Brand Name, (Manufacturer): RoActemra® (Roche)
BNF Therapeutic Class: 10.1.3
Additional Licensed Indication: Juvenile idiopathic polyarthritis in patients 2 years and older who have responded inadequately or with intolerance to methotrexate or in whom methotrexate is inappropriate. May be given as monotherapy or together with methotrexate.
Dosage and Administration:
Patients weighing less than 30kg: 10 mg/kg by IV infusion every 4 weeks.
Patients weighing 30 kg or over: 8 mg/kg every 4 weeks.
Marketed: Licensed in EU for polyarticular JIA (pJIA), 30 May 2013
Cost Comparisons: Cost for 3 months’ treatment for a range of patient weights, based on whole vial costs, MIMS December 2013.

### Summary

- **Tocilizumab (RoActemra®)** is already licensed for rheumatoid arthritis and systemic juvenile idiopathic arthritis, with NICE guidance for these indications. This review covers its extended indication for treating polyarticular juvenile idiopathic arthritis (pJIA) in patients who have not responded adequately to or who are intolerant of methotrexate.
- **Tocilizumab** is a human monoclonal antibody that inhibits receptor mediated signalling by interleukin-6 (IL-6), an important cytokine in the pathogenesis of rheumatoid arthritis. Other biologics licensed for pJIA include etanercept (supported by NICE guidance for this indication) and adalimumab. Both inhibit binding of tumour necrosis factor to cellular receptors.
- One randomised placebo controlled withdrawal trial lasting 24 weeks (unpublished in full) found it to be superior to placebo in relieving symptoms.
- **Tocilizumab** is administered once every 4 weeks, less frequently than other biologic agents licensed for this indication. However it needs to be administered by intravenous (IV) infusion over an hour, unlike etanercept and adalimumab which are given subcutaneously. This may necessitate day case administration, at least for initial doses, increasing costs compared with subcutaneous administration of the other agents.

### Introduction

The term juvenile idiopathic arthritis (JIA) covers a group of relatively rare diseases with an estimated incidence of about 0.01% in children. Around 1000 cases are diagnosed each year in the UK and in a recent UK cohort, around 23% presented with polyarticular JIA (also known as juvenile idiopathic polyarthritis). Aims of treatment for these patients include control of joint pain, swelling and movement limitation which occur as a result of inflammation in affected joints; uveitis may also be a problem. Persistent disease may result in joint deformity and lifelong disability. Drug treatments include NSAIDs, corticosteroids and disease modifying drugs (DMARDs) of which methotrexate (MTX) is one of the most commonly used. Biologic treatments have been more recently introduced and include etanercept, adalimumab and most recently, tocilizumab.

Patients with polyarticular disease have a poor prognosis with only around 15% achieving remission within 10 years. Many need further care for joint disease as adults and around 30 to 40% of patients with this form of JIA are likely to need early joint replacement.

### Evidence

The licensed indication for pJIA is based on a single trial supported by the manufacturer (‘CHERISH’), which has yet to be published in full, however details appear in the product’s EPAR. Patients aged 2 to 17 with 5 or more joints with active disease were recruited (n=188). They were either rheumatoid factor negative or positive, or had extended oligoarticular JIA. They needed to have had JIA for at least 6 months and have had either an inadequate response to MTX or be unable to tolerate it. Those with evidence of systemic infection, tuberculosis within the previous two years or a history of allergic reactions to infusions or biologic therapy were excluded. Around a third of the patients had...
previously received other biologic therapies, it is unclear whether these had been effective.

The trial comprised three phases, the last of which is ongoing.

During the initial 16-week phase (Part I), all patients were treated with tocilizumab. Those weighing over 30kg were given a dose of 8mg/kg. Those weighing below 30kg were then randomised to either 8mg/kg or 10mg/kg, in a 1:1 ratio. All patients received 4 doses at 4-weekly intervals. Response to treatment at the end of this period was rated using American College of Rheumatology (ACR) score. This is a 6-part grading system to assess clinically important outcomes. These are: physical activity, patient/parent global assessment of overall well-being; functional ability; number of joints with active arthritis; number of joints with limited range of motion; and raised erythrocyte sedimentation rate. Grades of response, ACR30/50/70/90 represent a 30%/50%/70% or 90% improvement in at least three outcomes, with no more than one of these worse by greater than 30%. At the end of Part 1, 89.4% of patients achieved ACR30, 83% ACR50, 62.2% ACR70 and 26.1%, ACR90.²

Twenty two patients withdrew in this part of the trial, 15 for lack of efficacy, 3 for adverse events and 4 for other reasons. Tocilizumab was therefore ineffective or not tolerated in 18 (9.6%) of patients who started the trial.

