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REVIEW

Clinical evaluation of the safety, efficacy and tolerability of sarilumab in the treatment of moderate to severe rheumatoid arthritis

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Abstract: Rheumatoid arthritis (RA) is an autoimmune disease that is characterised by synovial inflammation and progressive joint disorder with significant pain and stiffness, which lead to functional disability and systemic complications if left untreated. Although methotrexate (MTX) is the cornerstone in the RA therapy, it is ineffective or intolerable in up to 50% of patients. In addition, tumour necrosis factor (TNF) inhibitors which are regarded as the standard of care for those patients, have not been proven a panacea creating a therapeutic gap. In this direction, other cytokines such as the interleukin (IL)-6 in combination with MTX or as monotherapy have been approved. Sarilumab has already been approved for the treatment of moderate to severe RA, but more studies are on their way including polymyalgia rheumatica, giant cell arteritis, juvenile idiopathic arthritis, and indolent systemic mastocytosis. On the other hand, a study was prematurely discontinued after approximately 1.5 years, when the ankylosing spondylitis development program was discontinued due to lack of efficacy. Regarding safety, efficacy and tolerability of the molecule, three pivotal clinical trials have established sarilumab as one of the safe and efficacious choices for the treatment of RA (mobility, target and monarch trials). Significant decreases in progression of structural damage have been demonstrated. Infections and neutropenia are two of the most common adverse events. Sarilumab is beyond any doubt another molecule that can be added to the clinicians' armamentarium for the treatment of patients with moderate to severe RA with a good safety and efficacy profile.

Keywords: interleukin-6, sarilumab, monoclonal antibody, tocilizumab, immunogenicity

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that is characterised by synovial inflammation and progressive joint disorder with significant pain and stiffness. If left untreated, functional disability and systemic complications may appear leading to poor quality of life.[1,2] Extra-articular manifestations and systemic comorbidities are not infrequent.[3] The prevalence of RA worldwide is approximately 1% making it the most common autoimmune inflammatory arthritis in adults.[4] Women are more often affected than men while the onset of the disease tends to occur between the fourth and the sixth decade of life.[5]

In the last years, better and more effective treatments and strategies are constantly being developed. Our understanding of the molecular mechanisms underlying RA pathogenesis is the main reason. Although the exact aetiology is unknown, genetic susceptibility, epigenetic contributions, and environmental triggers have all been implicated in the pathogenesis of RA.[3] Treat-to-target and tight control strategies are

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recommended currently.[6] Nowadays, there are several therapeutic choices relied on three different classes of medications: a) conventional synthetic (cs) disease-modifying antirheumatic drugs (DMARDs), b) biological (b) DMARDs and, c) targeted synthetic (ts) DMARDs. In addition, biosimilars, a new subcategory of bDMARDs has emerged which are highly similar to the bio-originator in terms of safety, efficacy and tolerability.[7,8]

The American College of Rheumatology (ACR) guideline serves as a tool for the pharmacologic treatment decisions in patients with RA.[6] Patients with early RA can benefit from monotherapy with a csDMARD, preferably methotrexate (MTX). For those with moderate to high disease activity despite the use of a csDMARD as monotherapy, a combination treatment strategy with another csDMARD or adding a bDMARD/tsDMARD is recommended.[5] Although MTX is considered the cornerstone in the treatment of RA, it is ineffective or intolerable in up to 50% of patients.[9] Furthermore, tumour necrosis factor (TNF) inhibitors, which are regarded as the standard of care for those patients, have not been proved a panacea, creating a therapeutic gap.[10,11] In this direction, the inhibition of other cytokines such as the interleukin (IL)-6 has been approved. IL-6 inhibitors can be used as monotherapy or in combination with MTX which appears to have a synergistic effect.[12,13]

