National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: January 2018

Tocilizumab (RoActemra) for adults with giant cell arteritis - intravenous injection

NIHRIO (HSRIC) ID: 17187 NICE ID: 9731

LAY SUMMARY

Giant cell arteritis (GCA) is an autoimmune condition that causes the inflammation of large and medium sized blood vessels. An alternative name for this condition is "Temporal Arteritis" as the blood vessels in the temple area of the head (sides of the forehead) are commonly affected. The “giant” cells are abnormal large cells that develop in the wall of the inflamed arteries. GCA is very rare in people younger than 50 years, and is more common in women and people of northern European descent. The cause of GCA is not known. The most common symptoms of GCA include headache, with severe pain and tenderness over the temples and the scalp, prominent blood vessels at the temples, and pain in the jaw or tongue when talking or chewing. Visual loss occurs in up to 20% of patients, and this may be related to late recognition.

Tocilizumab is a disease modifying drug that acts by blocking specific proteins that signal the inflammatory processes affecting blood vessels in GCA. It is currently licensed for the treatment of GCA in adults as a subcutaneous (under the skin) injection, but reactions at the place of injection include redness, itching and pain. It is anticipated that these reactions would be avoided if the drug was given as an intravenous infusion.

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

Giant cell arteritis (GCA) in adults - newly diagnosed or relapsing/refractory to treatment with steroids.

TECHNOLOGY

DESCRIPTION

RoActemra binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis. IL-6 has been implicated in the pathogenesis of diseases including inflammatory diseases, osteoporosis and neoplasia.[1]

Tocilizumab is under development for the treatment of GCA in adults administered via intravenous injection at a dose of 8mg/kg every four weeks, in a phase II clinical trial (NCT01450137).[2] Tocilizumab (162 mg subcutaneous injection) is already licensed by the EMA for the treatment of GCA in adult patients.

Tocilizumab, in combination with methotrexate (MTX), is indicated for the treatment of rheumatoid arthritis in adults.[3] Tocilizumab (20 mg/ml concentrate for solution for infusion) is also licensed for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older, and for juvenile idiopathic polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older.[5]

Tocilizumab is in phase II and phase III clinical trial development for the following conditions:

- Schnitzler syndrome
- Cardiovascular disease
- Pulmonary arterial hypertension
- Amyotrophic lateral sclerosis
- Refractory adult polymyositis and dermatitis
- Takayasu arteritis
- Osteoarthritis of the hand
- Uveitis
- Systemic sclerosis[4]

INNOVATION and/or ADVANTAGES

The most common treatment for GCA is glucocorticosteroid treatment (prednisolone), which works by reducing the activity of the immune system to reduce inflammation in the blood vessels, treating the symptoms rather than curing the underlying condition.[8] While this treatment is effective for many patients, it is associated with significant drawbacks. The efficacy of prednisolone declines as the dose is reduced to a level better tolerated by patients, and many patients may require higher doses to achieve remission, which leads to more frequent adverse events.[5]

As a disease-modifying therapy that inhibits the part of the immune system that causes the inflammation, tocilizumab has the potential to be more effective than current treatments, and may be able to completely replace prednisolone. Injection site reactions are relatively common in tocilizumab when given as subcutaneous injection, which would be minimised if given as intravenous infusion.[5]

DEVELOPER

Roche Products Ltd and Chugai Pharma UK Ltd

AVAILABILITY, LAUNCH or MARKETING

Tocilizumab was designated Breakthrough Therapy in October 2016 and Priority Review Designation in January 2017 in the USA for GCA.[4]

Tocilizumab was awarded PIM status for GCA by MHRA in May 2017.[6]

PATIENT GROUP

BACKGROUND

GCA is an autoimmune condition characterised by inflammation of large and medium sized blood vessels. An alternative name for this condition is "Temporal Arteritis" as the blood vessels in the temple area of the head (sides of the forehead) are commonly affected.[7] The “giant” cells are abnormal large cells that develop in the wall of the inflamed arteries.[8] GCA is very rare in people younger than 50, and is more common in women and people of northern European descent.[9] The cause of GCA is not known.

The most common symptoms of GCA include headache, with severe pain and tenderness over the temples and the scalp, prominent blood vessels at the temples, and pain in the jaw or tongue when talking or chewing. Patients may also experience fatigue, fever, weight loss and problems with vision.[8] As the condition affects the main blood vessels supplying parts of the body, a reduction in blood and oxygen supply can occur to different organs; reduction in the blood supply to the brain can cause a stroke, and reduction in the blood supply to the eyes can lead to blurred vision or blindness.[7] People with GCA often have symptoms of polymyalgia rheumatica (PMR), with pain, stiffness and tenderness in the muscles of the shoulders, arms, hips and legs, especially in the mornings.[10] Diagnosis of GCA is based on careful patient history, blood testing for markers of inflammation, eye examination and biopsy of an affected artery.[11]

Visual loss occurs in up to 20% of patients, and this may be related to late recognition. Early recognition, referral and treatment are essential, and guidance states that GCA should be regarded as a medical emergency.[11]

People with less complex or severe forms of GCA may recover in 2 years, and the average time to recovery is around three and a half years. Most people make a full recovery.[12] There is a relapse rate of about 50%, and in most relapsed cases the patient will be take a small dose of steroid treatment indefinitely.[7]

