

Targeting IL-6: A review of data

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ABSTRACT

Compounds that target interleukin (IL)-6 pathways include antibodies against the IL-6 receptor or ligand, and inhibitors of IL-6 signal transduction. The anti-IL-6 receptor (IL-6R) monoclonal antibody tocilizumab has been licensed for several years; data from multiple studies demonstrate its efficacy and tolerability in rheumatoid arthritis as monotherapy or in combination with methotrexate. In addition, another anti-IL-6R monoclonal antibody, sarilumab, has recently been approved in both the US and EU. Anti-IL-6 monoclonal antibodies include olokizumab and clazakizumab, which both have data from phase II studies, as well as sirukumab which has completed phase III trials but may not be brought to the market. Comparative data for olokizumab versus tocilizumab intervention in rheumatoid arthritis suggest no difference in efficacy between blocking the receptor or the ligand. Head-to-head studies are needed to determine whether inhibition of the Janus kinase pathway is similar in its overall efficacy to direct inhibition of IL-6 or its receptor. The IL-6 inhibitors appear to be more effective when combined with methotrexate. However, they have shown superiority to tumour necrosis factor inhibitors when used as monotherapy, and may have an advantage in patients who cannot use methotrexate or any other conventional synthetic disease modifying anti-rheumatic drug. Regarding disease activity assessment, CDAI is a more appropriate measure than DAS28 when looking at the effect of IL-6 inhibition, as these agents interfere with the acute phase response, which is heavily weighted in the formula of DAS28.

A panel of international experts in the field of rheumatology recently came together to consider the data for agents that target the IL-6 pathway.

CONSIDERING THE TARGETING OF IL-6 PATHWAYS

Compounds that target IL-6 pathways include antibodies against the IL-6 receptor such as tocilizumab, which has been licensed for almost a decade, and sarilumab, which has recently been approved in both the US and the EU.^{1,2} Antibodies against the IL-6 ligand have also been developed but have not yet been approved, including olokizumab and clazakizumab; the development of another anti-IL-6 antibody, sirukumab, has been stopped following a negative review from the FDA (see below).

In addition, there are inhibitors of IL-6 signal transduction such as the Janus kinase (JAK) inhibitors baricitinib (licensed in the EU³ and US) and tofacitinib (licensed in the US and EU^{4,5}).

CONSIDERING ANTI-IL-6 RECEPTOR ANTIBODIES

Considering tocilizumab

Tocilizumab is a humanised monoclonal antibody against the α -subunit of the IL-6 receptor. Phase III studies in rheumatoid arthritis included tocilizumab monotherapy versus

methotrexate in methotrexate-naïve/-free patients and tocilizumab in combination with methotrexate or another conventional synthetic disease modifying anti-rheumatic drug (csDMARD) versus placebo in patients with an inadequate response to methotrexate/csDMARD or tumour necrosis factor (TNF) inhibitors (table 1).⁶⁻¹⁰

The American College of Rheumatology 50% improvement criteria (ACR50) and 70 response rates at week 24 in the phase III trials taken together show a typical picture of higher responses in methotrexate-naïve/-free patients than in those with active disease despite methotrexate or another csDMARD, with even lower responses in those who have previously been treated with a TNF inhibitor (figure 1).^{6, 10, 11} With respect to physical function, data from OPTION show significant improvement in Health Assessment Questionnaire (HAQ) score for tocilizumab 4 or 8 mg/kg plus methotrexate versus placebo alone (with methotrexate in the background), surpassing the clinically important change from baseline of -0.22 after approximately 3 weeks of treatment.⁷

The phase III studies also showed an effect of tocilizumab on C reactive protein (CRP), with a reduction into the normal range with the 8 mg/kg dose either as monotherapy or in combination with methotrexate, whereas the 4 mg/kg dose or methotrexate monotherapy did not reduce CRP to the same extent.^{6, 7, 9, 10, 12} In addition, tocilizumab treatment down-regulates hepatic production of hepcidin leading to a highly significant improvement in haemoglobin within 2 weeks, correcting the anaemia that is a hallmark of chronic systemic inflammation.⁷ Finally, the LITHE study included a structural outcome and showed a radiographic benefit at week 52 with both 4 and 8 mg/kg doses of tocilizumab in combination with methotrexate versus placebo (P<0.01 for 8 mg/kg dose).¹²