The role of IL-6 in RA

IL-6 is crucially implicated in the activation of the acute inflammatory response. It acts locally by promoting joint inflammation and destruction, but also systemically leading to systemic manifestation of RA. Other important cytokines that are implicated in the acute inflammatory response are several proinflammatory cytokines, including the tumor necrosis factor (TNF)-α, and IL-1.[14] Thus, targeting these cytokines as a therapeutic intervention is a rational and efficient choice. The TNF-α was the first cytokine that was targeted for the treatment of RA. The rationale of using IL-6 inhibition as a therapeutic target appeared later (monotherapy or in combination with MTX), showing to be an efficacious and safe choice for the RA patients covering also a part of the unmet needs in the RA therapeutics.[15] The first IL-6 agent was tocilizumab, approved for the treatment of moderately to severely active RA by the Food and Drug Administration (FDA) in 2010. In 2011, the FDA approved tocilizumab for the treatment of systemic juvenile idiopathic arthritis while in 2017 for giant cell arteritis. Other IL-6 agents that were/are under development are: clazakizumab,[16] olokizumab,[17] sirukumab[18] and sarilumab. To date, only sarilumab has been approved by the FDA, European Medicines Agency (EMA) and Canada (2017) for the treatment of patients with moderately to severely active RA who had an inadequate response to ≥1 DMARDs[12] or as monotherapy.

The IL-6 molecule sarilumab

Despite the advances in RA treatment, patients are still in a need of new treatment options. Sarilumab is expected to work in this direction. It is a human, IgG1 monoclonal antibody produced in Chinese Hamster Ovary cells by recombinant DNA technology that binds to the α-subunit of the membrane-bound and soluble IL-6 receptors inhibiting IL-6 signaling.[19]

Indications, pharmacokinetics and dosage scheme

As mentioned above, sarilumab is indicated for the treatment of moderately to severely active RA in adult patients. It can be given in combination with MTX in patients who have responded inadequately to, or who are intolerant to one or more DMARDs, but also as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

It comes as a pre-filled syringe and pre-filled pen in 150 mg and 200 mg dose. The recommended dose is 200 mg once every 2 weeks as a subcutaneous (s.c.) injection but it can be reduced to 150 mg once every 2 weeks in patients who develop neutropenia, thrombocytopenia, and liver dysfunction.[19]

Regarding the pharmacokinetics of the drug, it has a C_{max} of 2–4 days after administration reaching a steady state within 14–16 weeks. The half-life is concentration-dependent. Thus, for the 150 mg dose is <8 days while for the 200 mg dose it can reach up to 10 days. No dose-adjustments are required for patients with hepatic or renal impairment as it is not excreted by the hepatic or renal systems. Non-detectable levels of the drug can be achieved 28 days after discontinuation for the 150 mg dosage scheme or 43 days after the discontinuation of the 200 mg dosage scheme.[20]

Safety, efficacy, tolerability and immunogenicity of sarilumab

Sarilumab through a well-documented Clinical Development Program demonstrated a good profile regarding the safety and efficacy of the molecule in RA patients[21] (Table 1).

Mobility part A was a phase II clinical trial evaluating the safety and efficacy of sarilumab in patients with moderate to severe RA. A total of 306 patients were randomised to receive placebo or s.c. sarilumab plus MTX. Different dosage schemes have been tried with 100/150 mg weekly, 100/150 mg every 2 weeks, or 200 mg every 2 weeks. The 150 mg and 200 mg

