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Role of Interleukin 6 Inhibitors in the Management of Rheumatoid Arthritis

Ronald Man Lung Yip, FRCP (Edin), FHKCP and Cheuk Wan Yim, FRCP, FHKCP†*

Abstract: Rheumatoid arthritis (RA) is a multisystem disease that affects the joints and various organs, resulting in compromised quality of life and increased mortality. A wide spectrum of treatment options is available for RA. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are the first-line of treatment for RA, whereas tumor necrosis factor α inhibitors are commonly used as a second-line biological disease-modifying antirheumatic drug following inadequate response to csDMARDs. However, remission remains difficult to achieve. No single agent is effective for all patients. It is important to consider patients' comorbidities, perspectives, and preferences when selecting treatment.

Interleukin 6 (IL-6) plays a prominent role in the pathophysiology of RA and is an important therapeutic target for RA. Tocilizumab and sarilumab are approved IL-6 inhibitors, which have demonstrated good efficacy and tolerability as combination therapy or monotherapy in RA patients with inadequate response to csDMARDs or tumor necrosis factor α inhibitors. Apart from alleviating joint symptoms, inducing remission, and reducing structural damage, tocilizumab and sarilumab exhibit additional advantages in alleviating extra-articular symptoms, such as fatigue and morning stiffness, and have positive effect on anemia and glucose metabolism. Additionally, evidence showed that certain patient subgroups, such as those with comorbidities including anemia and diabetes mellitus, those with early RA, those with high baseline IL-6 levels, those at high risk of tuberculosis infection, or those intolerant to methotrexate monotherapy, may benefit from IL-6 inhibition. Given these advantages, tocilizumab and sarilumab can be considered earlier as a rational choice for treating RA in suitable patients. Future clinical investigations will help refine the use of these agents.

Key Words: candidates for IL-6 inhibition, IL-6 inhibitors, rheumatoid arthritis, sarilumab, tocilizumab

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Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation and multiple deformities in the joints. It is a multisystem disorder affecting various organs.[1] Its prevalence increases with age and affects women much more than men. Key disease characteristics include damage and disability of synovial joints leading to functional disability and reduced productivity.[2] Sleep disturbance and depression are common in RA patients.[3,4] Large cohorts have confirmed RA as an independent risk factor for cardiovascular diseases[5] and osteoporosis.[2,6] Mortality rates are nearly twice as much for RA patients than the general population.[7] Hence, prompt effective treatment should be initiated to reduce inflammation and pain, prevent progressive joint destruction, minimize systemic complications, and restore patients' function.

The pathophysiology of RA is complex. Recent histopathological and immunopathological studies envisage RA as a clinical syndrome with different subsets.[8,9] These subsets involve variable dysregulated interactions among helper T cells, B cells, macrophages, and fibroblasts, as well as proinflammatory cytokines, such as interleukin 1 (IL-1), IL-6, IL-10, IL-18, and tumor necrosis factor α (TNF-α). They all lead toward a common pathway in which persistent synovial inflammation and associated damage to the articular cartilage and underlying bone are present.[2,10]

In the treatment of RA, prompt initiation of disease-modifying antirheumatic drugs (DMARDs) is very important. The RA treatment armamentarium includes conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs). Conventional synthetic DMARDs are the mainstay of RA treatment; methotrexate (MTX) is considered the first-line csDMARD in the European League Against Rheumatism and American College of Rheumatology (ACR) guidelines.[11,12] If there is insufficient response to the initial csDMARD therapy, guidelines recommend to add a bDMARD or a tsDMARD (introduce a bDMARD first).[11,12] However, if patient is not suitable for csDMARD cotherapy, guidelines recommend to consider monotherapy with an IL-6 pathway inhibitor or a tsDMARD, which may have some advantages compared with other bDMARDs.[12]

Among the bDMARDs, TNF-α inhibitors have the longest safety data and are usually the initial choice for patients who require bDMARD therapy.[1] However, not all patients respond to TNF-α inhibitor therapy; randomized clinical trials suggest that approximately 30% of patients fail to respond to them.[13] This led to the use of other bDMARDs that target other pathways for the treatment of RA, such as tocilizumab and sarilumab (IL-6 signaling blockade), abatacept (T-cell costimulation blockade), and rituximab (B-cell depletion).[1,14]

Although a variety of agents are available for treatment of RA, sustainable remission remains a challenge. No single agent is effective for all patients. Patients' comorbidities, perspectives (such as feeling of fatigue), and preferences (such as ease of use) are important factors to consider when selecting treatment. In this review, we summarize the efficacy and safety of 2 approved IL-6 inhibitors, tocilizumab and sarilumab, in alleviating the articular and extra-articular symptoms of RA and discuss their position in the RA treatment armamentarium.

