Tocilizumab (RoActemra) for active polyarticular juvenile idiopathic arthritis – second line

SUMMARY

Tocilizumab (RoActemra), in combination with methotrexate (MTX) or as monotherapy (if treatment with MTX is not tolerated or where continued treatment with MTX is inappropriate) is intended for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients aged 2 years and older who have responded inadequately to previous therapy with MTX. If licensed, tocilizumab may provide a new treatment option for patients with pJIA and has the potential to improve response rates and reduce joint damage. Tocilizumab is a humanised anti-interleukin-6 (IL-6) receptor monoclonal antibody shown to inhibit receptor mediated signalling of IL-6, a key cytokine in rheumatoid arthritis (RA) pathogenesis. It is currently licensed for the treatment of moderate to severe active RA in adults whose disease has not responded adequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists; and the treatment of active systemic JIA in patients aged 2 years and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids.

Juvenile idiopathic arthritis (JIA) is a relatively rare disease, with an estimated incidence in the UK of 0.1 per 1,000 children, equivalent to 1,000 children diagnosed per year. The prevalence is in the order of 1 per 1,000 children, and about 10,000 children in the UK are affected. Approximately 23% of these children present with pJIA. The population of children and young people with pJIA in England who are non-responders to MTX, and who would be eligible for treatment with tocilizumab, is estimated to be around 1,194.

Management of JIA includes drug therapy, physical therapy, and surgical intervention to control joint pain and inflammation; reduce joint damage, disability and loss of function; and maintain or improve quality of life. NICE has issued guidance on the use of etanercept (a TNF inhibitor) for the treatment of pJIA in children and adolescents who have not responded adequately to, or who have been intolerant of MTX. Current treatment options for pJIA include NSAIDs, DMARDs and corticosteroids. Tocilizumab is currently in a phase III clinical trial comparing its effect on improving arthritis and wellbeing against placebo.
TARGET GROUP

- Polyarticular juvenile idiopathic arthritis (pJIA) in patients ≥2 years of age: active – second line; following inadequate response to treatment with methotrexate (MTX).

TECHNOLOGY

DESCRIPTION

Tocilizumab (RoActemra; RG1569) is a humanised anti-interleukin-6 (IL-6) receptor monoclonal antibody. It has been shown to inhibit both soluble and membrane bound receptor mediated signalling of IL-6, a key cytokine in rheumatoid arthritis (RA) pathogenesis. IL-6 synovial fluid levels are elevated in patients with RA, and correlate with clinical and laboratory markers of disease activity. Tocilizumab, in combination with MTX, or as monotherapy (if treatment with MTX is not tolerated or where continued treatment with MTX is inappropriate) is intended for the treatment of active pJIA in patients aged 2 years and older who have responded inadequately to previous therapy with MTX. Tocilizumab is administered by intravenous (IV) infusion at 8mg/kg (in patients weighing ≥30kg) or 10mg/kg (in patients weighing <30kg) every 4 weeks.

Tocilizumab, in combination with MTX or as monotherapy (if treatment with MTX is not tolerated or where continued treatment with MTX is inappropriate), is licensed for:

- the treatment of moderate to severe active RA in adults whose disease has not responded adequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.
- the treatment of active systemic JIA in patients aged 2 years and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids.

Tocilizumab is in phase III clinical trials for the treatment of systemic sclerosis. A subcutaneous formulation of tocilizumab is also in phase III clinical trials for the treatment of RA.

The most commonly reported adverse reactions associated with tocilizumab treatment are upper respiratory tract infections and hypercholesterolaemia.

INNOVATION and/or ADVANTAGES

If licensed, tocilizumab may provide a new treatment option for patients with pJIA which has the potential to improve response rates and reduce joint damage.

DEVELOPER

Roche Products Ltd.
Juvenile idiopathic arthritis (JIA) describes a heterogeneous group of syndromes in which the onset of inflammatory arthritis occurs before the age of 16 years and lasts for more than 6 weeks. JIA is characterised by persistent joint swelling, pain, and limitation of movement, and encompasses several different subgroups with distinct clinical signs and symptoms, and in some cases, genetic background. It can lead to growth retardation, joint contractures, eye problems, destructive joint disease, and permanent disability.

There are seven categories of JIA: systemic-onset polyarticular, juvenile oligoarthritis (pauciarticular) – persistent and extending, polyarticular with rheumatoid factor (RF), polyarticular without RF, spondylarthropathies (enthesitis related arthritis), psoriatic rheumatism, and unclassified types of arthritis (types that do not correspond to any, or to more than one category). pJIA, also called polyarticular-course JIA or polyarthritis, affects five or more joints and can develop at any age during childhood.