Table 1 Clinical program of sarilumab in RA patients

Phase	Study number	Enrollment	Study description
Phase I	NCT01055899	15	To test the safety and tolerability of sarilumab and placebo in patients with RA
	NCT01026519	32	Single-dose, double-blind, placebo-controlled, parallel group safety, tolerability and PD study who were receiving concomitant MTX
	NCT01011959	60	To test the safety and tolerability of multiple doses of sarilumab in RA patients who were receiving treatment with MTX
	NCT01328522	32	To assess the comparative safety and tolerability of two SAR153191 drug products after a single dose administration in RA patients
	NCT01850680	61	To assess the safety and tolerability of a single dose of s.c. administered sarilumab in Japanese patients with RA who are receiving concomitant treatment with MTX
	NCT02097524	105	Single-dose study to describe the PD and safety of sarilumab and tocilizumab in adults with RA
Phase II	NCT01061736 Part A (MOBILITY)	306	To demonstrate that sarilumab on top of MTX was effective on reduction of signs and symptoms of RA at 23 weeks
	NCT01217814	16	To demonstrate that sarilumab (SAR153191/REGN88) on top of MTX was superior in efficacy to placebo for the relief of signs and symptoms of RA, in participants with active RA who had failed up to 2 TNF-α antagonists
Phase III	NCT01061736 Part B (MOBILITY)	1369	To demonstrate that sarilumab added to MTX was effective in a) reduction of signs and symptoms of RA at 24 weeks, b) inhibition of progression of structural damage at 52 weeks and, c) improvement in physical function at 16 weeks
	NCT01768572 (ASCERTAIN)	202	To assess the safety of sarilumab and tocilizumab in participants with RA who were inadequate responders to or intolerant of TNF antagonists
	NCT02057250 (EASY)	217	To collect real-use data of the sarilumab auto-injector device used by RA patients
	NCT02121210 (EXTEND)	132	To evaluate the immunogenicity of sarilumab administered as monotherapy
	NCT01709578 (TARGET)	546	To evaluate the effect of sarilumab added to other RA drugs in patients with RA who are not responding to or intolerant of anti-TNF therapy
	NCT02332590 (MONARCH)	369	Efficacy and safety of sarilumab and ADA monotherapy in patients with RA
	NCT01764997 (COMPARE)	776	To demonstrate the treatment effect of sarilumab and MTX compared to ETN and MTX in participants with RA and an inadequate response to ADA and MTX by evaluation of the DAS28
	NCT02293902 (KAKEHASI)	243	To demonstrate that sarilumab added to MTX reduce signs and symptoms of RA in Japanese RA participants with an inadequate response to MTX and to assess the safety of the molecule

Abbreviations: RA, rheumatoid arthritis; PD, pharmacodynamic; MTX, methotrexate; TNF: tumour necrosis factor; s.c.: subcutaneous; ETN: etanercept; ADA: adalimumab; DAS28: disease activity score for 28 joints.

regimen every 2 weeks had the most favourable safety and efficacy profile and it was further evaluated in phase III. Compared to placebo, sarilumab achieved higher ACR20 response (72% vs 46.2%).[22] Adverse events ranged from 43–72% depending on the different treatment regimens and 47% with placebo. Infections were the most common adverse events but they were not serious. Neutropenia and increased alanine aminotransferase (ALT) levels were also noted.

Mobility part B was a 62-week, phase III clinical trial that recruited a total of 1369 patients. The three primary endpoints were: a) the proportion of patients who achieved ACR20 response at week 24, b) change from baseline in physical

function (HAQ-DI index – health assessment questionnaire disability index) at week 16, and c) the change from baseline in the modified Sharp/van der Heijde score (SHS) of radiographic damage at week 52. Patients who received sarilumab 150 mg or 200 mg every 2 weeks plus MTX had an ACR20 response of 58% and 66.4% respectively at week 24, while patients who received placebo plus MTX had an ACR20 score of 33.4%. HAQ-DI scores had a mean change of −0.53, −0.55, and −0.29 respectively. Finally, the SHS mean change at week 24 from baseline was 0.90 and 0.25 compared with 2.78 in the placebo group. Infections were again the most common adverse events (150 mg: 40.6%, 200 mg: 39.6%, placebo: 31.1%) with serious infections occurring in 2.6%, 4% and 2.3% respectively. Opportunistic infections, hypersensitivity reactions, increase in ALT levels, elevations in fasting total cholesterol levels, reductions in the absolute neutrophil count and neoplasms have also been described.[23]