ROLE OF IL-6 IN HEALTH AND DISEASE

Interleukin 6 is a pleiotropic cytokine that plays an important role in systemic immune defense against pathogens. It is generated in response to external pathogens and induces signaling in a wide range of cells, including B and T lymphocytes, monocytes, neutrophils, macrophages, endothelial cells, and so on.[15,16] While

From the *Integrated Diagnostic and Medical Centre, Tung Wah Group of Hospitals, Kowloon; and †Department of Medicine, Tseung Kwan O Hospital, New Territories, Hong Kong.

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Correspondence: Ronald Man Lung Yip, FRCP (Edin), FHKCP, Integrated Diagnostic and Medical Centre, 5th Floor, Kwong Wah Hospital, 25 Waterloo Road, Kowloon, Hong Kong.
E-mail: Ronald.yip@tungwah.org.hk.

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transient expression of IL-6 is essential to activate the immune system in the body, persistent dysregulated activation of IL-6 can do more harm than good and has been shown to be linked to the pathogenesis of various chronic inflammatory diseases and autoimmune diseases including RA.[16] In addition, IL-6 is implicated in the pathogenesis of many clinical manifestations, such as anemia, insulin resistance, fatigue, mood disorders, osteoporosis, and risk for cardiovascular diseases.[15] For example, IL-6 is a major inducer of hepcidin, a key regulator of iron metabolism and mediator of anaemia in inflammation.[17,18] Because of the central role of IL-6 in the pathogenesis of anemia and other manifestations in RA, IL-6 blockade is a promising strategy to alleviate these extra-articular symptoms.[15]

Interleukin 6 plays an integral role in the pathophysiology of RA. It is abundantly expressed in the synovium of RA patients, and it induces joint inflammation and damage, cartilage degradation, joint erosion and narrowing, and progression toward chronic inflammation. Interleukin 6 levels correlate with measures of chronic synovitis and the severity of joint destruction.[15,19,20] Furthermore, reduction in IL-6 levels has been shown to a better prognostic marker than other cytokines for improvements in clinical outcomes in RA patients.[20] These findings indicate IL-6 as an important therapeutic target for RA.

IL-6 INHIBITORS IN RHEUMATOID ARTHRITIS

The prominent role of IL-6 in RA has stimulated the development of inhibitors of IL-6 signaling for RA treatment. Tocilizumab and sarilumab are inhibitors of the membrane-bound and soluble forms of IL-6 receptor α (IL-6Rα)[21,22] and are approved for the treatment of RA in many countries, including Europe and the United States. Three other IL-6 inhibitors are undergoing investigation in clinical trials for the treatment of RA, clazakizumab and olokizumab, which target IL-6, and ALX-0061, which binds to IL-6R, whereas sirukumab was withdrawn because of concerns with increased mortality.[19,23–25]

Tocilizumab

Characteristics

Key characteristics of tocilizumab are presented in Table 1. Tocilizumab is a recombinant humanized monoclonal immunoglobulin G1 (IgG1) antibody against IL-6Rα with a dissociation constant (K_D) of 2.5 pM.[33] Age, sex, race, and ethnicity had no effects on the pharmacokinetics of tocilizumab.[26] The approved dose in Europe is intravenous (IV) 8 mg/kg every 4 weeks (q4wk).[27] In the United States, the recommended starting dose is 4 mg/kg q4wk, which may be increased to 8 mg/kg q4wk.[28] For the subcutaneous (SC) formulation, the recommended dose in Europe is 162 mg every week.[29] In the United States, the recommended dose is 162 mg q2wk, followed by an increase to 162 mg every week based on clinical response for patients less than 100 kg in weight. For patients at or greater than 100 kg, the recommended dosing is 162 mg every week.[28] The SC formulation is available as a prefilled syringe or autoinjection pen.[34]

Efficacy

Tocilizumab has been available for the treatment of RA since 2010. Tocilizumab is indicated for the treatment of moderate-severe RA in combination with conventional RA agents or as monotherapy in patients with inadequate response or who are intolerable to previous RA treatment (Table 1). A number of clinical trials have demonstrated its safety and efficacy as combination therapy and monotherapy. Several meta-analyses of these trials have also been performed. Key efficacy data for tocilizumab from major clinical studies, summarized according to therapy type, are shown in Table 2.