Those who completed the first part of the study and achieved at least an ACR30 response to tocilizumab (n=163, 86.7% of the group), progressed to Part II. This was a 24-week withdrawal trial where patients were randomised to either placebo or continued treatment with tocilizumab. If any of those receiving placebo experienced a ‘flare’ of their disease during this period they were eligible to move to open-label tocilizumab. The primary efficacy endpoint of the study overall was the difference in JIA ACR 30 ‘disease flare’ between groups at the end of Part II. At week 40, more patients in the placebo group (39/81, 48.1%) had experienced a ‘flare’ compared with those receiving tocilizumab (21/82, 25.6%), and the difference was statistically significant, p=0.0024.

Secondary endpoints included the proportions of patients in each ACR response category at week 40, the change in mean number of ‘active’ joints at week 40 compared with week 16, and change in mean visual analogue scale (VAS) pain score from week 16 to 40. In all of these categories, patients who had continued on tocilizumab scored better than those switched to placebo and the differences were statistically significant (see Appendix 1 for details).

No published data are yet available from Part III of the trial (an open label extension with tocilizumab treatment for all patients).

There is currently a lack of detailed information about the trial. For example, although patients were stratified as to continued corticosteroid and/or MTX treatment during the trial, there are no data on whether they responded any differently. The effect on the uveitis (if present) was not recorded. Those patients weighing below 30kg who received the higher dose responded better and more achieved JIA ACR 30 (88.6% vs 76.5%) and ACR 50 (80.0 vs 70.6%), but the numbers are small and statistical information not available. Finally, around a third of the patients had previously received other biologic treatments for their arthritis according to the EPAR, but detailed information about their responses to tocilizumab compared with their previous treatment is not available.³

Safety

Infections (pneumonia, bronchitis and cellulitis) were the most common adverse events in the trial. Rises in liver function tests (AST/ALT) occurred in 3.7% of patients. Neutropenia (3.7%) and thrombocytopenia (1.1%) were also seen. Raised LDL cholesterol occurred in 11.4% of the trial population; the significance of this is unclear.

NHS Impact

This is a rare disease but the burden of disease is high for patients and their families.

Current first line treatments including NSAIDs, corticosteroids and methotrexate are often inadequate, leading to the need for treatment with biologic agents. There is currently little evidence to support choice of agent within this group and there is also a lack of comparative data on efficacy and/or side effects. However there is some evidence that adalimumab is effective in chronic uveitis,¹⁰ an inflammatory disorder that occurs in about 13% of JIA patients¹¹ and can threaten sight if not treated. Adalimumab may therefore be preferred in patients with uveitis.

Tocilizumab is given by IV infusion needing admission to hospital, which increases cost of treatment. This needs to be weighed against the subcutaneous administration of other licensed agents. However these need to be administered more frequently than tocilizumab.

Appendix I: Clinical trial.

Risk Management Issues:

Patients treated with biologic agents should be monitored carefully for signs of infection or recurrence of infectious disease such as tuberculosis, in addition to normal monitoring.
References


Key papers are highlighted in bold.
Appendix I: Clinical Trial

‘CHERISH’ trial. Patients (n=163) who had completed Part I (16 weeks’ tocilizumab) and achieved at least ACR 30 were randomised to placebo or continuation of tocilizumab for a further 24 weeks.

Part II: Patient response rates at week 40.

<table>
<thead>
<tr>
<th></th>
<th>Tocilizumab continued, n=82</th>
<th>Placebo, n = 81</th>
<th>Statistical significance compared with placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
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<tr>
<td>Overall response – JIA ACR 30 flare</td>
<td>21/82, 25.6%</td>
<td>39/81, 48.1%</td>
<td>P=0.0024, significant compared with placebo</td>
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<tr>
<td>Secondary endpoints</td>
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<tr>
<td>JIA ACR 30</td>
<td>74.4%</td>
<td>54.3%</td>
<td>p&lt;0.01 (significant)</td>
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<tr>
<td>JIA ACR 50</td>
<td>73.2%</td>
<td>51.9%</td>
<td></td>
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<tr>
<td>JIA ACR 70</td>
<td>64.6%</td>
<td>42%</td>
<td></td>
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<tr>
<td>Mean number of ‘active’ joints at week 40 compared with week 16</td>
<td>-14.3</td>
<td>-11.4</td>
<td>p = 0.0435 (significant)</td>
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<tr>
<td>Change in physician’s global assessment of disease activity baseline to week 40 using 100mm visual analogue scale</td>
<td>-45.2mm</td>
<td>-35.2mm</td>
<td>p = 0.0031 (significant)</td>
</tr>
<tr>
<td>Change in mean pain score baseline to week 40 using 100mm visual analogue scale</td>
<td>-32.4mm</td>
<td>-22.3mm</td>
<td>P=0.0076 (significant)</td>
</tr>
</tbody>
</table>

Key: ACR = American College of Rheumatology score