

New biologics for rheumatoid arthritis

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ABSTRACT Rheumatoid arthritis (RA) is a chronic inflammatory arthritis with many systemic manifestations. Several monoclonal antibodies targeting different components of the immune systems have been licensed for treatment of RA. Inflammatory cytokines such as interleukin-6 (IL-6) are found abundantly in the blood and the joints. The biologic effect of IL-6 on leukocyte, osteoclast, hepatocytes and bone marrow may mediate the articular and systemic inflammation in RA. Recently, an anti-IL-6 receptor monoclonal antibody, tocilizumab, has been licensed for the treatment as monotherapy or in combination with methotrexate of moderate to severe RA, when disease modifying anti-rheumatic drugs or anti-tumour necrosis factors (TNF) have failed. It improves symptoms and signs as well as reducing joint damage. Tocilizumab monotherapy has been shown to be superior to methotrexate. Its side-effects include infections, decrease in neutrophils, and increases in lipid and liver transaminases. Overall, tocilizumab has a well-defined and manageable safety profile that supports a favourable benefit/risk ratio for patients with RA.

KEYWORDS Rheumatoid arthritis, treatment, monoclonal antibody, interleukin-6, tocilizumab

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by inflammation and destruction of synovial joints. Mortality is increased in patients with RA compared with the normal population. National and international guidelines recommend prompt treatment with disease modifying anti-rheumatic drugs (DMARDs) once diagnosis is established to improve symptoms, reduce the risk of joint damage and mortality.

Traditional DMARDs have limited efficacy and frequent side-effects. The introduction of biologics agents in the late 1990s transformed the management of RA. The first biologic agents approved for the treatment of RA were tumour necrosis factor (TNF) inhibitors: etanercept and infliximab. Since then several biologic agents have been approved for the treatment of RA: anakinra, adalimumab, rituximab and abatacept. Recently, three more biologic agents have been licensed for the treatment of RA: two new TNF inhibitors, certolizumab pegol and golimumab, and a new interleukin-6 (IL-6) receptor inhibitor, tocilizumab. The efficacy and safety profile of certolizumab pegol and golimumab are similar to currently available TNF inhibitors. This review will focus on tocilizumab which is the first licensed biologic agent that targets IL-6 signalling.

TABLE 1 Possible role of interleukin-6 in rheumatoid arthritis

Serum levels of interleukin-6 and soluble IL-6R correlate with disease activity ³⁻⁵
IL-6 increases auto-antibody production through B-cell differentiation and maturation ⁶
Stimulates proliferation and differentiation of T-cells to cytotoxic T-cells ⁶
Increases migration and survival of neutrophil leucocytes ⁷
Stimulates the liver to release acute phase reactants such as C-reactive protein ⁶
Promotes pannus formation through increased production of vascular endothelial growth factor ⁸
Increases osteoclast maturation ⁶
Increases hepcidin production by hepatocytes, which inhibits the transfer of iron from the depots to the bone marrow, thereby causing anaemia ⁹

TOCILIZUMAB

Tocilizumab is a humanised IL-6 receptor monoclonal antibody that inhibits IL-6-anti-mediated signalling.¹ It is administered as intravenous infusion 8 mg/kg every four weeks. Tocilizumab is licensed for the treatment of RA both as monotherapy or in combination with methotrexate.

The role of IL-6 in RA

Interleukin-6 binds to IL-6 receptor (IL-6R) and the complex induces cellular activation through another cell surface molecule, gp130. Both membrane and soluble IL-6 receptor (sIL-6R) can bind to IL-6 to cause cellular activation.² Hence interleukin-6R is a therapeutic target. IL-6 is a cytokine that has diverse immunologic and inflammatory effects including T-cell activation, B-cell maturation, induction of acute phase response and stimulation of haematopoietic precursor cell growth factors.¹ Many of the articular and systemic manifestations of RA can be attributed to the biologic effects of IL-6 (see Table 1).

EFFICACY OF TOCILIZUMAB

Tocilizumab monotherapy

A 24-week double-blind, placebo control trial in 673 patients with RA compared tocilizumab monotherapy 8 mg/kg with oral methotrexate (target dose 20 mg/week).¹⁰ Significantly more patients treated with tocilizumab monotherapy achieved an American College of Rheumatology (ACR)20 response (69.9% versus 52.5%), or ACR50 (44.1% versus 33.5%) and ACR70 responses (28% versus 15.1%) compared with methotrexate-treated patients.

