National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: November 2017

Subcutaneous Tocilizumab (RoACTEMRA) with or without methotrexate for the treatment of inadequate responders in systemic juvenile idiopathic arthritis

NIHRIO (HSRIC) ID: 10891 NICE ID: 7923

LAY SUMMARY

Juvenile idiopathic arthritis is a name for a group different arthritis conditions which happen in children (below 16 years). One of these types of arthritis is systemic juvenile idiopathic arthritis (sJIA). Symptoms of sJIA include fevers, rashes and joint pain and swelling. sJIA is an autoimmune disease, meaning the body's own immune system, which usually fights infection, attacks the body instead. It is thought that IL-6 (a molecule involved in inflammation) may have an important role in the development of sJIA and it is found in high levels in people with sJIA.

Tocilizumab is a drug that targets and blocks the IL-6 pathway and is currently used for the treatment of many diseases, including sJIA, rheumatoid arthritis and Giant Cell Arteritis (GCA). It is now being developed for patients with sJIA that may have been treated with, and have not responded to another drug called methotrexate. It is being developed to be administered as an injection under the skin (subcutaneous) as opposed to the usual intravenous infusion preparation and this has the potential to reduce patient inconvenience and clinical burden.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Systemic Juvenile Idiopathic Arthritis (patients = or > 2 years, with inadequate response to previous therapy with NSAIDs and systemic corticosteroids) – first line biologic; monotherapy (where methotrexate treatment is inappropriate) or in combination with methotrexate.

TECHNOLOGY

DESCRIPTION

Tocilizumab (RoACTEMRA) is a monoclonal antibody which works by binding to soluble and membrane bound IL-6 receptors, blocking the action of IL-6 (a proinflammatory cytokine produced by numerous inflammatory cells) which has a range of actions including T cell activation and induction of immunoglobulin secretion.[1] IL-6 is thought to have an important role in the pathogenesis of systemic juvenile idiopathic arthritis (sJIA), being found in elevated levels in the blood and synovial fluid of sJIA patients and being correlated with disease activity.[2]

The recommended dose for this indication is consistent for the summary of product characteristics (SPC) for intravenous infused tocilizumab for the existing licenced JIA indication: in patients >2 years of age is 8 mg/kg once every 2 weeks in patients weighing > or =to 30 kg or 12 mg/kg once every 2 weeks in patients weighing <30 kg. The dose should be calculated based on the patient's body weight at each administration and changes in dose should only be based on a consistent change in the patient's body weight over time.[1]

Tocilizumab (with or without methotrexate) has been licenced for use in the treatment of:

- Severe, active, progressive rheumatoid arthritis (RA) in adults previously untreated with methotrexate.
- Moderate to severe active RA in adults with an inadequate response to, or intolerant of, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.
- Active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids
- Juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with methotrexate.
- Giant Cell Arteritis in adults.

Very common (> and = 1/10) adverse events reported for tocilizumab across a variety of indications include: upper respiratory tract infections and hypercholesterolemia. Common (prevalence >1/100, <1/10) adverse events reported for tocilizumab across a variety of indications include: cellulitis, pneumonia, oral herpes simplex, herpes zoster, abdominal pain, mouth ulceration, gastritis, rash, pruritus, urticaria, headache, dizziness, increased hepatic transaminases, weight increased, increased total bilirubin, hypertension, leukopenia, neutropenia, peripheral oedema, hypersensitivity reactions, conjunctivitis, cough and dyspnoea.[1]

Tocilizumab is currently in phase III clinical trials for systemic sclerosis.

Tocilizumab is currently in phase II trials for:

- Pulmonary Arterial Hypertension

- Amyotrophic Lateral Sclerosis
- Polymyositis
- Dermatomyositis
- Polymyalgia Rheumatica
- JIA associated uveitis

INNOVATION and/or ADVANTAGES

If licensed, subcutaneous tocilizumab will offer an additional treatment option for children (= and > 2 years) with sJIA who currently have often have poor clinical outcomes and quality of life. As this is a subcutaneous preparation (as opposed to the intravenous infusion preparation which tocilizumab is usually administered as), this has the potential to reduce patient inconvenience and clinical burden.

Additionally, as this drug targets IL-6, a molecule correlated with disease progression and active sJIA disease, it may have the potential to benefit this patient group through its novel mechanism of action in this population.

DEVELOPER

Roche Products Ltd.

PATIENT GROUP

BACKGROUND

Juvenile Idiopathic Arthritis (JIA) is a collective term referring to a variety of chronic (lasting more than 6 months) arthritis, all of which begin in childhood (before 16 years). There are seven types of JIA; systemic, persistent oligoarticular, extended oligoarticular, rheumatoid factor positive polyarticular, rheumatoid factor negative polyarticular, psoriatic and enthesitis-related arthritis.

Systemic JIA (sJIA) affects approximately 10% of JIA cases. It is characterised by bouts of fever (which can be over 103°F), a salmon coloured rash, inflammation of the internal organs and joints (although joint swelling may not become apparent until months or years after disease onset), anaemia and elevated white blood cell count.[3] sJIA is an autoimmune disease, occurring when the body's immune cells attack the synovium (joint lining), causing inflammation and swelling.