In a further study (ACT-RAY) including 553 patients with active rheumatoid arthritis despite methotrexate treatment, patients were randomised to receive tocilizumab in addition to methotrexate or to switch to tocilizumab monotherapy.¹³ Combination therapy was superior to monotherapy in terms of both the proportion of patients with Disease Activity Score 28 (DAS28) below 2.6 at week 52 and the proportion of patients without radiographic progression, although monotherapy was also effective. A study conducted in Japan (SURPRISE) showed a similar pattern at week 24, the time of the primary endpoint, although DAS28 remission rates became comparable at week 52.¹⁴ However, x-ray changes were significantly worse in patients switching to monotherapy. The ADACTA study (n=325) compared tocilizumab monotherapy with adalimumab monotherapy in early rheumatoid arthritis, showing superior Clinical Disease Activity Index (CDAI) remission (≤ 2.8) with tocilizumab (17.2% v 9.3%; P<0.05).¹⁵ Finally, the FUNCTION study compared tocilizumab and methotrexate as monotherapy versus the two drugs combined. The proportion of patients with DAS28 (ESR) below 2.6 (the primary endpoint) was significantly

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Table 1 Tocilizumab phase III studies^{6–10}

Patient population	Patients, n	Treatment arms	Clinical endpoint	Study duration
MTX-naïve/free* AMBITION ⁶	673	TCZ monotherapy vs MTX	Signs and symptoms	6 months +LTE
MTX-IR† OPTION ⁷	623	TCZ + MTX vs MTX	Signs and symptoms	6 months +LTE
MTX-IR† LITHE ⁸	1190	TCZ + MTX vs MTX	Prevention of joint damage Improvement in physical function and disability	2 years + 3 year extension
csDMARD-IR‡ TOWARD ⁹	1220	TCZ + DMARD vs DMARD	Signs and symptoms	6 months +LTE
Anti-TNF-IR§ RADIATE ¹⁰	499	TCZ + MTX vs MTX	Signs and symptoms	6 months +LTE
Total	4205			

AMBITION is a comparison of TCZ monotherapy versus MTX monotherapy; in the other studies listed, MTX=placebo (+background MTX)

*MTX-naïve or MTX-free for 6 months before randomisation.

†MTX-IR is patients with an inadequate response to MTX.

‡csDMARD-IR is patients with an inadequate response to ≥ 1 csDMARD.

§Anti-TNF-IR is patients with an inadequate response to ≥ 1 TNF inhibitor.

DMARD, disease modifying anti-rheumatic drug; LTE, long term extension; MTX, methotrexate; TCZ, tocilizumab; TNF, tumour necrosis factor.

higher in both tocilizumab arms compared with methotrexate alone, but only combination therapy was statistically superior to methotrexate alone for most secondary endpoints including ACR20, 50, and 70 response rates (tocilizumab monotherapy achieved numerically, but not statistically significantly, higher response rates).¹⁶

Considering endpoints including acute phase reactants

In the light of the FUNCTION results, it is of interest to compare DAS28 remission and ACR responses for therapies with different mechanisms of action. For example, with drugs that do not interfere directly with the

acute phase response, such as abatacept (a T cell co-stimulation inhibitor) and rituximab (a B cell depleting agent), DAS28 remission occurs less frequently than ACR50 or ACR70 responses.^{17,18} However, with the IL-6 receptor inhibitor tocilizumab, DAS28 remission was more frequent than ACR70 response in OPTION and even more frequent than ACR50 in RADIATE.^{7,10} This has also sometimes been seen with TNF inhibitors, such as in the COMET trial in early rheumatoid arthritis.¹⁹ This may equate to the TNF control of IL-6 expression.

It is self-evident that a measure allowing remission to be more frequent than a 70% (or even a 50%) improvement in response cannot be considered

