half-life of approximately 27 days[44]. Antidrug antibodies were found in up to 16.7% of patients in the phase III SAR study but immunogenicity was not associated with hypersensitivity reactions[45]. Associations with drug levels are not known.

5.0 Drug Efficacy

5.1 Rheumatoid Arthritis

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[37]. 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.

Phase II: Safety and efficacy of SAR was evaluated in Monoclonal antiBody to IL-6Rα In RA patients: A pivotal Trial with X-raY(MOBILITY)[39]. Part A was a Phase II multicenter, randomized, double-blind placebo controlled study in 306 RA patients[46] with active disease despite a stable dose of methotrexate (10–25 mg/week, mean dose of 16.6 mg/week). Patients were randomized to placebo or one of five subcutaneous SAR dosing regimens: 100 mg Q2W, 150 mg Q2W, 200 mg Q2W, 100 mg qW and 150 mg QW. Patients with a history of non-response to anti-TNF therapy were excluded[47]. Significant ACR20 responses compared to placebo were seen after 12 weeks of treatment across all doses of 150 mg q2 weeks or greater. DAS28 CRP responses showed a dose response relationship with SAR and the highest remission response, defined as DAS28 CRP< 2.6, was seen in the 150 mg q week regimen. Greater than 60% of the SAR 150 mg Q week and higher doses achieved ACR 20%, and 17% of the SAR 200mg Q2W dose group achieved ACR 70 response; 20–30% of subjects achieved DAS28CRP <2.6 by week 12.

*Phase III:*Press reports indicate that 2500 RA patients have been enrolled in seven phase III studies submitted with the FDA application. However, the only phase III data published and available for review is from the MOBILITY study. As noted, this was a seamless design Phase II/III study in MTX-IR RA patients with erosions or CCP positivity. It offered as an extension to Phase II a 52 week double blind placebo controlled treatment period. Patients were allocated to one of three arms: placebo (n=398), SAR 150 mg every 2 weeks (n=400) and SAR 200 mg every 2 weeks(n=399)[45]. Results in all domains, disease response, function and radiographic scores, were favorable for SAR. A high placebo response was seen with an ACR20 response of more than 33%, but even higher ACR20 responses of 58% and 66% were seen in the 150 and 200 mg groups. All three primary endpoints for the trial were met at 24 weeks and were sustained at 52 weeks. ACR70 major clinical response and maintenance for 24 weeks was seen in 3% of placebo versus 12.8% and 14.8% of the 150 mg and 200 mg groups respectively, with 34.1% of the 200 mg group achieving week 24 DAS28-CRP remission. Functional assessment measured using the Health Assessment Questionnaire (HAQ) showed statistically significant improvement throughout the 52 week study period. Structural changes assessed with the Sharp-van der Heijde score (SHS) showed improvement compared to placebo, with a 2.78 placebo change versus 0.9 for the 150 mg and 0.25 for the 200 mg dose at week 52. While this was a statistically significant change, SHS scores greater than 4.6 are thought to be clinically significant to impact therapy[48]. However, given the relatively short time of evaluation, the trend and dose response imply a clinically significant effect. Looked at another way, 39% of the placebo group had no radiographic progression at 1 year versus 48–56% of the SAR treated patients. Across the board, considering signs and symptoms, functional response and structural damage, SAR showed significant efficacy in MTX-IR RA patients.

The phase III TARGET study, presented at the ACR 2015 annual scientific meeting, evaluated SAR in combination with non biologic DMARDs versus placebo in 546 active RA patients with inadequate response or intolerant of 1 or more TNF inhibitors[49]. In this randomized placebo controlled study, SAR in doses of 150 mg and 200 mg resulted in week 24 ACR 20 responses of 56% and 61% versus 34% in placebo. ACR70 responses of 20% and 16% were also seen in the 150 mg and 200mg groups with improvement in physical

function. In both MTX-IR and TNF non-responders, SAR demonstrated efficacy in improving the signs, symptoms, and outcomes in patients with moderate to severe RA.