This topic is relevant to:

JIA is a relatively rare disease, with an estimated incidence in the UK of 0.1 per 1,000 children, equivalent to 1,000 children diagnosed per year. The prevalence is around 1 per 1,000 children, and about 10,000 children in the UK are affected. Approximately 23% of these children present with pJIA. It is estimated that each year 200 children with JIA will start treatment with TNF inhibitors following the failure of MTX treatment. The population of children and young people with pJIA in England who are non-responders to MTX, and who would be eligible for treatment with tocilizumab, is estimated to be around 1,194.

JIA affects children's personal and social development. Children often miss school and normal childhood activities, and as adults, have reduced employment prospects. JIA may also have a considerable emotional and financial impact on a child's family; parents may restrict or give up work to care for their child. Treatment-resistant JIA results in joint destruction and growth retardation, which leads to major functional limitations. About 50% of children with JIA do not achieve remission despite treatment and require further rheumatological care as adults. Patients with polyarticular onset have the worst prognosis, with a remission rate of only 15% over 10 years. Around 30 to 40% of children with polyarticular onset disease require early joint replacement. In England, there were 8,609 admissions for juvenile arthritis (ICD10 M08), resulting in 3,604 bed days and 8,665 finished consultant episodes in 2010-11.

a JIA is sometimes referred to as juvenile rheumatoid arthritis (USA) or juvenile chronic arthritis (UK).
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


Other Guidance

- BSPAR. Standards of care for children and young people with juvenile idiopathic arthritis. 2009.

EXISTING COMPARATORS and TREATMENTS

Management of JIA includes drug therapy, physical therapy, and surgical intervention to control joint pain and inflammation; reduce joint damage, disability and loss of function; and maintain or improve quality of life. NICE has issued guidance on the use of etanercept (a TNF inhibitor) for the treatment of pJIA in children and adolescents who have not responded adequately to, or who have been intolerant of MTX.

Current treatment options for pJIA include:

- NSAIDs: ibuprofen, naproxen, diclofenac sodium, piroxicam – first line.
- DMARDs: MTX (unlicensed for JIA) and biological therapies – etanercept, abatacept, adalimumab, hydroxychloroquine – second line.
- Intra-articular, intravenous, or oral corticosteroids – adjuvant.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
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<tbody>
<tr>
<td>Participants</td>
<td>n=19; 2-19 years of age; active polyarticular-onset JIA or oligoarticular-onset JIA; RF positive or negative; &lt;16 years old at onset; refractory to or intolerant of other medications including MTX; not received any DMARD, IV immunoglobulin or cytotoxic agent, or IV or intra-articular corticosteroid injections 14 days prior to baseline.</td>
<td>n=19; completed trial NCT00144664.</td>
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<td>Schedule</td>
<td>Tocilizumab 8mg/kg IV every 4 weeks for 12 weeks.</td>
<td>Tocilizumab 8mg/kg IV every 4 weeks for ≥36 weeks.</td>
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<td>Follow-up</td>
<td>Active treatment period 12 weeks; then 48 week extension study (NCT00144625).</td>
<td>Active treatment period 48 weeks. At the end of the study, patients may transfer to a locally run protocol (such as a safety extension study or named patient supply) depending on local country requirements.</td>
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<td>Primary outcome/s</td>
<td>JIA ACR 30”, safety.</td>
<td>JIA ACR 30, safety.</td>
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<td>Secondary outcome/s</td>
<td>Proportion of patients with JIA ACR 30/50/70/90, each variable of the JIA ACR core set, CRP, pain (VAS).</td>
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<td>Key results</td>
<td>JIA ACR 30, 50, 70, and 90 response rates, respectively: 94.7%, 94.7%, 57.9%, and 10.5% at week 12; 100%, 94.1%, 88.2%, and 64.7% at week 48. Mean DAS28c, at baseline, 5.9; week 4, 3.9; week 8, 3.1; week 12, 2.8; week 24, 1.6; week 36, 1.9; and week 48, 1.7. Number of patients with remission: week 4, 4; week 8, 7; week 12, 10; and week 48, 14. Percentage of patients with good response (EULAR response criteria d): week 12, 73.7%; week 24, 94.1%; week 48, 100%.</td>
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<td>Adverse effects (AEs)</td>
<td>The most common AEs (%) were: nasopharyngitis (47.4%), upper respiratory tract infection (47.4%), insect bite (21.1%), gastroenteritis (21.1%), pharyngitis (15.8%), abdominal pain (15.8%), diarrhoea (15.8%), and stomatitis (15.8%).</td>
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<td>Trial</td>
<td>CHERISH, NCT00988221, WA199777, 2009-011593-15; EUCTR2011-001097-25-DE; tocilizumab; phase III.</td>
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<td>Sponsor</td>
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<td>Status</td>
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<td>Source of information</td>
<td>Trial registry“©”on-manufacturer.</td>
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<tr>
<td>Location</td>
<td>EU (inc UK), USA, Canada and other countries.</td>
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<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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| Participants | n=188; 2-17 years of age; pJIA ≥6 months duration; active disease (≥5 active joints, American College of Rheumatology (ACR) criteria comprises a core set of six outcome variables for the assessment of clinically important improvement: physical global assessment of disease 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 erythrocyte sedimentation rate. ACR30/50/70/90 represents a 30%/50%/70%/90% improvement in at least three response criteria (and with no more than one response variable worse by greater than 30%).