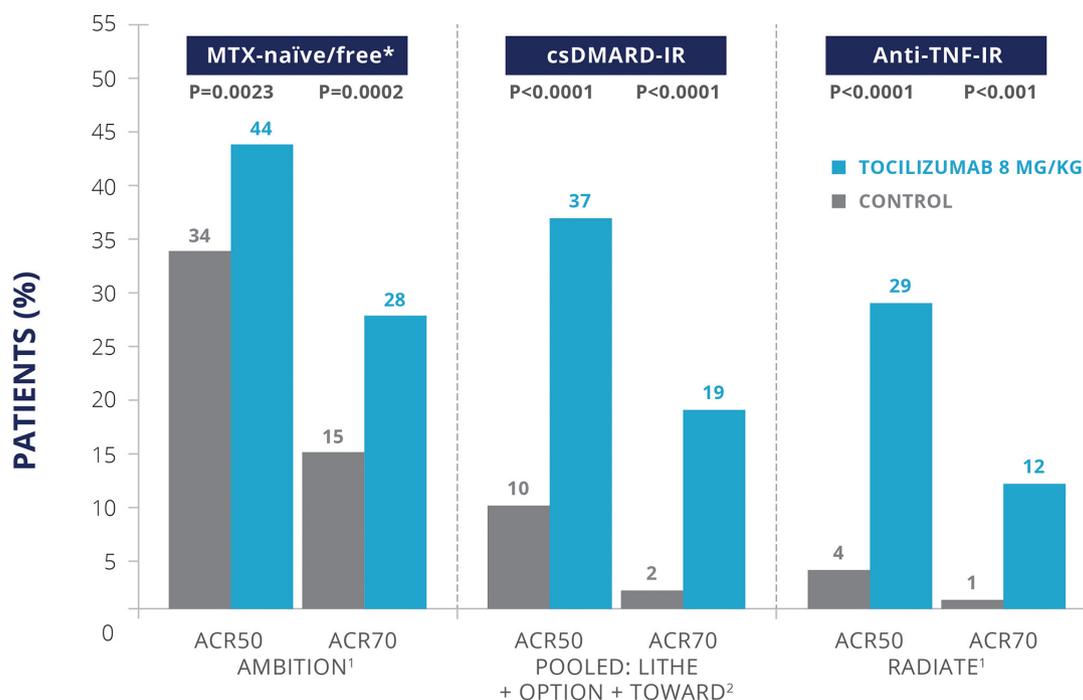


Figure 1 Tocilizumab ACR50 and ACR70 response rates at week 24.^{6,10,11} *MTX-naïve or MTX-free for 6 months before randomisation. DMARD-IR, disease modifying anti-rheumatic drug inadequate responders; TNF-IR, tumour necrosis factor inadequate responders.

$$\text{DAS28} = (0.56 \times \sqrt{\text{TJC}}) + (0.28 \times \sqrt{\text{SJC}}) + (0.70 \times \ln\text{ESR}) + (0.014 \times \text{GH})$$

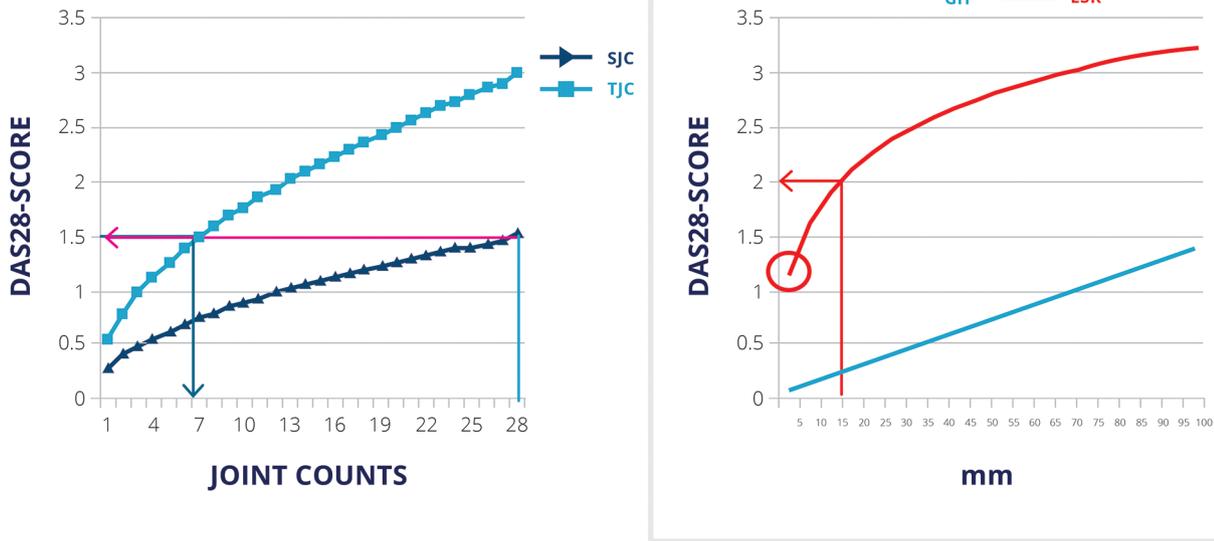


Figure 2 Problems with DAS28: contribution of individual variables across their whole respective range to the DAS28.^{20 21} ESR, erythrocyte sedimentation rate; GH, general health or patient's global assessment of disease activity on a 100 mm visual analogue scale; SJC, swollen joint count; TJC, tender joint count.

