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New insights and long-term safety of tocilizumab in rheumatoid arthritis

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Abstract: Rheumatoid arthritis is a leading musculoskeletal cause of disability in Western society. Therapeutic options have expanded rapidly with the advent of biological agents as treatment options. One of these, tocilizumab, targets the interleukin-6 receptor and has been approved since the late 2000s in many jurisdictions. This approval was based on 6–12 month trials. It is now appropriate to look at longer-term studies and what new insights they have provided into this agent. Data are based largely on observational studies with their well-known limitations as well as some further randomized trials and provide a number of important observations regarding both efficacy and safety. In conclusion, the longer-term data suggest tocilizumab efficacy increases over time for both signs and symptoms and radiographic change. It is also corticosteroid sparing. The safety data are consistent with the shorter-term trials and are largely reassuring but some questions still remain over cardiovascular safety and cancer risk.

Keywords: cohort, database, long term, rheumatoid, tocilizumab, trials

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Introduction

Rheumatoid arthritis (RA) is a relatively common inflammatory arthritis. It is self-reported by 2% of the Australian population (www.aihw.gov.au/report-statistics/rheumatoid-arthritis), and this is similar in other Western countries. It is a serious illness with high rates of pain, disability, comorbidity and higher mortality. Traditionally, RA was treated with anti-inflammatory drugs and disease-modifying antirheumatic drugs (DMARDs). The latter agents were modestly effective at treating symptoms, slowing disease progression and decreasing mortality, and methotrexate became the cornerstone agent.[1] However, there remained a large unmet need in RA. There have been great advances in our understanding of the pathophysiology with the elucidation of many critical cytokine pathways.[2] Many of these have been successfully targeted leading to the development of biological DMARDs, which have become a mainstay of treatment for moderate to severe RA. Tocilizumab is one of these agents and can bind to both soluble interleukin (IL)-6R and transmembrane IL-6R and inhibit IL-6 binding to its receptors, leading to the blockade of the IL-6 signalling through both receptors, but not blocking the signalling of other IL-6 family cytokines.[3] It also blocks the action of IL-6 without increasing the IL-6 half-life.[4]

Tocilizumab was approved based on a suite of placebo-controlled trials initially as an intravenous formulation and then as a subcutaneous formulation.[5] However, these trials tended to enrol otherwise well patients with RA and were not designed to assess long-term efficacy and safety with the longest placebo-controlled trial being 12 months. The aim of this review is to provide an update into new insights into tocilizumab with long-term therapy (defined as greater than 12 months)

We performed a literature search using the terms RA, safety and long term. Papers identified by this search were screened for relevance and then included in this narrative review.

Efficacy

One cannot use long-term open-label studies to determine efficacy for a number of reasons. These

include the lack of a control group and varying numbers due to progressive dropout of those originally enrolled in these studies. However, one can make a number of observations. The first is that generally greater efficacy for signs and symptoms is seen with longer follow up. While this varies in the different studies, efficacy (however defined) appears to plateau around 12–24 months of therapy.[6–9] This is quite different from other biological DMARDs where efficacy appears to peak between 12 weeks and 24 weeks suggesting a longer period of therapy may be warranted in those with a suboptimal initial response. Similar observations have been made with regard to radiographic progression where the rate of change in radiographs becomes indistinguishable from zero in the second year of therapy (despite progressing by a small amount in the first year).[10,11] Given this high rate of remission over time, it may seem desirable to withdraw therapy. However, both total cessation and a decrease in dose[12] have resulted in substantial flare rates within a short timeframe suggesting that this approach is not warranted at this point in time. This increase in flare rate is greater in those on monotherapy compared with those taking tocilizumab and methotrexate.[13] Lastly, it is also clear that higher doses have greater efficacy[5] and most jurisdictions have approved a weekly 162 mg subcutaneous dosing and an 8 mg/kg 4-weekly intravenous dosing. Tocilizumab use also appears to be corticosteroid sparing in long-term studies.[6,14] Kremer and colleagues suggested that stopping methotrexate does not worsen disease control in those on tocilizumab.[15] However, they base this on a predefined limit for noninferiority, but show that those stopping methotrexate have significantly worse disease control even though it is within the margin of noninferiority. A novel recent trial showed that using a second tumour necrosis factor inhibitor (TNFi) worked reasonably well in those with a suboptimal response to the first TNFi, however, changing mode of action to other biological DMARDs (including tocilizumab) was superior for signs and symptoms of RA[16] suggesting this is the preferred approach . Lastly, the presence of rheumatoid factor appears to predict greater efficacy with tocilizumab based on a meta-analysis of clinical trials.[17]

Persistence

In the long-term follow-up studies of patients in trials, very few stopped therapy due to loss of efficacy.[8,9] For example, of those in the Actemra *versus* Methotrexate double-Blind Investigative Trial In mONotherapy (AMBITION) extension (which was a 5-year open-label follow up of those who took part in the original trial), only 1 out of 234 stopped therapy due to loss of response,[8] and these low discontinuation rates were seen regardless of co-therapy. Similar results were observed in the STREAM study.[6] Reasons for this are unclear but may be due partly to the low rate of antibodies observed in many of these studies.[7] It should be noted that there remain technical issues with measurement of these antibodies. Weekly injections seem to have better persistence than fortnightly injections with 25% escaping to weekly injections over 2 years.[11] Database studies also support this implied greater persistence with an Australian study showing higher average duration of use for tocilizumab *versus* TNFi regardless of line of use of therapy.[14] The difference in persistence between mode of action is partly due to the effect of co-therapy. Co-therapy made little difference to tocilizumab persistence but dramatically shortened TNFi persistence if patients were not taking a traditional DMARD with the therapy.[14]

Safety

Longer-term studies are essential to determine safety over time and use in populations at higher risk. The safety profile of tocilizumab is well understood. However, there are some long-term questions.