Target was a multicenter, randomised, double-blind, placebo-controlled, phase III clinical trial that evaluated the safety and efficacy of sarilumab in 546 patients who did not respond to TNF inhibitors therapy. Sarilumab of 150 mg and 200 mg every 2 weeks in combination with MTX versus placebo plus MTX were evaluated for a period of 24 weeks. The results shown that both primary endpoints (ACR20 response at week 24 and change from baseline in the HAQ-DI score at week 12) were achieved. In detail, ACR20 response for the 150 mg sarilumab was 55.8% and 60.9% for the 200 mg while for the placebo group the ACR20 was 33.7%. In addition, the HAQ-DI scores had a mean change of −0.46, −0.47 and −0.26 respectively. Furthermore, an ACR50 response achieved by the 37%, 40.8% and 18.2% of patients respectively while an ACR70 response achieved by the 19.9%, 16.3% and 7.2% of patients respectively. Approximately the same adverse reactions were noted as in the mobility trial.[24]

Monarch was a multicenter, randomised, double-blind, double-dummy, phase III clinical trial that evaluated the safety and efficacy of sarilumab 200 mg plus placebo once every 2 weeks versus adalimumab 40 mg plus placebo once every 2 weeks in patients with active RA for a period of 24 weeks. Sarilumab has been shown to be superior to adalimumab in the prementioned dosage schemes. The disease activity score 28 erythrocyte sedimentation rate (DAS28-ESR) mean change scores from baseline to week 24 were −3.28 versus −2.2 respectively. Furthermore, it has shown a 3-fold greater probability of achieving remission at week 12 and a 5-fold probability at week 24. As far as it concerns the ACR20 response, 71.7% of the sarilumab group have reached the goal versus 58.4% of the adalimumab group. A higher percentage of patients from the sarilumab group achieved also better ACR50 and ACR70 responses (45.7% versus 29.7% and 23.4% versus 11.9%). Finally, sarilumab has been shown to achieve better scores in HAQ-DI, clinical disease activity index (CDAI) and short form (SF)-36 physical component. The SF-36 mental component and functional assessment of chronic illness therapy-fatigue (FACIT-F) were similar between the 2 groups. Both groups showed similar incidence rates for several adverse and serious adverse events. Sarilumab had a greater percentage of neutropenias and injection site reactions while adalimumab had a greater percentage of headaches and dyslipidemias.[25]

Easy was a 12-week, multicenter, randomised, open-label, parallel-group usability study of the sarilumab pen and prefilled syringe in a total of 217 patients. The primary endpoint was the number of validated product technical failures. Only one product technical failure had been observed whereas most of the patients were satisfied with the pen. No difference in adverse events between the two groups (syringe versus pen) was observed. The study demonstrated the ease of use of the sarilumab pen when used by patients with RA in an unsupervised setting.[26]

In the ascertain study, a randomised, double-blind, double-dummy study, sarilumab (150 mg or 200 mg every 2 weeks) has been compared with tocilizumab (4 mg/kg every 4 weeks intravenously, increased to 8 mg/kg if clinically indicated) in terms of safety and tolerability when administered as single or multiple doses in patients with RA. The primary outcome was the number of participants with treatment emergent adverse events in a time frame up to 211 days (all adverse events that occurred from the first dose of the study drug administration up to 60 days after the end of treatment visit). At the end of the study neutropenia and infections were the two more common adverse events in both groups and no clinically meaningful differences were found. Adverse events occurred more frequently in the groups receiving higher doses of the drugs.[27]

Extend was an open-label, randomised, parallel group study assessing the immunogenicity and safety of sarilumab administered as monotherapy in patients with active RA in a period of 24 weeks. The primary endpoint was to assess the percentage of participants with incidence of antidrug antibodies (ADAs) in the two dosage schemes (150 mg and 200 mg every 2 weeks s.c.). The results shown that 8 (12.3%) versus 4 (6.1%) patients had persistent ADAs of whom 7 (10.8%) versus 2 (3%) patients had neutralising ADAs in the 150 mg and 200 mg group respectively but they did not meaningfully

impact the safety or efficacy or either dose of sarilumab over the 24 weeks period.[28]

Compare was a randomised, controlled study of sarilumab and MTX versus etanercept (ETN) and MTX in patients with RA and an inadequate response to 4 months of treatment with adalimumab and MTX. Unfortunately, the study was prematurely terminated due to small number of participants entering randomisation and not due to any identified safety concerns.[29]