a valid endpoint for true remission. In clinical practice, such a measure could lead to therapy being stopped in patients with high residual disease activity. In this regard, it is essential to consider how the DAS28 score is determined. For example, the tender joint count is weighted twice as heavily as the swollen joint count.²⁰ However, joint damage is associated more with swollen than tender joints. Similarly, erythrocyte sedimentation rate (ESR) is also highly weighted in the equation, such that an ESR at the upper limit of normal (20 mm/h) contributes two points, which is more than the contribution of 28 swollen joints.²¹ Importantly, the curve for ESR is steepest in the normal range (figure 2). Thus, it is essential to reflect on both the DAS28 score and the individual variables contributing to the overall clinical assessment when deciding on endpoints in clinical trials and practice.

An analysis of patients in the tocilizumab clinical trials illustrates the problem.^{22 23} The 270 patients in the phase III studies who were in DAS28 remission were separated into those with CDAI remission, low disease activity (LDA), and moderate disease activity (MDA). While in patients with DAS28 remission exhibiting CDAI-MDA the tender joint count was approximately two, the swollen joint count was, on average, approximately 6, which is very high for patients to be in true remission (as defined by the term 'DAS28 remission'). The reason for this is that the ESR was approximately 6 mm/h in patients in CDAI remission but 2 mm/h in those with MDA. This small deviation within the normal range masks the relevance of the six swollen joints in the clinical assessment and affects the DAS28 definition for 'remission.' CDAI is thus a more appropriate measure than DAS28 when looking at the effect of IL-6-directed inhibitors. This also has implications for choice of measures in treat-to-target strategies.

Another phenomenon is seen when looking at DAS28 remission with JAK inhibitors. In this case, DAS28(CRP) remission occurs more than three times more frequently than DAS28(ESR) remission owing to different effects of JAK inhibition on CRP and ESR.²⁴ This may be due to inhibition of JAK-2 as well as JAK-1, resulting in a lack of improvement in haemoglobin in some patients, with ESR remaining high.

Considering sarilumab

Sarilumab is a human monoclonal antibody against the IL-6 receptor. A phase II study showed suppression of CRP concentrations with higher doses of sarilumab.²⁵ MOBILITY was a phase III study in which 1197 patients with moderate to severe rheumatoid arthritis (duration approximately 9 years) and an inadequate response to methotrexate were randomised to subcutaneous sarilumab 150 or 200 mg or placebo in combination with methotrexate for 52 weeks.²⁶ Both doses of sarilumab achieved significantly higher ACR20, 50, and 70 responses at weeks 24 and 52 versus placebo, with some suggestion of a dose response (figure 3). Radiographic changes were also assessed, and progression of joint damage was significantly reduced by sarilumab, again with a suggestion of a dose response.

The TARGET study evaluated the safety and efficacy of sarilumab plus csDMARD in 546 adults with active, moderate to severe rheumatoid arthritis with an inadequate response to or intolerance of at least one TNF inhibitor.²⁷ As expected in this population, the ACR response rates were slightly lower than in MOBILITY. ACR20 response rates at week 24 were 33.7% for placebo, 55.8% for sarilumab 150 mg every other week, and 60.9% for sarilumab 200 mg every other week (both $P < 0.001$ versus placebo); ACR50 responses were 18.2%, 37.0%, and 40.8%, respectively, and ACR70 responses were 7.2%, 19.9%, and 16.3%, respectively. Mean change from baseline in HAQ-DI score at week 12 was significantly greater for both sarilumab doses (-0.5 for both) than for placebo (-0.3) ($P < 0.001$), and the incidence of CDAI LDA (CDAI ≤ 10) at week 24 was significantly greater at 32.0% for 150 mg ($P = 0.0019$) and 35.3% for 200 mg ($P = 0.0001$), compared with 18.2% for placebo.²⁷ In terms of safety, the profile was similar to that seen for tocilizumab, with a slight increase in liver enzymes, increases in lipid levels, occurrence of leucopenia in a proportion of patients (14%), and occasional thrombocytopenia.