Cardiovascular disease safety

First, it is well known that tocilizumab increases lipid levels but at the same time decreases C-reactive protein levels. The effect of these on cardiovascular (CV) endpoints is unclear from the clinical trials as there were relatively few events and no long-term follow up. The longer-term open-label studies do not show any trend for an increase in cardiovascular disease (CVD) over time.[6–9] The postmarketing worldwide database actually suggests a decrease in risk over time[18] but these data lack a denominator making it somewhat suspect. A large US study[19] compared risk of CVD in those initiating tocilizumab with those initiating TNFi, which is a nice design as they will have similar RA disease severity. This found a small nonsignificant decrease in CVD risk with tocilizumab (0.84, 95% confidence interval 0.56–1.26) and significant decreases in any CV event and revascularization thus effectively excluding any major increase. The use of statins was common in this cohort but made little difference to

the results if they were excluded. However, the study only followed them for 12 months and our opinion is that much longer studies are still needed to answer this question. Tocilizumab appears to decrease the amount of damage after a coronary event[20] so may limit the size of an infarct if one happens while on therapy.

Infections

Tocilizumab increases the risk of some infections. A meta-analysis of the trials[21] suggested a higher rate of infection with tocilizumab but only when combined with methotrexate. This was not significant for monotherapy. There was an approximate doubling or risk for serious infections with or without methotrexate but this did not reach statistical significance. A UK database study also found a slight but significantly higher rate of serious infection with tocilizumab compared with etanercept.[22] A US study showed no difference in the rate of hospitalization for infection with tocilizumab.[23] Infection rates stay stable in many of the long-term extension studies (where there is no control group),[6,8,9] but again appears to decrease in the postmarketing data.[16] A French database attempted to identify risk factors for infection in those using tocilizumab.[24] Significant factors increasing infection risk included a higher disease activity score in 28 joints, negative anti-citrullinated protein antibodies (ACPA), a neutrophil count greater than five prior to starting therapy and leflunomide co-therapy (risk ration [RR] 2.18). Clinically it is the last of these that is important and suggests caution when using both leflunomide and tocilizumab together. Methotrexate co-therapy did not change risk (RR 1.14). Surprisingly, prednisone was not a risk factor but was analysed at the unusual cut-point dose of 15 mg/day. It would have been useful for the authors to have reported on factors predicting infection while on therapy especially the effect of neutropenia. A study looked at the effect of neutropenia on infection rates in clinical trials and suggested that any drop in neutrophil count approximately halved the rate of infection compared with those with no drop in neutrophils,[25] which suggests tocilizumab does not impair neutrophil function.

Hypersensitivity

A large US study showed that patients with RA taking the biological agents, rituximab and infliximab and, to a lesser extent, intravenous tocilizumab, were most strongly associated with hypersensitivity reactions. However, the absolute incidence rates of hypersensitivity events for all RA biological agents were low[26] at 1–2/1000 patient years and have been rare for subcutaneous tocilizumab. A French study found similar results and that ACPA positivity and lack of a traditional DMARD increased the risk of infusion reactions.[27]

Cancer

Data to date suggest no change in cancer risk with tocilizumab although event rates have been low.[28] Postmarketing data suggest a slightly lower rate overall (incidence rate ratio 0.79).[18] Longer periods of study will be required to answer definitively this question due to the low rates of cancer in these studies.

Use in pregnancy

Tocilizumab should be avoided in pregnancy due to lack of data. There have been 339 pregnancies.[29] Tocilizumab appears to be associated with higher risk of spontaneous miscarriage (22%) and preterm birth (31%), but no change in stillbirth (one only) or malformation rates (4.5%) has been shown. This information can be used to counsel woman about risk if they inadvertently fall pregnant while on tocilizumab.

Conclusion

The key findings from long-term studies are:

(1) efficacy appears to peak between 12 months and 24 months;
(2) tocilizumab is corticosteroid sparing;
(3) long-term persistence does not appear to be affected by the use of traditional DMARDs;
(4) efficacy is commonly lost if therapy is withdrawn or the dose decreased;
(5) infection rates appear similar in the postmarketing studies;
(6) despite an increase in lipids, there appears to be no increase in CV endpoints;
(7) pregnancy data suggest an increase in miscarriage rate and preterm birth;
(8) hypersensitivity is a rare but serious side effect and is mainly seen with intravenous tocilizumab.

The longer-term data to date suggest tocilizumab efficacy increases over time and is corticosteroid sparing. The safety data are consistent with the

shorter-term trials and are largely reassuring but some questions still remain over CV safety and cancer risk.

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Conflict of interest statement

GJ's salary is provided by the National Health and Medical Research Council. He was chief investigator on the AMBITION trial and has served as an adviser and speaker for Roche.

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