A comparison of American College of Rheumatology (ACR) response rates for SAR from the MOBILITY trial with TCZ in MTX-IR patients shows comparable results between the two medications (Table 3). Both can be given subcutaneously, with TCZ requiring weekly injections as opposed to every 2 week injections for SAR.

5.2 Other indications

Nine SAR trials with non-RA indications have been registered on clinicaltrials.gov. Most are in non-infectious uveitis and have not been reported. The ALIGN study in patients with AS was a randomized, multicenter, double blind parallel group placebo controlled trial of 100/150/200 mg every 2 weeks or 100/150 mg weekly for 12 weeks in 300 patients. The primary endpoint, ASAS20 in SAR versus placebo was not met, and further development for AS is not ongoing.

6.0 Drug administration/dosage

SAR is administered as a subcutaneous injection. In the Phase 2, Part A trial of the MOBILITY study, doses of 100, 150 and 200 mg were given weekly or at 2 week intervals[39]. The 150 and 200 mg q 2 week groups both showed similar efficacy to the weekly dosing groups. Some trends in safety measures favored the q 2 week dosing groups. Given these data and the fact that every other week dosing has greater convenience for the patient, the Phase 3 Part B trial of MOBILITY used 150 and 200 mg, each dosed at 2 week intervals. The dose or doses that have been requested for licensing approval in the FDA application have not been disclosed.

7.0 Safety and Tolerability

In the phase I studies, a total of 83 patients were evaluated for SAR safety and tolerability[50]. Four patients withdrew due to adverse events, 3 in the SAR group and 1 in placebo; reasons for withdrawal were RA flare, upper respiratory tract infection, and ALT elevation. In the 16 week follow up period, 1 patient each in placebo and SAR groups had ALT elevation of 3–5× upper limit of normal (ULN) and 1 patient in SAR had >5× ULN. Five patients in the SAR group had transient neutropenia (0.5–1.0 × 10^3/uL). No dose limiting toxicities were observed.

In the MOBILITY Part A (phase II) trial of 306 patients with active RA and concurrent stable methotrexate, dose-related neutropenia was observed. ALT increased to 3× upper limit of normal in 4% and mean cholesterol was elevated in 10–20% at 12 weeks. Treatment emergent adverse events (TEAE) were more frequent in the SAR100 mg qW dosing group, with infection and neutropenia as the primary reasons for treatment discontinuation. While there were increased TEAE in SAR vs placebo, there was no dose trend to the serious adverse events, and no serious infections.

In Mobility part B (phase III) trial in which 1282 patients were included in the safety analysis, adverse events (AE) and serious adverse events (SAE) were more common in SAR (11.3% in the 200 mg group vs. 5.4% placebo 5.4%; Table 5). Events leading to drug discontinuation occurred in 13.9% of the SAR 200 mg dose group. Infections were the most common AE and SAE. One patient in the SAR 150 mg group who was on concomitant aspirin and had a history of gastroesophageal reflux disease had a perforation of a duodenal ulcer and died. Given reported gastrointestinal perforations with TCZ, this event might be considered treatment related. Injection site reactions were reported in approximately 10% of the SAR treated patients. Eight malignancies occurred, with a higher number in the SAR treated patients; no lymphomas were reported. Neutropenia in the range of 0.5–1.0 × 10^9/liter was observed in 5.1% of the SAR 150 mg and 7.8% in the 200 mg groups. Neutropenia occurred in a dose dependent manner with 9.3% and 14.4% in the 150 mg and 200 mg SAR groups respectively. Overall, grade 3 or 4 neutropenia normalized either during continued treatment or with discontinuation in 24/26 (92%) in the 150 mg SAR dose versus 29/36 (81%) in the 200 mg SAR dose; 9/62 (15%) subjects had grade 3 or 4 neutropenia that never normalized during the study. Neutropenia led to treatment discontinuation in 2.1% of patients in 150 mg and 2.4% in 200 mg SAR, but the grade of neutropenia was not associated with infection. ALT greater than 3× ULN occurred in 9.5% of the 150 mg SAR group versus 2.1% of placebo. Increase in serum cholesterol occurred in 43% of the SAR group versus 18% of placebo. Antidrug antibodies were found in 16.7% of the SAR 200 mg dose, but were not associated with hypersensitivity, drug discontinuation, or lack of efficacy.