Finally, the MONARCH study looked at monotherapy with sarilumab versus adalimumab.²⁸ As was seen with tocilizumab, the response rates were significantly higher with sarilumab monotherapy than with adalimumab monotherapy (figure 4).

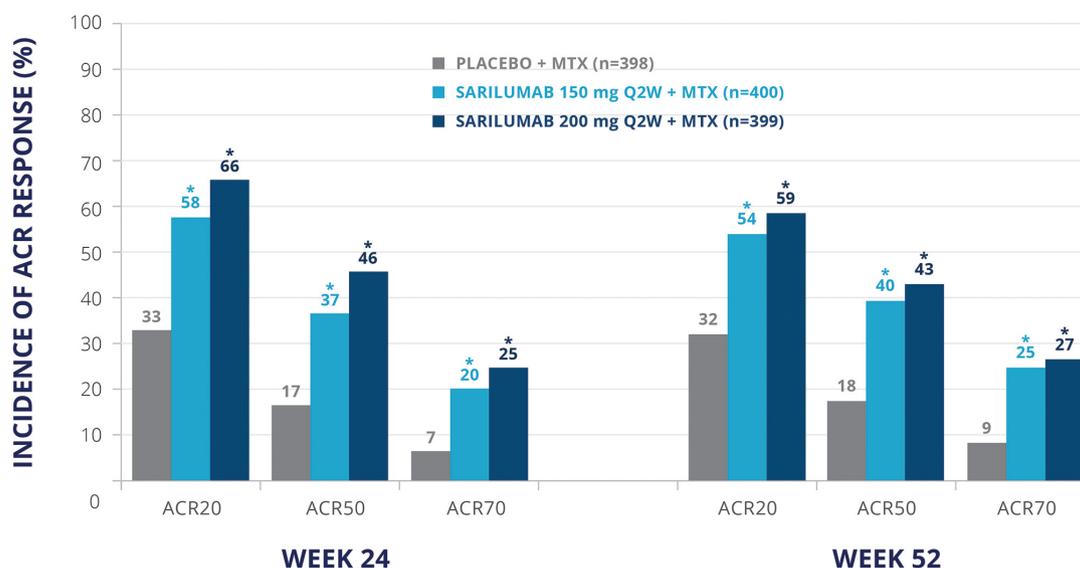


Figure 3 MOBILITY: ACR20 co-primary endpoint at week 24.²⁶ Patients aged 18–75 years who fulfilled the 1987 ACR revised criteria for rheumatoid arthritis and had active rheumatoid arthritis with diagnosis for ≥ 3 months despite MTX treatment. Rheumatoid arthritis as defined by swollen joint count ≥ 6 (out of 66), tender joint count ≥ 8 (out of 68), and high sensitivity CRP ≥ 0.6 mg/dL (upper limit of normal < 0.6 mg/dL) * $P < 0.0001$ vs placebo + MTX (results based on non-responder imputation). MTX, methotrexate; Q2W, every two weeks.

CONSIDERING ANTI-IL-6 ANTIBODIES

Considering olokizumab and clazakizumab

To date, only phase II data are available for olokizumab and clazakizumab, which are both humanised monoclonal antibodies against IL-6. In a phase IIb study of olokizumab 60, 120, or 240 mg every 2 or 4 weeks in patients with rheumatoid arthritis with an inadequate response to TNF inhibitors, decreases from baseline in DAS28(CRP) were observed from week 1. There was some indication of a dose response, with the higher doses achieving a decrease in DAS28(CRP) comparable to that seen with tocilizumab 8 mg/kg every 4 weeks.²⁹ Another phase II study in Japan looked at 60, 120, and 240 mg doses of olokizumab every 4 weeks compared with placebo in 119 patients with rheumatoid arthritis who had responded inadequately to TNF inhibitors.³⁰ The baseline HAQ-DI score in this study was lower than is usually seen, with an overall median of 1.13. ACR response rates at week 12 were higher in the olokizumab treatment groups than with placebo, with all cumulative doses showing significant improvements. Safety data were similar to the anti-IL-6 receptor data. Olokizumab is now in phase III studies.

In a phase IIb study, various doses of clazakizumab from 25 mg to 200 mg, with or without methotrexate, led to ACR20 responses at week 12 varying between 55% and 76% (compared with 39% for placebo and 76% for adalimumab plus methotrexate), with no clear dose-response pattern.³¹ The safety data at this stage looked similar to those for the anti-IL-6 receptor agents.