It is not known what begins this autoimmune response in JIA but it has been hypothesised that a previous infection may be a possible trigger.[4] However, research suggests IL-6 has an important role in the pathogenesis of sJIA as it is seen in significantly elevated levels in the blood and synovial fluid of patients with sJIA and correlated with sJIA disease activity.[2]

All JIAs can have a significant impact on quality of life, negatively affecting mood, sleep and sometimes normal growth.[5] sJIA can also cause a variety of complications including macrophage activation syndrome (a potentially life threatening complication), hemophagocytic lymphohistiocytosis (a type of life threatening immunodeficiency), high levels of triglycerides and ferritin, osteoporosis and secondary amyloidosis. There are often poor outcomes for people with sJIA as there is a high risk of long term functional impairment.[2]

CLINICAL NEED and BURDEN OF DISEASE

There are an estimated 12,000 (1 in 1000) children under 16 years with JIA, with 1 in 10,000 children diagnosed with JIA per year in the UK (the equivalent of 1,000 – 1,500 people).[4] Approximately 10% JIA patients have sJIA.[6]

For Juvenile arthritis with systemic onset (ICD10 M08.2) there were 1,289 admissions and 1,307 finished consultant episodes in the UK during 2016-2017.[7]

Morbidity due to disease activity and complications is common in JIA. Progressive joint damage in JIA patients mean 7-28% patients with require joint replacement surgery and 10-20% (mostly those with systemic and polyarticular JIA) will have impaired growth. Uveitis is also a common complication of JIA, affecting 30-50% of children with JIA, which if left untreated can cause cataracts, glaucoma and macular oedema and visual impairment (occurring in 50-70% JIA cases).[8]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal guidance in development. Juvenile idiopathic arthritis – adalimumab (ID385). Expected publication date TBC.
- NICE Technology appraisal guidance in development. Juvenile idiopathic arthritis – abatacept (ID27). Expected publication date TBC.
- NICE Technology appraisal guidance. Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis (TA373). December 2015.
- NICE Technology appraisal guidance. Tocilizumab for the treatment of systemic juvenile idiopathic arthritis (TA238). December 2011.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA). NHS England E03X04. July 2015.
- 2013/14 NHS Standard Contract Paediatric Medicine: Rheumatology. E03/S/b.
- 2013/14 NHS Standard Contract for Severe Immunodeficiency and Related Disorders Service (Children). B04/S(HSS)/b.

OTHER GUIDANCE

- American College of Rheumatology. *2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis.* October 2013.
- British Society for Paediatric and Adolescent Rheumatology. Standards of care for children and young people with juvenile idiopathic arthritis. 2009.

CURRENT TREATMENT OPTIONS

The aim of treatments for sJIA is to control symptoms and improve quality of life. Treatment options include drug and non-drug therapies and treatment will usually include a combination of these treatments.[9, 10]

Drug therapies:

- Painkillers – for pain relief (e.g. paracetamol and codeine)
- NSAIDs – to reduce pain, swelling and stiffness (e.g. ibruprofen, piroxicam, naproxen and diclofenac)
- Steroids – to reduce symptoms. Can be given orally, subcutaneously or by IV. Steroids are not commonly used in children due to their side effect profile.
- DMARDs – to reduce inflammation and slow disease progression. Most commonly methotrexate is used in JIA by weekly oral or IV dose.
- Biological therapies – to reduce symptoms and slow disease progression and used in those who do not respond to methotrexate.
    - Tocilizumab – recommended for treatment of JIA in >2 years old patients who have responded inadequately to NSAIDs, corticosteroids and methotrexate (NICE do not recommend use of this drug in JIA patients > 2years who respond to methotrexate or who have not been treated with methotrexate).
    - Canakinumab – for the treatment of sJIA. NICE were unable to provide a recommendation for this drug as no evidence submission was received from the company.

Non drug therapies:

- Physiotherapy
- Pain relief techniques – e.g. TENS, acupuncture, massage, hydrotherapy and relaxation
- Splints – to support the joints
- Insoles – to support the feet and ankles
- Mobility aids – e.g. crutches and wheelchairs, for those with limited mobility.