(i) Combination Therapy in Patients With Incomplete Response to MTX/csDMARD

In studies where tocilizumab was used as a step-up in patients with incomplete response to MTX (MTX-IR), meta-analysis yielded odds ratio (OR) of 4.25 (95% confidence interval [CI], 2.70–6.69), 4.45 (95% CI, 2.63–7.55), and 5.00 (95% CI, 1.68–14.48) for ACR20/50/70 values, respectively, in favor of tocilizumab versus placebo.[43] Improvement in physical function was greater in patients treated with 4 or 8 mg/kg tocilizumab + MTX compared with those who received placebo + MTX, as indicated by the change in Health Assessment Questionnaire–Disability Index (HAQ-DI) from baseline to the end of study[35] (Table 2). More patients achieved remission with both doses of tocilizumab than the

TABLE 1. Key Characteristics of Tocilizumab and Sarilumab

Characteristic	Tocilizumab[26–29]	Sarilumab[30–32]
Molecule	Recombinant humanized monoclonal IgG1 antibody	Human monoclonal IgG1 antibody
Mechanism of action	Binds to soluble and membrane bound IL-6Rα	Binds to soluble and membrane bound IL-6Rα
Route of administration	IV or SC	SC
Presentation	• IV infusion vial • Prefilled SC syringe • Autoinjection pen with button	• Prefilled SC syringe • Buttonless autoinjection pen
Dosage and frequency	IV 4 or 8 mg/kg q4wk SC 162 mg q2w or weekly Increase low starting dose based on clinical response or reduce dosing to manage lab abnormalities	200 mg q2wk, reduce to 150 mg q2wk to manage lab abnormalities
Storage and stability	IV—store 2°C–8°C; once removed from refrigeration, use within 24 h SC—store 2°C–8°C; once removed from refrigeration, use within 8 h	Store 2°C–8°C; once removed from refrigeration, use within 14 d
Indication	Active moderate-severe RA in patients with IR to MTX or other csDMARDs, or TNF-α inhibitors • Combination therapy with MTX, other csDMARDs • Monotherapy for patients intolerant or unsuitable for csDMARDs	Active moderate-severe RA in patients with IR to MTX or other csDMARDs, or TNF-α inhibitors • Combination therapy with MTX, other csDMARDs • Monotherapy for patients intolerant or unsuitable for csDMARDs

TABLE 2. Efficacy of Tocilizumab in Key Clinical Trials

Study Name; Therapy Type; Patient Population	Study Length	Treatment Arms	N	ACR20/50/70 (%)	DAS28 Score <2.6 (%)	HAQ-DI Change From Baseline
OPTION[35]; combination; MTX-IR	24 wk	TCZ 8 mg/kg + MTX	205	59/44/22	27	−0.55
		TCZ 4 mg/kg + MTX	213	48/31/12	13	−0.52
		Placebo + MTX	204	26/11/2	0.8	−0.34
LITHE[36]; combination; MTX-IR	52 wk	TCZ 8 mg/kg + MTX	398	56/32/13	47.2	—
		TCZ 4 mg/kg + MTX	399	47/25/11	30.2	—
		Placebo + MTX	393	25/10/2	7.9	—
TOWARD[37]; combination; csDMARD-IR	24 wk	TCZ 8 mg/kg + cDMARDs	803	60.8/37.6/20.6	30	—
		Placebo + csDMARDs	413	24.5/9/2.9	3	—
ROSE,[38]; combination; csDMARD-IR	24 wk	TCZ 8 mg/kg + csDMARDs	409	44.4/30.1/18	38.4	—
		Placebo + csDMARDs	205	25/11.2/4	1	—
RADIATE[39]; combination; TNF-IR or refractory	24 wk	TCZ 8 mg/kg + MTX	170	50/28.8/12.4	30.1	−0.39
		TCZ 4 mg/kg + MTX	161	30.4/16.8/5	7.6	−0.31
		Placebo + MTX	158	10.1/3.8/1.3	1.6	−0.05
ADACTA[40]; monotherapy; MTX-IR or MTX-intolerant	24 wk	TCZ 8 mg/kg	163	65/47.2/32.5	39.9	−0.7
		Adalimumab 40 mg	162	49.4/27.2/17.9	10.5	−0.5
SATORI[41]; monotherapy; MTX-IR	24 wk	TCZ 8 mg/kg	61	80.3/49.2/29.5	43.1	—
		MTX	64	25/10.9/6.3	1.6	—
AMBITION[42]; monotherapy; MTX naive	24 wk	TCZ 8 mg/kg	286	70.6/44.1/28	33.6	−0.7
		MTX	284	52.1/33.5/15.1	12.1	−0.5