Considering sirukumab

Sirukumab is a human anti-IL-6 monoclonal antibody that has completed phase III. Two of the phase III studies were SIRROUND-D in patients with an inadequate response to methotrexate and SIRROUND-T in patients with an inadequate response to TNF inhibitors. The baseline characteristics in SIRROUND-D were similar to previous trials in the same type of population.³² At week 16, the ACR20 response was 55% for a sirukumab dose of 50 mg every 4 weeks and 54% for 100 mg every 2 weeks, compared with 26% for placebo (both $P < 0.001$). ACR50 responses at week 24 were 30.2%, 33.2%, and 12.4%, respectively, and the proportions of patients with CDALDA at week 24 were 29.4%, 30.2%, and 15.5%, respectively (all $P < 0.001$ for sirukumab versus placebo). Mean change from baseline in HAQ-DI at

week 24 was also significant ($P < 0.001$) for both sirukumab doses (-0.43 for 50 mg every 4 weeks and -0.46 for 100 mg every 2 weeks, compared with -0.22 for placebo). Radiographic data show that progression of joint damage was almost halted in patients receiving sirukumab (figure 5).³⁰ While various aspects of the safety profile were in line with the known adverse event profile for IL-6 receptor inhibitors, there was an imbalance in deaths between placebo and sirukumab-treated patients, necessitating further prospective investigations.^{32–34} Therefore, the decision was made to stop development of the drug.^{35 36}

SIRROUND-T randomised 878 patients refractory to TNF inhibitor (TNFi) therapy (lack of benefit from ≥ 1 or intolerance to ≥ 2 TNF inhibitors) to sirukumab 50 mg every 4 weeks or 100 mg every 2 weeks versus placebo.³³ Patients continued any csDMARDs if they had been taking a stable dose for at least 4 weeks; previous exposure to non-TNFi biologics, including tocilizumab, was allowed. Overall, 27% of patients had received 3 or more previous biologics, 88% had discontinued TNF inhibitor therapy because of a lack of efficacy, and 19% were not taking a csDMARD at baseline. Approximately 12% of patients had previously taken tocilizumab. ACR responses were slightly lower than was seen in some of the studies of similar rheumatoid arthritis populations described for the other agents above, possibly owing to a relatively high proportion of patients not taking methotrexate or another csDMARD; ACR20 responses at week 24 were 42.8% for both sirukumab doses compared with 25.9% for placebo ($P < 0.001$). ACR50 and 70 responses, respectively, were 8.8% and 4.1% for placebo, 20.9% and 8.6% for sirukumab 50 mg every 4 weeks, and 21.6% and 9.9% for sirukumab 100 mg every 2 weeks.³³ Mean change from baseline in HAQ-DI at week 24 was -0.125 for placebo, -0.314 for sirukumab 50 mg every 4 weeks, and -0.329 for sirukumab 100 mg every 2 weeks (both $P < 0.001$ versus placebo). The safety profile was as expected, with some abnormalities in liver enzymes, haematology results, and lipids but no apparent relation to dose. However, while there were no deaths in any arm the first 24 weeks, the placebo-controlled phase, five deaths occurred in the subsequent 24 weeks, a finding that suggested some potential imbalance similar to the SIRROUND-D trial.

As previously mentioned, sirukumab development and registration has been halted following negative review from the FDA.