Overall, adverse events appeared to be dose dependent across the studies. SAE were rare, but comparable with what is observed with other biologics and tofacitinib[51, 52]. Adverse events with SAR are similar to those with TCZ.

8.0 Conclusion

Phase II and III clinical trials have established that SAR is an effective treatment for patients with moderate to severe RA who have had an incomplete response to MTX. The efficacy and safety profiles are very similar to the available IL6 targeting drug TCZ, and include significant decreases in progression of structural damage. SAR was not effective in AS, which is also similar to findings with TCZ[53]. This is despite the fact that circulating IL-6 levels correlate with disease features in AS, and is another reminder that predictions based on biologic data do not always translate into therapeutic effects[54]. Infections were the most common adverse events with SAR, similar to findings with TNF blockade, while neutropenia, transaminitis and elevated cholesterol are more specific for the IL6 pathway.

9.0 Expert Opinion

Sarilumab is an efficacious drug for the treatment of RA patients with at least moderately active disease who have had an incomplete response to MTX. In addition to controlling symptoms, it has an impressive effect on structural damage. Despite pharmacologic differences showing that SAR has greater target affinity than TCZ, efficacy outcomes are similar. Similar to the differences between two TNF inhibitors adalimumab and etanercept, SAR offers patients and clinicians an additional subcutaneous IL-6 inhibitor to TCZ of SC

dosing every 2 weeks as opposed to every week. SAR is likely to obtain FDA approval, as it meets the agency guidelines for efficacy, and safety is not significantly different from TCZ[55]. The field of RA therapeutics is crowded, but there is still a need for new effective therapies that improve sustained remission. The bigger question is not if SAR is effective, but where SAR will fit into treatment algorithms[12]. Moreover, with 4 other IL-6 blocking agents being tested; IL-6 may become the next TNF in RA, highlighting the need for more comparative effectiveness trials between IL-6 and TNF based therapeutics[12, 35].

This equilibrium of TNF-first could be disrupted, however, by availability of new data from head-to-head trials of IL-6 and TNF-targeting therapeutics. The SARIL-RA-MONARCH trial comparing SAR and adalimumab monotherapy has been completed, and press releases claim that SAR had significantly better efficacy, but these data have not yet been presented in abstract or published form. The Hoffman-La Roche ENTRACTE trial, which compares cardiovascular outcomes in RA patients at high risk of cardiovascular disease treated for up to 5 years with either etanercept or TCZ, may produce data about whether these treatments have different risk profiles. If TCZ does not show significantly more adverse outcomes, this may lay to rest the concerns about raising cholesterol levels in a population that is already at risk for cardiovascular disease. Basically, differences in either efficacy or adverse outcomes could tip the balance one way or the other between IL-6 and TNF blockade as first-line strategies in MTX-IRs. The other dimension is whether treatment failures with one class can be rescued by treatment with the other, and if so, which drugs work best. A Phase II study comparing the humanized anti-IL6 antibody olokizumab to TCZ in TNF incomplete responders showed that both had efficacy[56]. This at least suggests that the principle of targeting IL-6 in patients without good responses to TNF blockers may be valid. But to improve individual treatment, biomarkers that predict the likelihood of a favorable response to a given therapeutic are needed.

The bottom line is that while sarilumab likely will win FDA approval, finding its niche in the panoply of available RA therapeutics may be a challenge.