EFFICACY and SAFETY

Trial	WA28118, JIGSAW-118, NCT01904292, EudraCT-2012-003490-26, UKCRN-14202, MCRN234, IRAS-130144; children aged 1 to 17 years; tocilizumab only; phase I	WA29231, NCT02165345, EudraCT-2013-005212-98, UKCRN-16472, MCRN3262; children aged 2 to 18 years; tocilizumab only; phase I extension
Sponsor	Hoffmann-La Roche	Hoffmann-La Roche
Status	complete but unpublished	Ongoing - recruiting
Source of Information	trial registry[11]	Trial registry[12]

Location	5 EU countries (including UK), USA, Canada and countries in South America	5 EU countries (including UK), USA, Canada, Australia, Russia and countries in South America
Design	non-randomised, uncontrolled, open label trial	non-randomised, uncontrolled, open label extension trial
Participants	n=42 ; aged 1-17 years; systemic JIA; inadequate clinical response to NSAIDs and corticosteroids	N=96; aged 2 to 18 years; took part in the JIGSAW studies - WA28117 (for participants with pJIA) or study WA28118 (for participants with sJIA); adequate disease control with the use of SC tocilizumab
Schedule	All participants received 162mg dose of tocilizumab by subcutaneous injection every week (participants which weigh >30kg) or every 2 weeks (participants which weigh <30kg) for 52 weeks.	All participants received 162mg dose of tocilizumab by subcutaneous injection every week (participants which weigh >30kg) or every 2 weeks (participants which weigh <30kg) for till commercial availability of the drug OR 3 years
Follow-up	Active treatment for 52 weeks	Up to 3 years
Primary Outcomes	•Pharmacokinetics: Area Under the Concentration-Time Curve (AUC) of Tocilizumab • Aged <2 years: 0 hours (h) on Days (D): 0 and 84 • Age>=2 years: 0, 6, 12h on D0 and 84; Weight >=30kg: 0, 6, 12h on D0, 91 •Pharmacokinetics: Maximum Plasma Concentration (Cmax) of Tocilizumab: • Age <2 years: 0h on D0 • Age >=2 years: 0, 6, 12h on D0, 84. Weight >=30 kg: 0, 6,12h on D0 and 91 •Pharmacokinetics: Minimum Plasma Concentration (Cmin) of Tocilizumab: Weight <30 kg: predose (0h) on Days 0 and 84. Weight >= 30 kg: predose (0h) on Days 0 and 91	•Juvenile Arthritis Disease Activity Score (JADAS-71): Baseline up to 3 years •Percentage of Participants With Adverse Events (AEs), Serious AEs (AEs) and AEs of Special Interest: Baseline up to 3 years
Secondary Outcomes	•Pharmacodynamics: Serum Interleukin-6 (IL6) Levels • Age<2 years: 0h on Days 0, 84; • Age >=2 years: 0, 6, 12h on Days 0 and 84; Weight >=30kg: 0, 6, 12h on Days 0 and 91 •Pharmacodynamics: Soluble IL-6 Receptor (sIL-6R) Levels • Age<2 years: 0h on Days 0, 84;	•Childhood Health Assessment Questionnaire (CHAQ) Score: Baseline up to 3 years •Percentage of Participants With Protocol Defined Inactive Disease/Clinical Remission: Baseline up to 3 years

	• Age >=2 years: 0, 6, 12h on Days 0 and 84. Weight >=30kg: 0, 6, 12h on Days 0 and 91 •Pharmacodynamics: Serum C-Reactive Protein (CRP) Levels • Age <2years: Days 0, 14, 28, 42, 70, 84, 98, 126, 154, 182, 210, 238, 266, 294, 322, 350, 364. • Age >=2years: Days 0, 14, 28, 42, 70, 98, 126, 154, 182, 210, 238, 266, 294, 322, 350, 364. Weight >=30kg: Days 0, 7, 14, 21, 28, 42, 56, 70, 84, 91, 95, 96, 98, 182, 266, 294, 322, 350, 364 •Pharmacodynamics: Serum Erythrocyte Sedimentation Rate (ESR) • Age <2years: Days 0, 14, 28, 42, 70, 84, 98, 126, 154, 182, 210, 238, 266, 294, 322, 350, 364. • Age >=2years: Days 0, 14, 28, 42, 70, 98, 126, 154, 182, 210, 238, 266, 294, 322, 350, 364. Weight >=30kg: Days 0, 7, 14, 21, 28, 42, 56, 70, 84, 91, 95, 96, 98, 182, 266, 294, 322, 350, 364 •Pharmacodynamics: Percentage of Participants with Anti-Tocilizumab Antibodies • Age <2 years: Days 0, 84, 182, 266, 364. Weight <30 kg, • Age >=2 years: Days 0, 84, 182, 266, 364. Weight >=30 kg: Days 0, 91, 182, 266, 364 •Safety: Percentage of Participants with At Least 1 Adverse Event at 57 weeks	
Key Results	Not reported	-
Adverse effects (AEs)	Not reported	-
Expected reporting date	-	Primary completion date 6 November 2020

ESTIMATED COST and IMPACT

COST

Tocilizumab (RoACTEMRA) is already marketed in the UK for the treatment of moderate to severe rheumatoid arthritis (alone or in combination with methotrexate) with inadequate response to at least one DMARD or TNFα inhibitor at a cost of £102 per 80mg/4ml vial, £256 per 200mg/10ml vial and £512 per 400mg/20ml vial.[13]

A Patient Access Scheme is available for RoActemra.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other:

☒ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services: reduced need for services to deliver intravenous infusions

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☒ Other reduction in costs: as this is a subcutaneous preparation, this will result in reduction of costs usually incurred due to intravenous infusion.

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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