A phase III randomised, open-label control trial conducted in Japan examined the effect of tocilizumab monotherapy on joint damage in 306 patients with RA.¹¹ Patients were randomised to receive either 8 mg/kg tocilizumab or conventional DMARDs. Radiographs of hands and forefeet were evaluated by an assessor blinded to the treatment allocation. Patients in the tocilizumab group showed statistically significantly less progression in joint destruction as assessed by the van Der Heijde Modified Sharp Score (mean 2.3) than the DMARD group (mean 6.1).

Tocilizumab combination with methotrexate/DMARD

The OPTION trial was a phase III double blind placebo control trial which evaluated the clinical efficacy of tocilizumab in combination with methotrexate in 623 patients with active RA.¹² Patients who had active disease despite methotrexate were randomised to receive either placebo, 4 or 8 mg/kg of tocilizumab given four-weekly in addition. An ACR20 response was observed in 59%, 48% and 27% of patients receiving tocilizumab 8 mg/kg, 4 mg/kg and placebo respectively. Both ACR50 and ACR70 responses and reduction in FACIT-Fatigue score were also significantly superior in the tocilizumab-treated patients compared with placebo. C-reactive protein (CRP) levels dropped to the normal range after treatment in the 8 mg/kg group.

The LITHE trial is identical in design to OPTION but extends treatment to 52 weeks and one of its primary endpoints was to assess the effect of tocilizumab and methotrexate on radiographic joint damage.¹³ A total of

1,196 patients with partial responses to methotrexate were recruited. Clinical response (as assessed by the ACR response) was similar to those observed in the OPTION trial, with superior ACR responses observed in the tocilizumab 4 and 8 mg/kg groups compared with placebo. Patients treated with tocilizumab 4 or 8 mg/kg had less progression in radiographic joint damage compared with the control group.

TOWARD was a phase III trial similar in design to OPTION except it recruited 1,216 patients with active RA taking a range of DMARDs, and patients were randomised to receive either tocilizumab 8 mg/kg or placebo.¹⁴ At 24 weeks, statistically significant differences in ACR20, 50 and 70 responses were seen in the tocilizumab group in 60.8%, 37.5% and 20.5% versus 24.5%, 9% and 3% in the placebo group.

The efficacy of tocilizumab plus methotrexate in patients with inadequate response to TNF- α inhibitor was evaluated in the RADIATE trial. In this double-blind, randomised, placebo-controlled trial, 499 patients with inadequate responses to at least one TNF- α inhibitor were randomised to either treatment by tocilizumab 4 mg/kg, 8 mg/kg or placebo in combination with methotrexate.¹⁵ After 24 weeks, 50% of the patients treated with tocilizumab 8 mg/kg achieved ACR20 responses compared with 30.4% in the tocilizumab 4 mg/kg group, and 10.1% in the placebo group. Interestingly, ACR20 response was comparable regardless of the number of previously failed TNF- α inhibitors.

ADVERSE EVENTS WITH TOCILIZUMAB

In phase III randomised control trials, several adverse events were associated with tocilizumab treatment. These include infusion reactions, infection, neutropenia, increase in transaminases and lipids. A pooled analysis from three 24-week phase III randomised control trials¹⁶ reviewed a frequency of infusion reaction of 6 and 1 per 100 patient years (pyr) with combination therapy and monotherapy respectively. In 3,857 patients who enrolled into long-term safety studies, the infusion related adverse reaction was similar (5.7/100 pyr).¹⁶

Infection

Infection is always a potential risk with any immunomodulatory treatment. However, the range of the infections with IL-6 inhibition may well be quite different from TNF blockade especially related to reactivation of tuberculosis (TB), because the two biologics target different immune pathways. In the phase III OPTION trial, frequency of serious infection was slightly increased (2.9%) in the 8 mg/kg group compared with placebo (1%).¹² In a pool analysis of phase III trials and long-term extension study involving 4,009 patients and total treatment exposure of 9,414 pt-years (pyr), rate of serious infection was slightly increased, 4.7 pyr (95% CI: 4.2, 5.1), which is similar to other biologic agents. This did

not increase with long-term exposure (4.7/100 pyr).¹⁶ Cases of *Mycobacterium tuberculosis* infection have been reported in patients treated with tocilizumab. Therefore vigilance, screening and monitoring for infection are necessary in all patients treated with tocilizumab.