The NCT01217814 trial was a randomised, double-blind, parallel-group, placebo- and active calibrato-controlled study assessing the clinical benefit of SAR153191 s.c. on top of MTX in patients with active RA who have failed previous TNF-α antagonists. This study was terminated due to delay in the study and the impact on the development timelines, not due to any identified safety concerns.[30]

The NCT02293902, is a recently published, randomised, double-blind, multicenter, phase III study with a placebo-controlled period assessing the efficacy and safety of sarilumab added to MTX in Japanese patients with moderately to severely active RA who are inadequate responders to MTX therapy. The primary endpoint was the proportion of patients achieving ACR20 responses at week 24. Sarilumab 150 mg achieved an ACR20 response in the 67.9% of the patients followed by 57.5% and 14.8% for the sarilumab 200 mg and placebo respectively. The authors concluded that the safety profiles of both doses of sarilumab were generally similar and as expected based on IL-6 class.[31,32]

Other indications

Sarilumab has already been approved for the treatment of moderate to severe RA, but more studies are on their way.[33] Currently, there are five recruiting studies in total. Two for juvenile idiopathic arthritis (phase II studies), a phase II study for indolent systemic mastocytosis, and two, phase III studies for giant cell arteritis and polymyalgia rheumatica. In addition, there are two studies that are not recruiting yet regarding morphea and RA during pregnancy. On the other hand, a study was prematurely discontinued after approximately 1.5 years, when the ankylosing spondylitis development program was discontinued due to lack of efficacy in the DRI11073 study. In Table 2, sarilumab indications beyond RA are shown.

Conclusion

Sarilumab has a robust Clinical Development Program with a variety of clinical phase II and III studies already having positive results and there are more coming on different

Table 2 Other indications of sarilumab beyond RA

Phase	Study number	Status	Condition	Study description
–	NCT03378219	Not yet recruiting	RA	An observational study on sarilumab-exposed pregnancies
Phase I	NCT03679845	Not yet recruiting	Morphea, plaque form	Study to assess sarilumab in halting progression of morphea
Phase II	NCT02776735	Recruiting	JIA	An open-label, ascending, repeated dose-finding study of sarilumab in children and adolescents with polyarticular-course JIA
	NCT02991469	Recruiting	JIA	A repeated dose-finding study of sarilumab in children and adolescents with systemic JIA
	NCT01764997	Terminated	AS	Extension study for long term evaluation of sarilumab in patients with AS
	NCT03770273	Recruiting	Indolent systemic mastocytosis	Safety and efficacy of s.c. sarilumab in improving the quality of life in people with indolent systemic mastocytosis
Phase III	NCT03600805	Recruiting	GCA	Evaluation of efficacy and safety of sarilumab in patients with GCA
	NCT03600818	Recruiting	PMR	Evaluation of the efficacy and safety of sarilumab in patients with PMR

Abbreviations: RA, rheumatoid arthritis; JIA, juvenile idiopathic arthritis; AS, ankylosing spondylitis; GCA, Giant-Cell Arteritis; PMR, polymyalgia rheumatica.

indications. At the moment, it represents an effective biologic agent for the treatment of moderate to severe RA. As it lacks a head-to-head comparison with tocilizumab we cannot be directly sure about the superiority of the molecule, but because of the greater affinity to IL-6 than that of tocilizumab we can assume this. Nevertheless, the efficacy and safety profiles are very similar to the already available IL-6 targeting drug tocilizumab, and include significant decreases in progression of structural damage. On the other hand, sarilumab has already proved its superiority to the TNF inhibitor adalimumab when used as monotherapy. Notwithstanding the above, more clinical studies are needed to elucidate the exact pathophysiological mechanisms of IL-6 and if IL-6 is a better option than TNF inhibitors to be used from the start of RA.

Sarilumab is beyond any doubt another molecule that can be added to the clinicians' armamentarium for the treatment of patients with moderate to severe RA with a good safety and efficacy profile.

Disclosure

The authors report no conflicts of interest in this work.

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