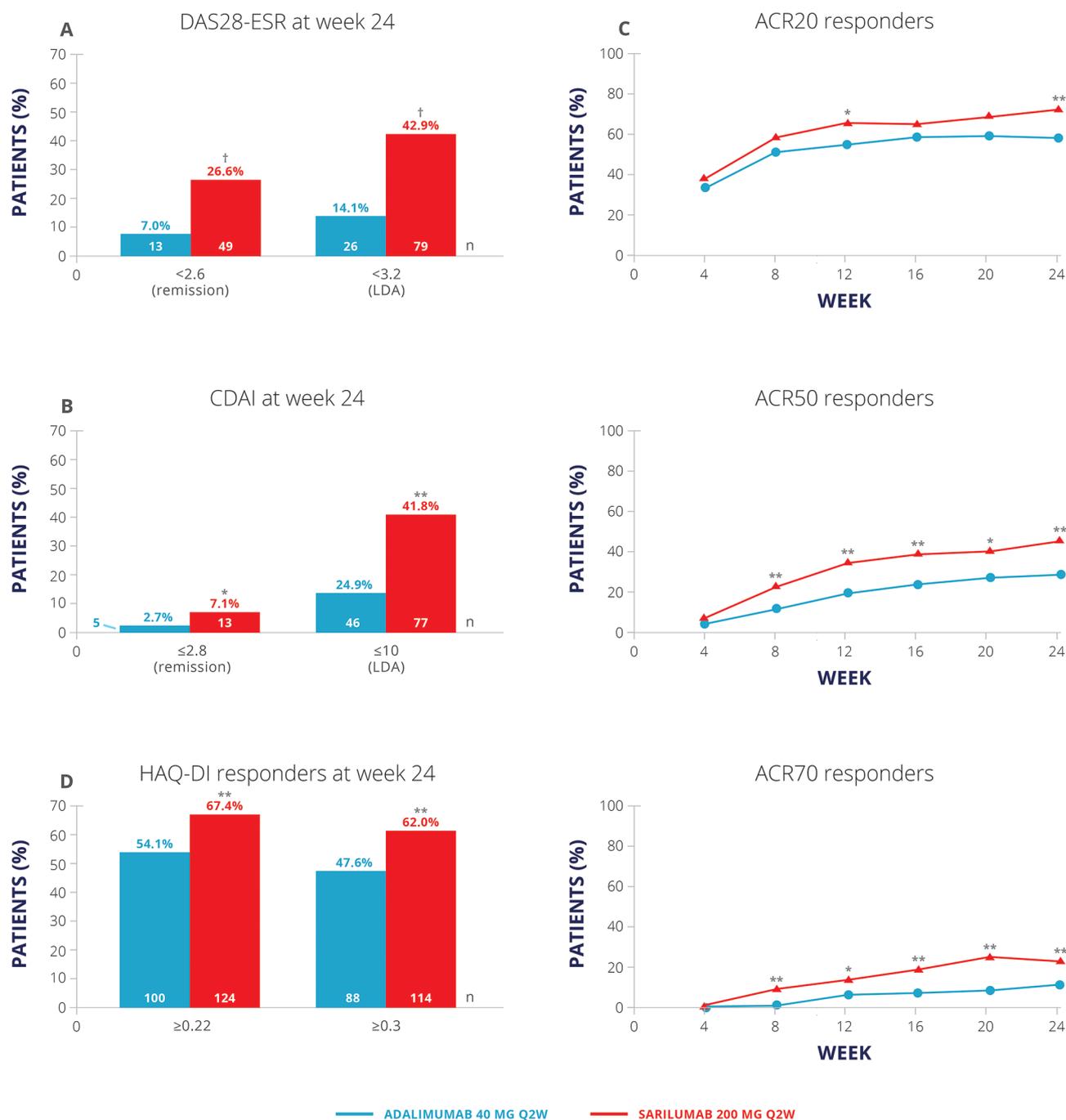


Figure 4 MONARCH: sarilumab versus adalimumab monotherapy.²⁸ Incidence of (A) DAS28-ESR remission or LDA, (B) ACR20, ACR50 and ACR70 response from weeks 4 to 24, (C) CDAI remission or LDA and (D) HAQ-DI responders achieving ≥ 0.22 or ≥ 0.3 units of improvement in patients receiving adalimumab 40 mg q2w or sarilumab 200 mg q2w. * $p < 0.05$ versus adalimumab; ** $p < 0.01$ versus adalimumab (CAI and HAQ-DI responders at week 24 are nominal p values); † $p < 0.0001$ versus adalimumab. ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; DAS28-ESR, 28-joint disease activity score using erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDA, low disease activity; q2w, every 2 weeks.

CONSIDERING THERAPEUTIC STRATEGIES

The newly updated EULAR recommendations for the management of rheumatoid arthritis state that biological DMARDs (bDMARDs) and targeted synthetic DMARDs should be combined with csDMARDs. However, they also state (with a high level of evidence) that in patients who cannot use csDMARDs as co-medication, IL-6 pathway inhibitors and targeted synthetic DMARDs may have some advantages over other bDMARDs.³⁷ The data reviewed in this article show that the anti-IL-6 receptor/ligand agents are, at

least numerically and often also statistically, more effective when combined with methotrexate, and the same is true for targeted synthetic DMARDs such as the JAK inhibitors. However, tocilizumab and sarilumab have been shown to be superior to TNF inhibition when the drugs are used as monotherapy, so these agents have an advantage in patients who cannot use methotrexate or another csDMARD.^{15,28}

