Sarilumab: a new IL-6 receptor blocker for rheumatoid arthritis

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Sarilumab (Kevzara) is the second monoclonal antibody against the IL-6 receptor to be licensed for the treatment of rheumatoid arthritis. This article examines its indications, efficacy and adverse effects.

Of the eight biological DMARDs licensed for the treatment of rheumatoid arthritis, five act by inhibiting TNF alpha (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), one modulates the activity of T cells (abatacept), one depletes B cells (rituximab) and one (tocilizumab) inhibits the activity of interleukin-6 (IL-6). All have been recommended by NICE for severe active disease in patients whose disease is not controlled using conventional DMARDs.1,2

Sarilumab (Kevzara) is a recombinant human monoclonal antibody. Like tocilizumab, it binds to soluble and membrane-bound IL-6 receptors and inhibits IL-6-mediated signalling. The pro-inflammatory cytokine IL-6 is produced by several cell types and, like TNF alpha, appears to have multiple roles in the pathogenesis of rheumatoid arthritis.

Indications and dosage
Sarilumab is licensed, in combination with methotrexate, for the treatment of moderately to severely active rheumatoid arthritis in adults who have responded inadequately to or who are intolerant to one or more DMARDs; and as monotherapy when methotrexate is not tolerated or not appropriate.

Sarilumab is administered as a subcutaneous injection of 200mg once every two weeks, reducing to 150mg every two weeks if neutropenia, thrombocytopenia or liver enzyme elevation occur. Treatment should not be initiated in patients with serious infection, or those with low neutrophil or platelet counts. No dose adjustment is recommended for elderly people or in patients with mild to moderate renal impairment. Sarilumab has not been evaluated in patients with hepatic impairment or severe renal impairment.

NICE has now recommended sarilumab in combination with methotrexate, as an option for severe active rheumatoid arthritis in adults whose disease has responded inadequately to intensive therapy with a combination of conventional DMARDs.3 Severe disease is defined as a disease activity score (DAS28) of more than 5.1. Sarilumab is also recommended with methotrexate in adults with severe active disease who have responded inadequately to, or who cannot take, other DMARDs, including at least one biological DMARD, and who cannot take rituximab. NICE adds that sarilumab can be used as monotherapy in patients who cannot take methotrexate because of a contraindication or intolerance.

KEY POINTS

- Sarilumab is, like tocilizumab, a human monoclonal antibody against the IL-6 receptor
- It is licensed, in combination with methotrexate, for the treatment of moderately to severely active rheumatoid arthritis in adults who have responded inadequately to or who are intolerant to DMARDs, and as monotherapy when methotrexate is unsuitable
- Compared with a conventional DMARD alone, and including patients unable to take a TNF inhibitor, adding sarilumab approximately doubles the response rate
- In one 24-week trial, sarilumab was more effective than adalimumab after failure of conventional DMARDs
- Common adverse effects include infection, neutropenia, thrombocytopenia, dyslipidaemia and elevated transaminases
- A year’s treatment costs approximately £11,900
Treatment should be continued only if there is at least a moderate response, as measured using the European League Against Rheumatism (EULAR) criteria at six months after starting therapy, or if the response to therapy is not maintained.

**Clinical trials**

Three phase 3 trials provide the key data for sarilumab. The MOBILITY trial randomised 1197 patients with moderate to severe active rheumatoid arthritis despite treatment with methotrexate to receive methotrexate plus sarilumab 150mg or 200mg fortnightly or methotrexate plus placebo. Patients who had previously not responded to treatment with a biological DMARD were excluded. The primary endpoints were the ACR20 response (the proportion of patients meeting American College of Rheumatology criteria for 20% improvement in disease activity) after 24 weeks; change in physical function measured by the Health Assessment Questionnaire disability index after 16 weeks; and change in radiographic joint damage at week 52.

Mean duration of rheumatoid arthritis was about nine years and mean disease activity score (DAS28) was approximately 6.0. Compared with methotrexate plus placebo, methotrexate plus sarilumab significantly increased the proportion of patients with ACR20 response at 24 weeks (66% and 58% with 200mg and 150mg sarilumab vs 33% with placebo; \( p < 0.0001 \)). Though responses were slightly diminished after 52 weeks (see Figure 1), treatment was associated with a significant improvement in physical activity and a significant reduction in radiographic progression (proportions with no progression at 52 weeks were 56% and 48% with 200mg and 150mg sarilumab vs 39% with placebo).

In TARGET, 546 patients with moderate to severe active rheumatoid arthritis after inadequate response or intolerance to TNF inhibitor therapy were randomised to receive sarilumab 150mg, sarilumab 200mg or placebo combined with conventional DMARD therapy (85% methotrexate). The primary endpoints were ACR20 response at 24 weeks and change in disability index after 12 weeks.

Mean duration of rheumatoid arthritis was about 12 years and mean DAS28 score was 6.2. More patients treated with sarilumab met ACR20 response criteria (61% and 56% with 200mg and 150mg sarilumab vs 34% with placebo; \( p < 0.0001 \)) and disability index improved significantly with both doses compared with placebo.

The MONARCH trial compared monotherapy with sarilumab 200mg or adalimumab 40mg, both given every two weeks, in 369 patients with moderate to severe active rheumatoid arthritis for whom methotrexate was discontinued due to intolerance or inadequate response. The primary efficacy endpoint was change in DAS28 at week 24 (in this study, DAS28 was assessed using the erythrocyte sedimentation rate [DAS28-ESR], which yields a higher score than when C-reactive protein (CRP) is used, as was the case in MOBILITY and TARGET).

Mean duration of rheumatoid was lower in patients assigned to adalimumab (6.6 vs 8.1 years); mean DAS28-ESR score was 6.8 (mean DAS28-CRP score was 6.0). About 55% of patients

![Figure 1. Improvement in rheumatoid arthritis disease activity over one year with methotrexate plus sarilumab vs methotrexate plus placebo, as measured by ACR20 response, in the MOBILITY trial](image1)

![Figure 2. Least squares (LS) mean change from baseline in disease activity score (DAS28-ESR) at 12 and 24 weeks with sarilumab vs adalimumab in the MONARCH trial](image2)
had previously stopped methotrexate due to inadequate effectiveness and 45% due to intolerance. Fewer patients assigned to sarilumab discontinued treatment (10% vs 15% with adalimumab).

After 24 weeks, the reduction in DAS28-ESR was significantly greater with sarilumab than adalimumab (-3.28 vs -2.20; p<0.0001) (see Figure 2) and more patients were in remission (DAS28-ESR <2.6) by this measure (27% vs 7.0%; p<0.0001). This was matched by changes in DAS28-CRP. The 24-week ACR20 response, a secondary endpoint, was significantly greater with sarilumab (72% vs 58%, p=0.0074).

**Adverse effects**

Treatment with sarilumab is associated with increased incidence of infections (including serious infections), neutropenia, thrombocytopenia, elevated transaminases, dyslipidaemia and injection-site reactions. In the MONARCH trial, adverse events more frequently associated with sarilumab than adalimumab included neutropenia (14% vs 0.5%) and injection-site erythema (7.6% vs 3.3%) but dyslipidaemia was less frequent (1.6% vs 4.3%); the frequencies of serious infections were similar.6

**References**


**Declaration of interests**

None to declare.

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