

IL-6 targeting compared to TNF targeting in rheumatoid arthritis: studies of olokizumab, sarilumab and sirukumab

Yoshiya Tanaka,¹ Emilio Martin Mola²

The combination of synthetic disease-modifying anti-rheumatic drugs (sDMARDs) such as methotrexate (MTX) and biologic DMARDs (bDMARDs) targeting inflammatory cytokines such as tumour necrosis factor (TNF) has enabled markedly efficient control of disease activity in patients with rheumatoid arthritis (RA) with inadequate response to MTX (MTX-IR).¹⁻⁷ Although TNF inhibitors have offered pivotal strategies for rheumatologists in daily practice and 20–50% of RA patients treated with TNF inhibitors achieve clinical remission within 6 months, the remaining patients still have active disease and progressive disability. IL-6 is also a pleiotropic cytokine with diverse activities and plays a central role in the pathogenesis of RA by contributing to T cell activation, B cell activation, synovocyte stimulation, endothelial activation, osteoclast maturation and production of acute-phase proteins. 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. 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 (TNF-IR).⁸⁻¹³ Tocilizumab was, therefore, approved as a first-line bDMARD in patients responding insufficiently to MTX or other sDMARDs in Japan and Europe. Also, in the 2013 EULAR recommendations for the management of RA,

tocilizumab was listed as a first-line TNF inhibitor in patients with sDMARD-IR.¹⁴ 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.

Olokizumab is a humanised anti-IL-6 mAb. Genovese *et al*¹⁵ report the findings of a 12-week phase IIb study to assess the safety and efficacy of subcutaneous olokizumab in RA patients with moderate-to-severe disease activity despite TNF inhibitors. A total of 221 patients were randomised to one of nine treatment arms receiving placebo or olokizumab (60, 120 or 240 mg) every 4 weeks (q4w) or every 2 weeks (q2w), or 8 mg/kg tocilizumab q4w. All patients received background MTX. Treatment with olokizumab met the primary endpoint (change from baseline in DAS28 C-reactive protein (CRP)) as compared to placebo at week 12 at all olokizumab doses tested (60 mg, $p=0.0001$; 120 mg and 240 mg olokizumab, $p<0.0001$). Olokizumab at various doses demonstrated similar efficacy to tocilizumab across multiple endpoints. The greatest improvement in DAS28-CRP scores was observed in the olokizumab 240 mg q2w group. In addition, pharmacokinetic modelling demonstrated a shallow dose–exposure response relationship in terms of the percentage of patients with DAS28<2.6. Olokizumab was also superior to placebo according to American College of Rheumatology (ACR) responses. Most treatment emergent adverse events (TEAEs) were comparable between the olokizumab and tocilizumab treatment groups, the incidence of serious TEAEs (SAEs) was similar between treatment groups, and no serious SAEs were reported by more than one patient. There was one recorded SAE of increased blood triglycerides in the tocilizumab group.

Sarilumab is a human anti-IL-6Ra mAb. The results of a 12-week phase II study to assess the safety and efficacy of subcutaneous sarilumab are reported by Huizinga

et al.¹⁶ A total of 306 patients with active RA despite MTX were randomised to one of six treatment arms receiving placebo or sarilumab (100 mg q2w, 150 mg q2w, 100 mg qw, 200 mg q2w or 150 mg qw for 12 weeks) with background MTX. The proportion of patients achieving the primary endpoint, an ACR20 response at week 12, compared to placebo was significantly higher for sarilumab 150 mg qw (72.0% vs 46.2%, multiplicity adjusted $p=0.0203$) and higher ACR20 responses were also attained with 150 mg q2w (67%; unadjusted (nominal) $p=0.0363$) and 200 mg q2w (65%; unadjusted $p=0.0426$) versus placebo. Infections were the most common TEAEs, although no serious infections were reported. At week 12, mean total cholesterol was higher in the four highest dose groups; the increase from baseline was 9.4%, 10%, 16.4% and 21.1%, respectively, in the 150 mg q2w, 100 mg qw, 200 mg q2w and 150 mg qw groups, compared to 4.9% in the placebo group.

