Janus kinase inhibitors in rheumatoid arthritis

Clinical applications

SUMMARY

Tofacitinib, an oral Janus kinase inhibitor, is an effective treatment for rheumatoid arthritis. Adverse effects are generally mild and include cytopenias and hyperlipidaemia. Opportunistic infections such as herpes zoster may occur with tofacitinib.

Introduction

Despite the advent of biological therapies for rheumatoid arthritis, many patients continue to experience unacceptable levels of disease. Furthermore, biological drugs have to be administered parenterally.

Janus kinase inhibitors are oral drugs. They interfere with signalling through type I and II cytokine receptors which have been shown to be critical in rheumatoid arthritis.1

Tofacitinib

Tofacitinib is an oral Janus kinase inhibitor with preferential inhibition of Janus kinase 3 and 1 over Janus kinase 2. It has an oral bioavailability of 74% and a mean elimination half-life of approximately three hours. Most (70%) of the drug is metabolised (CYP3A4 predominant) and 30% is renally excreted.2

Tofacitinib 5 mg twice a day has recently been approved by the US Food and Drug Administration for moderate to severe rheumatoid arthritis refractory to disease-modifying treatments.3

Phase II trials

In phase II studies, tofacitinib was superior to placebo when added to methotrexate in patients with rheumatoid arthritis.4,5 Responses were observed quickly, often within one week. Furthermore, small numbers of patients were able to switch from adalimumab to tofacitinib without difficulty.6 In the initial studies, tofacitinib was tolerable at doses of 5 mg and 10 mg twice daily.

Phase III trials

Several phase III trials have been conducted to assess the efficacy and safety of tofacitinib in patients with rheumatoid arthritis (see Table). The American College of Rheumatology 20 criteria (ACR 20) were used to measure response rates (see Box).
on a disability questionnaire (Health Assessment Questionnaire-Disability Index). However, among these patients with more resistant disease, there was no significant increase in rates of remission.\(^9\)

**ORAL Sync study**

The ORAL Sync study, reported as a conference abstract, assessed the addition of tofacitinib to treatment in patients who had ongoing disease despite receiving disease-modifying drugs. This trial design is likely to most closely reflect current clinical practice. Again, the study showed an improved response rate and disability score with tofacitinib, and a significant increase in the number of patients achieving remission.\(^10\)

**Radiological outcomes**

More recently, 12-month data looking at radiological outcomes with tofacitinib and methotrexate suggest that tofacitinib inhibits structural progression, both as solo therapy (to a greater level than methotrexate) and with background methotrexate use.\(^11,12\)

**Adverse events**

The most common adverse events with tofacitinib were diarrhoea, nasopharyngitis, urinary tract infection, nausea and headache. The risk of infection is an important consideration, although a recent meta-analysis concluded that it was similar to the risk with biological therapies.

There have been 12 cases of tuberculosis reported in the trial cohorts, 11 of whom initially screened negative for the disease. Ten cases occurred in countries endemic for tuberculosis.

The incidence of herpes zoster is also increased with tofacitinib. In a pooled analysis of phase II, III and long-term extension studies (4789 patients with 5651 patient-years of tofacitinib treatment), 239 patients experienced herpes zoster. One case was multidermatomal, none involved visceral dissemination and there were no fatalities.\(^13\)

Pooled analyses favour a 5 mg twice-daily dose of tofacitinib to reduce the risk of serious infection (seen in long-term extension studies). The transient effects of tofacitinib mean that its immunomodulatory effect can be rapidly reversed if sepsis occurs.\(^9,14,15\)

Hyperlipidaemia has been consistently observed in the trials and may relate to inhibition of interleukin-6 signalling.\(^16\) Atorvastatin appears to reduce the increase in cholesterol,\(^16\) but long-term cardiovascular effects will need to be assessed in the future.

Elevations in liver aminotransferases, neutropenia, thrombocytopenia and anaemia have all been reported. Changes are generally mild. A small rise in serum creatinine has been noted, but at this stage has not been clinically significant.\(^14,15\) As yet, there has been no reported increase in malignancy, but long-term data are still needed.

**Other indications**

Tofacitinib has shown promising results in phase II trials in other autoimmune diseases including ulcerative colitis and psoriasis. It is also being assessed as an immunosuppressant in renal transplant recipients.\(^17-19\)

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**Table: Phase III trials of tofacitinib in rheumatoid arthritis**

<table>
<thead>
<tr>
<th>Trials</th>
<th>Treatment given twice daily</th>
<th>Response rate ACR 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORAL Solo trial</td>
<td>tofacitinib 5 mg</td>
<td>59.8%</td>
</tr>
<tr>
<td>(3 month end point)(^7)</td>
<td>tofacitinib 10 mg</td>
<td>65.7%</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td>26.7%</td>
</tr>
<tr>
<td>ORAL Standard trial</td>
<td>tofacitinib 5 mg</td>
<td>51.5%</td>
</tr>
<tr>
<td>(6 month end point)(^8)</td>
<td>tofacitinib 10 mg</td>
<td>52.6%</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td>28.3%</td>
</tr>
<tr>
<td>ORAL Step study</td>
<td>tofacitinib 5 mg</td>
<td>41.7%</td>
</tr>
<tr>
<td>(3 month end point)(^9)</td>
<td>tofacitinib 10 mg</td>
<td>48.1%</td>
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<tr>
<td></td>
<td>placebo</td>
<td>24.4%</td>
</tr>
<tr>
<td>ORAL Sync study</td>
<td>tofacitinib 5 mg</td>
<td>52.7%</td>
</tr>
<tr>
<td>(6 month end point)(^10)</td>
<td>tofacitinib 10 mg</td>
<td>58.3%</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td>31.2%</td>
</tr>
</tbody>
</table>

ACR 20  American College of Rheumatology response criteria (see Box)

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**Box: Measuring response to treatment in rheumatoid arthritis**

The American College of Rheumatology (ACR) response criteria are a standard instrument used in rheumatoid arthritis trials. The ACR criteria of 20%, 50% or 70% improvement in clinical manifestations are an attempt to quantify response to therapy. Thus, a patient with an ACR 20 response to an intervention has demonstrated a 20% decrease in the combined number of swollen and tender joint counts, and a 20% improvement in any 3 of the 5 core-set measures which include Patient’s Global Assessment, Physician’s Global Assessment of disease activity (on 10 cm visual analogue scale), Patient’s Assessment of Pain score (on 10 cm visual analogue scale), Health Assessment Questionnaire – Disability Index (HAQ-DI), and acute phase reactants (erythrocyte sedimentation rate or C-reactive protein). The achievement of an ACR 20 response by an individual is considered to be the minimally achieved level of response that is of clinical relevance.

See: www.rheumatology.org
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**Conclusion**

Tofacitinib is not yet available in Australia, but its release will provide an alternative option and effective oral treatment for patients with rheumatoid arthritis resistant to standard therapy. While initial data are promising, longer-term studies are required to better assess the risk of malignancy, opportunistic infection and radiological changes. Other Janus kinase inhibitors are currently undergoing clinical trials for rheumatoid arthritis.1, 3

**Conflict of interest:** none declared

**REFERENCES**


**FURTHER READING**