TCZ indicates tocilizumab.

placebo group, based on the 28-joint Disease Activity Score (DAS28) scores[35,36] (Table 2). In addition, tocilizumab treatment retarded the progression of structural joint damage as compared with placebo. After 52 weeks of treatment, 84% of patients treated with tocilizumab + MTX did not have any progression, as indicated by the total Genant-modified sharp score, compared with 67% of patients treated with placebo + MTX.[36]

In patients with IR to other csDMARDs (csDMARD-IR), inclusion of tocilizumab to the existing csDMARD treatment, as opposed to placebo, significantly improved ACR20/50/70 responses and DAS28 remission rates[37,38] (Table 2).

(ii) Combination Therapy in TNF-IR

In the RADIATE study,[39] the efficacy of tocilizumab + MTX was compared with placebo + MTX in patients with IR to TNF-α inhibitors (TNF-IR). Both doses of tocilizumab yielded higher ACR 20/50/70 responses and higher DAS28 remission rates compared with placebo (Table 2). Improvement in HAQ-DI score was also greater with tocilizumab than with placebo (Table 2).

(iii) Monotherapy

In the ADACTA study,[40] tocilizumab monotherapy was compared with adalimumab (a TNF-α inhibitor) monotherapy in MTX-IR or MTX-intolerant patients. The ACR20/50/70 scores and DAS28 remission rates were superior for tocilizumab compared with adalimumab (Table 2). In other studies where tocilizumab monotherapy was compared with MTX monotherapy in MTX-IR or MTX-naive patients, tocilizumab yielded higher ACR responses and higher remission rates than MTX[41,42] (Table 2).

In addition, longer-term data of up to 5 years showed durable efficacy with tocilizumab monotherapy or combination therapy in RA patients, with sustained improvements noted with long-term use.[44–47] The beneficial effects of tocilizumab on disease remission, radiographic outcomes, and physical function maintained even after ≤5 years' treatment.[44–47]

Tolerability and Safety

Tocilizumab is generally well tolerated and has a good safety profile. Common adverse events (AEs) include infections, neutropenia, and liver enzyme abnormalities. The majority of AEs reported were of mild to moderate intensity. The proportion of patients who discontinued tocilizumab treatment due to any AEs was low (5% in the tocilizumab group vs. 3% in the placebo group).[26]

Infections were the most frequently reported treatment-emergent AEs, but no cases of tuberculosis (TB) were observed in clinical trials.[26] The most frequent serious AEs reported with tocilizumab are infections including bacterial pneumonia, cellulitis, urinary tract infection, herpes zoster, and gastroenteritis.[26] Malignancies are reported with tocilizumab, but the exposure-adjusted incidence is similar between tocilizumab and placebo groups (1.32 events/100 patient year (PY) and 1.37 events/100 PY, respectively).[26] Some patients may develop antitocilizumab antibodies, and among patients who were tested for it, 1.6% were positive.[26]

In long-term studies and real-world studies of up to 7 years, no new safety concerns emerged with either tocilizumab monotherapy or combination therapy over the treatment period.[44–49] During long-term tocilizumab treatment, there was no increase in the incidence of AEs, and the safety profile was consistent with the short-term trials and remained stable over time.[44–49]

Sarilumab

Characteristics

Key characteristics of sarilumab are listed in Table 1. Sarilumab is a fully human monoclonal IgG1 antibody with an affinity for IL-6Rα (K_D = 62 pM for monomeric human IL-6Rα)

about 20-fold higher than tocilizumab.[30] Age, sex, race, and body weight do not alter the pharmacokinetics of sarilumab. It is not excreted by the renal or hepatic systems, and no dose adjustments are required for patients with impairment in any of these organ systems.[31] Sarilumab is available as a SC formulation in prefilled syringe or buttonless autoinjector pen at a recommended dose of 200 mg q2wk, to be reduced to 150 mg in case of certain lab abnormalities.[31,32]

Efficacy

Sarilumab is indicated for the treatment of moderate-severe RA in patients with inadequate response or who are intolerable to previous RA treatment, either as combination therapy or monotherapy (Table 1). Four phase 3 clinical trials have been completed in which sarilumab was administered as monotherapy or in combination with MTX or other csDMARDs. Key efficacy data for sarilumab summarized according to therapy type are presented in Table 3.