Abnormal liver function test

Elevation of liver transaminases occurred especially when tocilizumab was used in combination with other DMARDs. In the monotherapy trial, no major differences were seen between tocilizumab 8 mg/kg and the methotrexate group.¹⁰ In pooled analysis of phase III studies, the incidences of alanine transaminase (ALT) and aspartate transaminase (AST) elevations >3x the upper limit of normal were 3.6% and 1.4%, respectively, during the first 24 weeks of treatment, and the rates did not increase over time.¹⁶ Monitoring of liver transaminases is necessary for patients receiving tocilizumab therapy particularly in combination with DMARD (especially methotrexate). Patients with persistent elevated transaminases (>3x upper limit of normal) should discontinue or reduce the dose of either DMARD or tocilizumab treatment.

Neutropenia

In long-term follow-up studies, clinically significant neutropenia (absolute neutrophil count <1.0x 10⁹/l, grades 3 and 4) during at least one visit occurred in 156 of 3,857 patients (4.0%) (grade 3, n=139; grade 4, n=17).¹⁷ Grade 3–4 neutropenia was reversible with tocilizumab interruption. Hence white cell and neutrophil count

should be monitored in patients receiving tocilizumab therapy. In patients who developed grade 3 or 4 neutropenia, tocilizumab and/or concomitant methotrexate therapy should be withdrawn.

Elevation in lipids

Increase in lipid levels after tocilizumab therapy is common, and patients should have lipids performed before and after therapy.¹⁸ Elevations in lipid levels decreased with treatment by statin.¹⁹ The pattern may be different from that typically seen in dyslipidemia where increases in low-density lipoprotein cholesterol (LDL-C) and decreases in high-density lipoprotein cholesterol (HDL-C) are typically observed. In phase III trial of tocilizumab, elevations were seen in both LDL-C and HDL-C. Rates of myocardial infarction/stroke were comparable with those reported for RA patients receiving biologics (<0.5 per 100 pyr) and remained stable over time.¹⁶ Again the clinical relevance of increased lipid levels after tocilizumab treatment will need to be addressed by further large scale follow-up studies.

SUMMARY

Tocilizumab monotherapy or in combination with methotrexate is an effective treatment for active RA. However, careful clinical and laboratory monitoring of patients is needed. Overall, tocilizumab has a well-defined and manageable safety profile that supports a favourable benefit/risk ratio for patients with RA.

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SELF-ASSESSMENT QUESTIONS

1. Which of the following statements about tocilizumab is correct?

- A. It is a monoclonal antibody against TNF α .
- B. It is a monoclonal antibody against TNF α receptor.
- C. It is a monoclonal antibody against interleukin-6.
- D. It is a monoclonal antibody against interleukin-6 receptor.
- E. It is a monoclonal antibody against B cells.

2. In rheumatoid arthritis, interleukin-6

- A. Stimulates the liver to produce C reactive protein.
- B. Stimulates production of haemoglobin.
- C. Promotes maturation of osteoclasts.
- D. Promotes B-cells to mature into plasma cells.
- E. Is elevated in patients with active disease.

3. Which three of the following statements about tocilizumab are correct?

- A. In patients with suboptimal response to methotrexate, adding tocilizumab improves symptoms and signs as well as reduces radiographic joint damage.
- B. Tocilizumab and methotrexate have the same clinical efficacy.
- C. Tocilizumab must be used in combination with methotrexate.
- D. Tocilizumab is an effective treatment for patients who have failed TNF inhibitors.
- E. Tocilizumab has been licensed for the treatment of rheumatoid arthritis refractory to disease-modifying antirheumatic drugs.

4. Which three of the following statements are true about tocilizumab safety data?

- A. Lipid elevations are common.
- B. Neutrophil increase is common.
- C. Transient liver transaminase/alanine transaminase elevations are seen in some patients.
- D. Infection rate is increased in patients taking tocilizumab.
- E. In clinical trials, rate of myocardial infarction and stroke is increased.

5. Patients on tocilizumab should not be treated in the following way:

- A. Before starting therapy, patients should have a liver biopsy.
- B. Blood count, liver enzymes and lipid level should be monitored before and after treatment.
- C. In patients with persistent elevation of liver transaminases $>3 \times$ ULN (upper limit of normal), methotrexate and tocilizumab treatment should be suspended or dose reduced.
- D. Patients with elevated lipids, statin treatment may be appropriate.
- E. Screening for latent tuberculosis should be performed before treatment is instituted.

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