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Abbreviation List

ACR	American College of Rheumatology
AS	Ankylosing Spondylitis
DMARD	Disease Modifying Anti-Rheumatic Drug
EULAR	European League Against Rheumatism

HAQ	Health Assessment Questionnaire
MTX	methotrexate
MTX-IR	methotrexate incomplete responders
RA	Rheumatoid Arthritis
SAE	serious adverse events
SAR	Sarilumab
SHS	Sharp-van der Heijde score
TCZ	Tocilizumab
TEAE	Treatment adverse events
TNF	Tumor necrosis factor
ULN	upper limit of normal range

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Drug Summary Box

Drug Name	**Sarilumab**
Phase	Pre-Registration.
Indication	Adults with active moderate to severe rheumatoid arthritis and incomplete response to methotrexate.
Pharmacology description	Fully human monoclonal IgG1 antibody that binds specifically to the interleukin-6 receptor alpha
Route of Administration	Subcutaneous injection 150 or 200 mg every 2 weeks
Pivotal Trials	MOBILITY[39, 45]

Table 1

Crowded market: biologics/synthetic small molecule inhibitors FDA approved or pending for treatment of RA[57–59]

Class	Drug	Approval year or Phase
TNF alpha inhibitors	Etanercept Infliximab Adalimumab Certolizumab Golimumab	1998 1999 2002 2009 2009
Anti-B cell Directed	Rituximab	2006
Co-stimulatory blockade	Abatacept	2005
IL-1 inhibitor	Anakinra	2001
Kinase Directed	Tofacitinib Baricitinib ABT 494 Filgotinib	2012 Phase III Phase III Phase III
IL-6 targeted	Tocilizumab Sarilumab Sirukumab	2010 Phase III Phase III

Table 2

Sarilumab Clinical Trials

Phase	Trial	Study Population	Efficacy Outcomes
I	Studies 801, 802, 803	Active RA on methotrexate	None evaluated.
II	ALIGN	Active Ankylosing Spondylitis despite conventional treatment	No clinically significant responses.
II	MOBILITY Part A	Active RA despite treatment with methotrexate	Significant ACR20 response at 12 weeks
III	MOBILITY Part B	Active RA despite treatment with methotrexate	Sustained clinical efficacy including improved radiographic scores.

Table 3

Comparison of phase III studies of sarilumab and tocilizumab in MTX-IRs: ACR response rates at 24 weeks

		Placebo	150 mg	200 mg
Sarilumab MOBILITY Study, part B[42] Genovese et al.	ACR 20	33%	58%	66%
	ACR 50	17%	37%	46%
	ACR 70	7%	20%	25%
		Placebo	4 mg/kg	8 mg/kg
Tocilizumab OPTION Study[29] Smolen et al.	ACR 20	26%	48%	59%
	ACR 50	11%	32%	11%
	ACR 70	2%	12%	22%
		Placebo	4 mg/kg	8 mg/kg
Tocilizumab LITHE Study[28] Kremer et al.	ACR 20	27%	51%	56%
	ACR 50	10%	25%	32%
	ACR 70	2%	11%	13%

Table 4

IL-6 targeted biologics in advanced human development for RA

IL-6 Agent	Industry association	Target	Phase
Tocilizumab	Genentech / Roche	IL-6R and soluble IL-6R inhibitor	IV
Sarilummab	Sanofi / Regeneron	IL-6R and soluble IL-6R inhibitor	III
Sirukinumab	GSK / Janssen	IL-6 blockade	II
Clazakizumab	Alder Biopharmaceuticals	IL-6 blockade	II
Olokizumab	UCB/ R-Pharm	IL-6 blockade	II
ALX-0061	Ablynx	IL-6 blockade	II

Table 5

Sarilumab treatment-emergent adverse events in phase III

Event type	Description	Prevalence (%) Low/High/Placebo	Comments
Infections: Serious Opportunistic	Infection most common emergent adverse event	2.6 / 4.0 / 2.3 0.7 / 0.9 / 0.5	No cases of TB One fungal bronchitis H. Zoster
Abnormal liver function tests	ALT more than 3× ULN	9.5/ 8.0 / 2.1	24 patients were discontinued due to elevations
Elevated total cholesterol	From < 240 mg/dl to ≥ 240 mg/dl	36.8 / 43.0 / 18.3	No cardiac events
Decreased neutrophil counts	0.5 – <1.0 × 10^9/L < 0.5 × 10^9/L	5.1 / 7.8 / 0.0 0.9 / 0.7 / 0.0	No relationship of low neutrophil count to infections.