(i) Combination Therapy in MTX-IR

The MOBILITY trial[50] enrolled MTX-IRs who were administered 150 or 200 mg sarilumab + MTX or placebo + MTX q2wk. The ACR20 response rates at week 24 were higher for both doses of sarilumab compared with placebo (Table 3). The results were maintained for up to 52 weeks. Improvement in physical function was greater with sarilumab than placebo, as indicated by the HAQ-DI scores at week 16 (Table 3). More patients achieved remission with sarilumab than in the placebo group, based on the DAS28 and Clinical Disease Activity Index (CDAI) scores at week 24 (Table 3). Progression of structural joint damage was significantly retarded with sarilumab compared with placebo by weeks 24 and 52.[50] Among patients who continued in the open-label extension phase of the trial, the observed clinical efficacy (in terms of ACR responses, physical function, remission, and radiographic outcomes) sustained until the end of the 1-year extension period.[54]

In the KAKEHASI trial in Japan,[51] MTX-IRs were randomized to receive sarilumab or placebo, in combination with MTX. The ACR response rates at week 24 were higher for both doses of sarilumab than in the placebo arm, and the response rates remained high at the end of the 52-week study (Table 3). The HAQ-DI scores and DAS28 and CDAI remission rates at week 24 were in favor of sarilumab over placebo (Table 3). These results are consistent with the observations in non-Japanese patients in the MOBILITY trial.[50]

(ii) Combination Therapy in TNF-IR

In the TARGET trial,[52] the efficacy of sarilumab + csDMARDs therapy was compared with placebo + csDMARDs in patients who had inadequate response or were intolerant to 1 or more anti–TNF-α therapy. More patients achieved ACR responses and DAS28 remission by week 24 with sarilumab treatment than with placebo (Table 3). The ACR20 responses were independent of the number of prior anti–TNF-α agents. Physical function, assessed by HAQ-DI score, improved significantly with both doses of sarilumab compared with placebo (Table 3).

(iii) Monotherapy

The MONARCH trial[53] was a head-to-head comparison of sarilumab monotherapy with adalimumab monotherapy in MTX-IR or patients who were intolerant or unsuitable for MTX treatment. The ACR responses and changes in HAQ-DI scores were in favor of sarilumab over adalimumab (Table 3). Compared with the adalimumab arm, more patients in the sarilumab arm achieved DAS28 and CDAI remission (Table 3).

(iv) Switching From Another IL-6 Inhibitor—Tocilizumab

The efficacy of open-label sarilumab + csDMARD treatment in patients previously treated with tocilizumab + csDMARD was evaluated in a post hoc analysis.[55] Among patients who had not responded to 8 mg/kg tocilizumab, a substantial proportion of patients responded to 200 mg sarilumab treatment by week 24. The ACR20/50/70 was achieved in 60%/46%/32% of patients

TABLE 3. Efficacy of Sarilumab in Key Clinical Trials

Study Name; Therapy Type; Patient Population	Study Length	Treatment Arms	N	ACR20/50/70 (%)	DAS28 Change From Baseline	CDAI Score <2.8 (%)	DAS28 Score <2.6 (%)	HAQ-DI Change From Baseline
MOBILITY[50]; combination; MTX-IR	52 wk[a]	SAR 200 mg + MTX	399	66.4/46/25	—	13.8	34.1	−0.55
		SAR 150 mg + MTX	400	58/37/20	—	10.3	27.8	−0.53
		Placebo + MTX	398	33.4/17/7	—	5	10.1	−0.29
KAKEHASI[51]; combination; MTX-IR	52 wk[b]	SAR 200 mg + MTX	80	57.5/38.8/15	−2.8	10	40	−0.6
		SAR 150 mg + MTX	81	67.9/43.2/18.5	−2.8	6.2	35.8	−0.5
		Placebo + MTX	81	14.8/9.9/3.7	−1.5	1.2	7.4	−0.3
TARGET[52]; combination; TNF-IR or intolerant	24 wk[c]	SAR 200 mg + DMARDs	184	60.9/40.8/16.3	−2.8	—	28.8	−0.47
		SAR 150 mg + csDMARDs	181	55.8/37/19.9	−2.4	—	24.9	−0.46
		Placebo + csDMARDs	181	33.7/18.2/7.2	−1.4	—	7.2	−0.26
MONARCH[53]; monotherapy; MTX-IR or intolerant	24 wk	SAR 200 mg	184	71.7/45.7/23.4	−3.28	7.1	26.6	−0.61
		Adalimumab 40 mg	185	58.4/29.7/11.9	−2.20	2.7	7	−0.43