Sirukumab is a human anti-IL-6 mAb. Smolen *et al*¹⁷ report the findings of two parts of a phase II study to assess the safety and efficacy of subcutaneous sirukumab in patients with active RA despite MTX. In part A, the proof of concept study, 36 patients were randomised to placebo or sirukumab 100 mg q2w through week 10, with crossover treatment during weeks 12–22. In part B (dose finding), 151 patients were randomised to sirukumab (100 mg q2w, 100 mg q4w, 50 mg q4w or 25 mg q4w) through week 24, or placebo through week 10 with crossover to sirukumab 100 mg q2w. The primary endpoint (ACR50 at week 12 in part B) was achieved only with sirukumab 100 mg q2w (26.7% vs 3.3% with placebo; $p=0.026$). Greater improvements in the mean DAS28-CRP score at week 12 were observed with sirukumab 100 mg q2w versus placebo in parts A (2.1 vs 0.6, $p<0.001$) and B (2.2 vs 1.1; $p<0.001$). Through week 12 in parts A and B, the incidence of TEAEs was similar among the sirukumab and placebo groups. There were no reports of opportunistic infections, tuberculosis or gastrointestinal perforations. Changes in laboratory values, including neutropenia, liver transaminases and total cholesterol, were consistent with reports for tocilizumab.

Promising findings in a phase IIb study using clazakizumab, a humanised anti-IL-6 mAb, for RA patients have also been previously reported.^{18 19} The combination of MTX and clazakizumab (80, 160 and 320 mg intravenously at day 1 and week 8) was associated with rapid and

¹The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan;

²Servicio de Reumatología, Hospital Universitario La Paz, Universidad Autónoma de Madrid, Paseo de la Castellana 261, Madrid, Spain

Correspondence to Professor Yoshiya Tanaka, The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, 1-1 Iseigaoka, Yahatanishi, Kitakyushu 807-8555, Japan; tanaka@med.uoeh-u.ac.jp

significant improvements in disease activity as measured by ACR20 and DAS28 in 127 RA patients with MTX-IR within 12 or 16 weeks after treatment.

The ACR20 response rates achieved with tocilizumab, olokizumab, sarilumab and sirukumab were significantly higher than with placebo and were generally consistent except for olokizumab in RA patients with MTX-IR, although the background characteristics of enrolled patients differed among the studies.^{8-10 15-17} Also, improvements in DAS28 were comparable between tocilizumab and olokizumab in TNF-IR patients.¹⁵ In general, clinical efficacy as well as safety profiles, as shown below, appear similar among the five mAbs (tocilizumab, olokizumab, sarilumab, sirukumab and clazakizumab), making it difficult to differentiate between them compared to tocilizumab. In fact, UCB has out-licensed olokizumab to R-Pharma after its phase II trial. Anti-IL-6R mAbs indiscriminately affect both the membrane form and the soluble form of the receptor, but these results suggest that anti-IL-6 mAbs could inhibit IL-6 from binding to soluble receptor or membrane receptor, which results in a similar efficacy profile among three anti-IL-6 mAbs and two anti-IL-6R mAbs. On the other hand, Nishimoto *et al* reported that serum levels of IL-6 in Castleman disease were lower than those in RA, while there was no difference in soluble IL-6R levels between the two conditions. However, the increase in IL-6 levels after tocilizumab therapy was much greater in Castleman disease than in RA.²⁰ Thus, the pathological relevance of the difference between serum IL-6 and soluble/membrane IL-6R remains unclear; it is also difficult to interpret the difference between ligand inhibition and receptor inhibition for the treatment of RA.

Several clinical and functional assessments indicate that switching to tocilizumab is successful in patients with TNF-IR.^{11 12} As described, olokizumab resulted in significant improvement in DAS28 as compared to placebo at week 12 in RA patients with TNF-IR.¹⁵ Furthermore, we reported that tocilizumab was a good treatment option for improving signs and symptoms and inhibiting progression of joint damage in 45 RA patients with structural as well as clinical TNF-IR in the REACTION study.¹³ Thus, bDMARDs targeting IL-6 were initially recommended as second-line therapy for patients with TNF-IR.²¹ However, recent clinical research such as the ADACTA study has changed the ranking of tocilizumab. In this study, comparison of tocilizumab and adalimumab monotherapy for RA patients with MTX-IR revealed that

tocilizumab monotherapy was superior to adalimumab for reducing disease activity in RA, that safety was comparable between both therapies, and that their adverse events (AEs) were consistent with previous findings.²² Tocilizumab is, therefore, ranked as a first-line bDMARD, similarly to TNF inhibitors in patients with MTX-IR.¹⁴