Methotrexate seems important in adding to the efficacy of various drug classes in rheumatoid arthritis. For example, pharmacodynamic

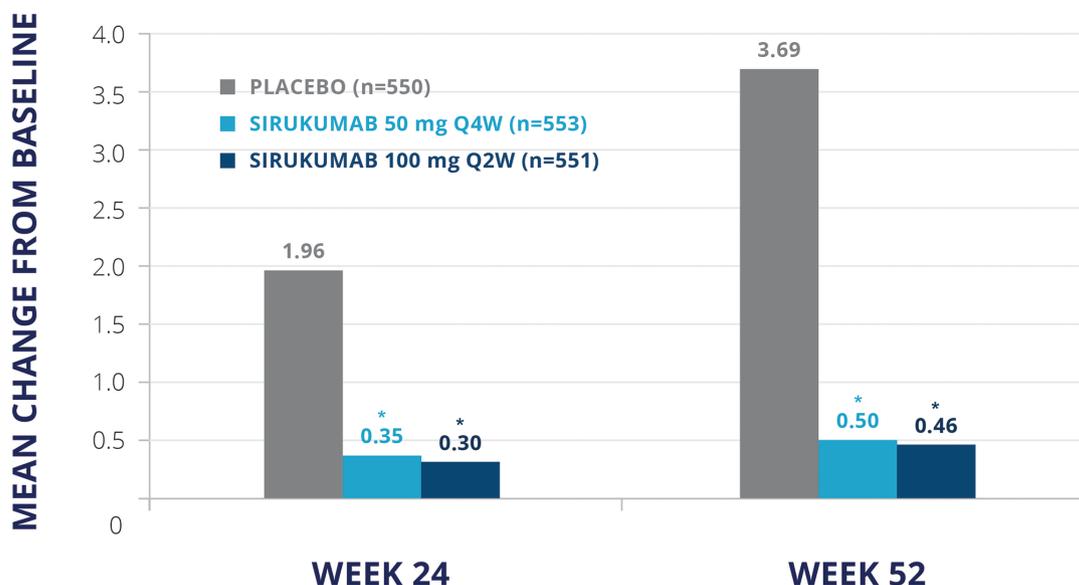


Figure 5 Change from baseline in Sharp/van der Heijde score results at weeks 24 and 52.³² * $P < 0.001$ versus placebo based on Van Der Waerden analysis of variance. q2w, every two weeks; q4w, every four weeks.

interactions prevent antidrug antibody formation when methotrexate is combined with a TNF inhibitor monoclonal antibody. However, methotrexate may also cover aspects not optimally targeted by individual biologics, such as messenger molecules that are not targeted by currently used anti-cytokine bDMARDs. It may also have some effect through interference with the IL-1 receptor and has recently been shown to interfere with the JAK/STAT pathway.³⁸

It will be interesting in the future to see head-to-head studies to determine whether inhibition of the JAK pathway is similar in its overall efficacy to direct inhibition of IL-6 or its receptor. One difference observed is that currently approved JAK inhibitors do not usually improve anaemia, probably owing to interference with JAK2.

With any biologic, the best predictor of long-term response appears to be early response. It is also the case that patients with high TNF concentrations need higher doses of TNF inhibitors to achieve a good response.³⁹ Similarly, it seems that the amount of IL-6 receptor is correlated with response to IL-6 inhibitors, with a lower response in patients with higher receptor concentrations. We note that higher doses of TNF inhibitors are used in gastroenterology than in rheumatology, and seem to be well tolerated, so there may be a case for trying higher doses of some biologics in patients with an insufficient response to lower doses.

TARGETING IL-6: A REVIEW OF THE DATA—A SUMMARY

Targeting the IL-6 pathway is not a new approach—although the anti-IL-6 receptor inhibitor sarilumab and the IL-6 signal transduction inhibitors tofacitinib and baricitinib have recently been approved, the anti-IL-6 receptor inhibitor tocilizumab has been licensed for nearly 10 years. Anti-IL-6 ligand antibodies have now also been developed with apparent similar efficacy to blocking the IL-6 receptor. Of importance to those patients who cannot use methotrexate or other csDMARDs, a review of the data suggests that anti-IL-6 pathway agents seem to be more effective as monotherapy than TNF inhibitors. However, when reviewing the data with respect to the overall clinical assessment, the disease score and its contributing parameters should be considered to ensure that valid endpoints are used.

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