[a]HAQ-DI results are for week 16; other results are for 24 weeks.

[b]Results shown are for week 24.

[c]HAQ-DI results are for week 12.

who had not responded to tocilizumab, respectively. Remissions in DAS28 and CDAI were achieved in 46% and 22% of patients, respectively.[55] Among those who responded to tocilizumab, the majority of them maintained response even after switching to sarilumab.[55]

In addition, the durable efficacy of sarilumab was demonstrated in long-term studies of up to 5 years.[56–58] Reduction in disease activity and improvements in physical function and radiographic outcome were maintained over the study treatment period.[56–58]

Tolerability and Safety

Sarilumab has demonstrated a good tolerability and safety profile in clinical trials, similar to tocilizumab.[31] The majority of the AEs were of mild-moderate intensity. The most commonly reported AEs were infections, neutropenia, and liver enzyme abnormalities.[31] Relatively few patients discontinued treatment because of AEs. In 52-week studies, discontinuation of treatment due to AEs was reported in 13% and 11% of patients treated with sarilumab 200 and 150 mg, respectively, compared with 5% of patients treated with placebo.[31]

Infections were the most frequently reported treatment-emergent AEs.[31] Neutropenia occurred more frequently with sarilumab (6% and 4% with 200 and 150 mg, respectively) than with placebo (0%). But the decrease in absolute neutrophil count was not associated with higher incidence of infections.[31] Liver enzyme abnormalities are observed more often with sarilumab (29% and 27% of patients with elevated aspartate aminotransferase, and 45% and 40% of patients with elevated alanine aminotransferase with sarilumab 200 and 150 mg, respectively) than with placebo (13% of patients with elevated aspartate aminotransferase and 24% of patients with elevated alanine aminotransferase). However, for majority of the patients, the elevated enzyme levels were ≤3 times upper limit of normal.[31]

Malignancy or immunogenicity occurred at a similar rate in sarilumab and placebo. The incidence of malignancies in sarilumab or placebo was 1.0 events/100 PY.[31] The incidence of immunogenicity was 4.0% and 5.6% with sarilumab 200 and 150 mg, respectively, and 2.0% with placebo. Neutralizing antibodies were detected in 1.0%, 1.6%, and 0.2% of patients treated with sarilumab 200 and 150 mg and placebo, respectively.[31]

Evaluation of long-term use of sarilumab for up to 7 years reflected a consistent profile when used either as combination therapy or as monotherapy. The safety profile remained fairly stable over the treatment period; no new safety signals or increase in the incidence of AEs was identified.[56–59]

Extra-articular Effects

Although predominantly an articular disease, RA is accompanied by a number of extra-articular manifestations, which further complicate disease management. Both tocilizumab and sarilumab have demonstrated additional clinical benefits in alleviating some extra-articular manifestations of RA, which confer to them the added advantage of being particularly suitable for patients who are afflicted with these manifestations. The extra-articular benefits observed with tocilizumab and sarilumab are described below.

Pain, Fatigue, and Quality of Life

Tocilizumab treatment was associated with reduced fatigue in RA patients, as measured by a consistent increase in mean functional assessment of chronic illness therapy-fatigue scores from baseline to week 96 (increase from baseline 7.3 ± 10.4).[60] Improvements were noted from week 4 onward (increase from baseline 5.0 ± 9.7).[60] Systematic literature review also showed improvements in mood and mental status, and physical and mental quality of life in RA patients treated with tocilizumab.[61]