Furthermore, tocilizumab appears to have several advantages: (i) tocilizumab monotherapy is significantly superior to MTX, in contrast to monotherapy with TNF inhibitors²³⁻²⁶; (ii) tocilizumab is highly effective for systemic juvenile idiopathic arthritis characterised by spiking fever, evanescent skin rash, lymphadenopathy, hepatosplenomegaly and serositis in addition to arthritis^{27 28}; and (iii) tocilizumab ameliorates the amyloidosis secondary to RA because it normalises serum levels of amyloid A.^{29 30} These promising results in tocilizumab studies have encouraged the development in other bDMARDs targeting IL-6. On the other hand, TNF inhibitors are superior to tocilizumab for the treatment of ankylosing spondylitis and inflammatory bowel diseases, indicating that differential use of TNF inhibitors and IL-6 inhibitors could be another theme to be addressed. Furthermore, although good radiological results with tocilizumab have been documented in multiple reports, studies comparing IL-6 inhibitors with TNF inhibitors should be carried out in order to clarify their similar effects on structural damage.

Soon five bDMARDs will be available for targeting IL-6, which will raise questions as to when and how these agents should be employed. Although more treatment options may be better for patients, several crucial points remain unclear from a clinical point of view. For instance, if patients fail to respond to an anti-IL-6R mAb, might they respond to another anti-IL-6 or anti-IL-6R mAb as happens with TNF inhibitors? Are there any grounds for considering switching between IL-6 inhibitors or, as described above, switching from anti-IL-6R to anti-IL-6 or vice versa? Does switching between IL-6 inhibitors improve their efficacy? Further studies are warranted to establish whether there are important differences among the five IL-6 inhibitors, and to determine which inhibitor should be chosen for a particular patient from a clinical standpoint as regards clinical response and/or structural damage, AEs, and efficacy in patients with TNF-IR.

The safety profiles of olokizumab, sarilumab and sirukumab are similar to each other and to that of tocilizumab as

determined in clinical trials, post-marketing surveillance and clinical practice.^{31 32} Commonly reported AEs with IL-6 inhibitors include gastrointestinal disorders, upper and lower respiratory tract and urinary tract infections, and nervous system disorders, similar to those found for olokizumab, sarilumab and sirukumab and to AEs observed for tocilizumab and multiple bDMARDs targeting TNF. However, there were no reports of opportunistic infections, tuberculosis or gastrointestinal perforations in patients with diverticulitis, possibly because of the careful inclusion criteria for each trial (eg, patients with diverticulum were not included in the trials of olokizumab, sarilumab and sirukumab). Nonetheless, safety data from daily practical clinics should be collected. Common laboratory changes were primarily neutropenia and elevated liver function tests and serum lipids with excessive levels of total cholesterol, although the exact clinical consequences and mechanisms remain to be clarified. However, because these trials were too short and too small for strong conclusions on safety and there were no negative findings, safety should be determined with multiple long-term extension studies and nation-wide registries in clinical practice.

Taken together, the safety and efficacy profiles in clinical trials of olokizumab, sarilumab and sirukumab are similar and are consistent with those observed in RA patients treated with tocilizumab. Furthermore, the clinical efficacy of these IL-6 inhibitors is similar to that of TNF inhibitors in patients with MTX-IR and TNF-IR. Screening of biomarkers or genetics in each RA patient, for instance, baseline serum levels of TNF and/or soluble IL-6R, may help to predict the efficacy of each drug and to select patients for cytokine-oriented targeted therapies.³³ However, better strategies are warranted for selecting and identifying appropriate patients earlier once bDMARDs targeting IL-6 are launched in the near future. We also need to determine whether there are important differences between the many IL-6 inhibitors and which are suitable for particular patients, otherwise companies may waste time and money in development.

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