28-Joint Disease Activity Score (DAS28): combines information relating to the number of swollen and tender joints in addition to a measure of general health (VAS) and the acute phase response. The DAS28 is based on a count of 28 swollen and tender joints, with a score ranging from 0 to 9.4 (a value of ≤3.2 defined as the threshold for a low disease activity state and <2.6 as the threshold for remission).

European League Against Rheumatism (EULAR) response criteria: combines the DAS28 score at the time of evaluation with the change in DAS28 score between two time points to define improvement or response to treatment. Good response defined as DAS28 <3.2 after a decrease (from baseline) of >1.2.
≥3 with limitation of motion); inadequate response to, or intolerant to MTX; receiving MTX, oral corticosteroids and NSAIDs at stable dose (at least 8, 4 and 2 weeks, respectively) prior to baseline; biological therapies discontinued 1-20 weeks prior to study; no previous treatment with tocilizumab.

**Schedule**
- **3-part study as follows:**
  - **Part I: 16-week open-label lead-in phase**
    - All patients receive tocilizumab 8mg/kg IV for patients ≥30kg, or 8mg/kg or 10mg/kg IV for patients <30kg, every 4 weeks for 16 weeks.
  - **Part II: 24-week randomised withdrawal phase**
    - Patients with an adequate response in Part I randomised to either continue tocilizumab at the same dose, or placebo, every 4 weeks for up to 24 weeks.
  - **Part III: 64-week open-label phase**
    - After completion of part II or the occurrence of a JIA ACR 30 flare* (compared to week 16), placebo group crossover and all patients receive tocilizumab at the same dose as in Part I every 4 weeks for up to 64 weeks.

Subjects continue with standard of care therapy (NSAIDs, corticosteroids and/or MTX) throughout the study.

**Follow-up**
- Final efficacy assessment at week 104. Further follow up until week 112. At the end of the study, patients may transfer to a locally run protocol (such as a safety extension study or named patient supply) depending on local country requirements.

**Primary outcome**
- Proportion of patients with a JIA ACR30 flare in Part II.

**Secondary outcomes**
- JIA ACR core set variables; long-term efficacy and maintenance of clinical response; safety and tolerability.

**Expected reporting date**
- May 2013.

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* Disease flare defined as (1) a worsening of 30% or more from baseline in more than three of the six core ACR response variables, (2) no fewer than two active joints, and (3) improvement of greater than 30% in no more than one of the six criteria.
ESTIMATED COST and IMPACT

COST

The cost of treatment with tocilizumab at 8mg/kg every 4 weeks for 3 months is around £1,075f. The costs for other selected treatments are as follows20,29:

<table>
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<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost for 3 months</th>
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<tr>
<td>Methotrexate (Metoject)</td>
<td>For children ≥3 years 10–15mg/m² IV once weekly.</td>
<td>£199–£214</td>
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<tr>
<td>Abatacept (Orencia)</td>
<td>For children 6–17 years Body-weight &lt;75kg, 10mg/kg IV at weeks 2 and 4, then every 4 weeks.</td>
<td>£1,289</td>
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<td>Adalimumab (Humira)</td>
<td>For children 13–17 years 40mg SC on alternate weeks.</td>
<td>£2,145</td>
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<tr>
<td>Etanercept (Enbrel)</td>
<td>For children 4–17 years 400µg/kg SC twice weekly, with an interval of 3–4 days between doses.</td>
<td>£2,146</td>
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IMPACT - SPECULATIVE

Impact on Patients and Carers

☐ Reduced mortality/increased length of survival ☐ Reduced symptoms or disability
☐ Other ☐ No impact identified

Impact on Services

✔ Increased use of existing services ☐ Decreased use of existing services
☐ Re-organisation of existing services ☐ Need for new services
☐ Other ☐ None identified

Impact on Costs

☐ Increased drug treatment costs ☐ Reduced drug treatment costs: reduced unit cost compared to other biological therapy options.
☐ Other increase in costs ☐ Other reduction in costs
☐ Other ☐ None identified

Other Issues

☐ Clinical uncertainty or other research question identified ☐ None identified

REFERENCES

f Based on an average bodyweight of 33.25kg.
g Based on an average surface area 1.1m².
21 Prince FH, Otten MH and van Suijlekom-Smit LW. Diagnosis and management of juvenile idiopathic arthritis. BMJ (Clinical research edition) 2010;341:c6843.