In phase 3 trials, RA patients receiving sarilumab in combination with MTX or other csDMARDs, or as monotherapy experienced greater relief from pain and fatigue at weeks 24 and 52 when compared with the placebo group or adalimumab group.[62] At 24 weeks, the OR for greater than 30% improvement in visual analog scale for pain was 2.52 (95% CI, 1.62–3.92) and 1.70 (95% CI, 1.12–2.58) for sarilumab versus placebo and adalimumab, respectively. The OR for greater than 30% improvement in functional assessment of chronic illness therapy-fatigue score was 1.90 (95% CI, 1.22–2.94) for sarilumab versus placebo. Overall, pain improved in approximately 50% of the patients and fatigue in 40% of the patients after 52 weeks of treatment with sarilumab.[62]

Patients with RA treated with sarilumab + MTX also showed improvements in morning stiffness, productivity, social participation, health-related quality of life, and mood by week 24 compared with placebo + MTX.[63,64]

Anemia

Treatment with tocilizumab + MTX was associated with increase in serum hemoglobin levels from week 4 until week 24, according to a multicenter randomized controlled trial conducted in RA patients.[65] These effects were not seen in the placebo + MTX group.

In the MONARCH trial, sarilumab monotherapy was associated with a greater reduction in the proportion of RA patients who had anemia from baseline to week 24 than adalimumab (14.1% vs. 8.8%).[66] The increase in hemoglobin levels was greater in the sarilumab group than in the adalimumab group (least squares mean [LSM] change from baseline to week 24, sarilumab 0.591 g/dL, adalimumab 0.075 g/dL).[66]

Fasting Glucose and Glycated Hemoglobin

An observational study reported a significant decrease in glycated hemoglobin (HbA_{1c}) values after 3 months (−0.4% from baseline) of initiation of tocilizumab in RA patients.[67] Treatment with TNF-α inhibitors also elicited a decrease in HbA_{1c}, but to a lesser degree (−0.1% from baseline to 3 months).[67]

Subanalysis of RA patients with concomitant diabetes mellitus in the MOBILITY and TARGET trials revealed improvements in glycemic parameters with sarilumab in combination with MTX or other csDMARDs.[68] By week 24, fasting blood glucose (LSM difference, −1.22; 95% CI, −1.64 to −0.80) and HbA_{1c} levels (LSM difference, −0.69; 95% CI, −1.00 to −0.38) decreased significantly in the sarilumab group compared with the placebo group. These effects were independent of changes in body weight, C-reactive protein (CRP) levels, ACR5 responses, or remission status.[68]

In summary, tocilizumab and sarilumab have shown efficacy in alleviating RA symptoms in MTX-IR and TNF-IR. They reduce joint symptoms and structural damage to joints and induce disease remission. Both agents work well in combination with MTX or other csDMARDs and have demonstrated superior efficacy as a monotherapy over adalimumab. These observed clinical benefits persist with long-term use of both agents. It should be noted that IL-6 inhibition can directly decrease the synthesis of CRP by hepatocytes. Therefore, composite outcome measures that include CRP level may be unreliable for disease monitoring in patients treated with IL-6 inhibitors.[67] Nonetheless, other disease activity measure that does not include CRP, such as CDAI, and other clinical outcome measures of physical function and radiographic progression show consistent and significant improvements in treated patients.

Tocilizumab and sarilumab have a good safety and tolerability profile. There were no major AEs of concern, and the safety profile remains stable and consistent with long-term use of either of the agents. The most commonly reported AEs include infections, neutropenia, and liver enzyme abnormalities. Transient neutropenia induced by IL-6 inhibition reflects decreased mobilization of neutrophils into the peripheral blood rather than apoptosis or phagocytosis of neutrophils. Although recruitment of neutrophils to inflammation sites may be delayed, neutrophil functions associated with host defense against infections are not significantly compromised.[69] Elevations of liver enzymes associated with treatment with IL-6 inhibitors were mostly mild and are likely due to interference of IL-6 inhibitors with IL-6–mediated liver regeneration rather than direct toxicity.[19]

Besides, clinical improvements were noted when tocilizumab nonresponders switched to sarilumab. In addition, tocilizumab and sarilumab exhibit clinical benefits in alleviating some extra-articular manifestations of RA, such as fatigue and morning stiffness, and have positive effects on anemia and glucose metabolism.

POTENTIAL CANDIDATES FOR IL-6 INHIBITION

There are many effective therapeutic agents available for the treatment of RA. However, some agents are more suitable in certain patients than others because of the complex nature of the disease, differences in patients' response to different agents, and the diverse clinical manifestations encountered by patients. Here, we discuss specific patient subgroups who are more likely to have additional benefit from treatment with IL-6 inhibitors.

Patients With Early RA

Interleukin 6 is implicated in the manifestation of RA from the very beginning stages.[70] Blocking IL-6 signaling at an early stage would be beneficial and yield good prognosis. This hypothesis was tested in the FUNCTION study,[71] which enrolled more than 1000 patients with mean disease duration of 5 months. Tocilizumab either in combination with MTX or as monotherapy was associated with higher DAS28 remission rates at 24 weeks compared with the control group (placebo + MTX). Tocilizumab treatment also retarded the structural joint damage to a significantly greater extent compared with control.[71] In another study, more patients with early RA (diagnosis <12 months) attained sustained remission when tocilizumab was incorporated in the regimen versus placebo + MTX.[72] In both studies, the AE profile did not differ between treatment groups. These studies showed that tocilizumab with or without MTX is more effective and has a similar safety profile, compared with MTX monotherapy in patients with early RA, and may be considered for treatment initiation in patients with newly diagnosed RA.

Patients With High Baseline IL-6

Post hoc analyses of MOBILITY and MONARCH trials revealed that patients with high levels of IL-6 at baseline (highest tertile group; serum IL-6 at 3 times upper limit of normal) had more joint damage, greater disease activity, and elevated levels of CRP than patients with low levels of IL-6 at baseline (low-tertile group; serum IL-6 <12.5 pg/mL).[73] Patients with elevated baseline IL-6 levels had greater clinical response to sarilumab combination therapy or monotherapy compared with placebo + MTX or adalimumab than patients with normal IL-6 levels.[73] This suggests that patients with higher levels of IL-6 at baseline could be good candidates for IL-6 inhibitor therapy.

Patients With Anemia

Elevated levels of IL-6 are associated with the development of anemia in RA; some observations suggest that between 33% and 60% of RA patients suffer from anemia.[74] Treatment with tocilizumab and sarilumab has been shown to increase hemoglobin levels in RA patients.[19,57,65] Interleukin 6 inhibitors may be a good treatment option to consider RA patients with concomitant anemia.

Patients With Diabetes Mellitus

As discussed previously, treatment with tocilizumab or sarilumab has been shown to reduce hyperglycemia in RA patients.[67,68] These findings suggest that IL-6 inhibitors could be considered for RA patients with concomitant diabetes mellitus.

Patients at High Risk of TB Infection

It is estimated that 25% of the world's population carries latent TB infection, which could become active if the host's immune system weakens.[74] Tumor necrosis factor α inhibitors have been associated with latent TB infection reactivation.[74] Given proper TB screening and prophylaxis, only sporadic incidents of TB were reported with long term tociliziumabor sarilumab treatment.[49,75] The risk of TB reactivation with tocilizumab or sarilumab treatment is low, and both tocilizumab and sarilumab may be considered a good treatment option for RA patients at risk of TB.

Patients With MTX Intolerance

The European League Against Rheumatism and ACR guidelines recommend to add bDMARDs to MTX in patients with inadequate response to MTX therapy.[11,12] However, between 11% and 36% of RA patients exhibit intolerance to MTX.[76–78] For these patients, bDMARDs with demonstrated efficacy in monotherapy regimens can be considered.[12] Both tocilizumab and sarilumab have demonstrated clinical efficacy as monotherapy in RA patients,[53,79] making them a suitable treatment option for MTX-intolerant patients.

CONCLUSIONS

Clinical evidence has demonstrated tocilizumab and sarilumab to be efficacious and tolerable in RA patients. They are effective in controlling RA symptoms, retarding joint damage, and inducing disease remission, either in combination with csDMARD or as monotherapy. Besides, tocilizumab and sarilumab have demonstrated additional clinical benefits in alleviating some extra-articular manifestations of RA. In addition, clinical studies revealed that certain patient subgroups, such as those with comorbidities including anemia and diabetes mellitus, those with early RA, those with high baseline IL-6 levels, those at high risk of TB infection, or those intolerant to MTX monotherapy, are possible candidates who may benefit from treatment with tocilizumab or sarilumab. Considering these advantages, tocilizumab and sarilumab are a rational choice for the treatment of RA in suitable patients. Besides clinical factors, patient's perspectives, such as feeling of fatigue, and frequency and ease of administration are other important considerations when choosing a treatment for RA.

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