CLINICAL NEED and BURDEN OF DISEASE

Estimates for the number of people affected by GCA include:

- 22 people in every 100,000 are affected[9]; based on latest total population estimate for England and Wales (mid-2016) of 58,381,300[13], this equates to 12,844 people
- 1 in every 4,500 people will develop GCA each year[14]; based on latest population estimates, this equates to 12,974 people in England and Wales. However, a NICE scoping document implies that this rate is for people aged 40 years and over [15] (estimated population 29,120,412), equating to 6,471 persons
- Roche Products Ltd provided an estimated eligible population to receive tocilizumab as 31,829 on the UKPharmaScan record.[16]

There are wide variations in clinical practice, and GCA may be managed in primary or secondary care.[17] It is not therefore possible to state how many healthcare contacts are made for GCA.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Tocilizumab for treating giant cell arteritis (TA10172). Expected April 2018.
- NICE clinical knowledge summary. Giant cell arteritis. July 2014.

NHS ENGLAND and POLICY GUIDANCE

- NHS Clinical Commissioning Policy. Tocilizumab for Giant Cell Arteritis (adults) 16019/P. July 2016.
- NHS England. 2013/14 NHS Standard Contract for Specialised Rheumatology Services (Adults). A13/S/a.

OTHER GUIDANCE

Royal College of Physicians. Diagnosis and management of giant cell arteritis. August 2010.[17]

CURRENT TREATMENT OPTIONS

The two aims of treatment are to relieve patient's symptoms and prevent damage to organs (especially the eyes) due to reduced blood supply.[7] National guidelines recommend high-dose glucocorticosteroid therapy (prednisolone) should be initiated immediately:

- 40–60 mg (not less than 0.75 mg/kg) daily until resolution of symptoms and laboratory abnormalities for uncomplicated GCA

- intravenous methylprednisolone 500 mg to 1 g daily for three days followed by oral prednisolone for complicated GCA with evolving visual loss or history of amaurosis fugax
- at least 60 mg oral prednisolone daily for complicated GCA with established vision loss.[17]

The symptoms of GCA should respond rapidly to high-dose glucocorticosteroid treatment, followed by resolution of the inflammatory response. Steroid-related complications (e.g. weight gain, fractures, diabetes, hypertension, cataracts and bruising) are also common hence the importance of monitoring and titrating the dose down as soon as it is safe to do so. Low-dose aspirin has also been reported to decrease the rate of visual loss and cerebrovascular accidents in GCA, however the British Society for Rheumatology Guidelines show a low level of evidence and conflicting reports of efficacy in preventing ischaemic events in GCA patients.[17] It is also recommended that a proton pump inhibitor is prescribed for gastrointestinal protection.[18]

For relapsing GCA:

- Increase the daily dose of prednisolone to 60mg and refer to ophthalmologist for new-onset visual disturbance
- Increase the daily dose of prednisolone to 60mg and seek specialist advice if jaw claudication develops
- Increase prednisolone to the previous higher dose if the patient develops headaches without jaw claudication or develops only features of polymyalgia rheumatica[18]

In recurrent or resistant GCA, methotrexate or other immunosuppressives (e.g. azathioprine or leflunomide) may be used as adjuvant therapy to allow reduction in the cumulative glucocorticosteroid dose, or a higher probability of glucocorticosteroid discontinuation without relapse.[17]

EFFICACY and SAFETY	
Trial	NCT01450137; tocilizumab vs placebo; phase II
Sponsor	Roche Products Ltd
Status	Published
Source of Information	Trial registry[2] and publication[19]
Location	Switzerland
Design	Randomised, placebo-controlled, double blind study
Participants	n=30; aged ≥50 years; new onset or relapsed GCA
Schedule	Randomised to receive tocilizumab 8mg/kg intravenously and prednisone (starting at dose of 1mg/kg/day and tapered weekly by 0.1mg/kg/day until week 8, then weekly by 0.05 mg/kg reaching 0.1mg/kg by week 12, then reduced every month by 1mg per day to 0mg) every four weeks until week 52; or receive tocilizumab matched placebo intravenously and prednisone at dose of 0.1mg/kg/d every four weeks until week 52
Follow-up	Active treatment for 52 weeks
Primary Outcomes	Proportion of patients that have achieved complete remission of disease (normal ESR and CRP + absence of signs and symptoms) [time frame: 12 wks]
Secondary Outcomes	Proportion of relapse free patients [time frame: 12 mths]

	Cumulative dose of prednisone in mg [time frame: 12 mths] Time to first relapse after induction of remission [time frame: 12 mths]
Key Results	20 patients were randomly assigned to receive tocilizumab and prednisolone, and ten patients to receive placebo and glucocorticoid; 16 (80%) and seven (70%) patients, respectively, had new-onset giant cell arteritis. 17 (85%) of 20 patients given tocilizumab and four (40%) of ten patients given placebo reached complete remission by week 12 (risk difference 45%, 95% CI 11-79; p=0.0301). Relapse-free survival was achieved in 17 (85%) patients in the tocilizumab group and two (20%) in the placebo group by week 52 (risk difference 65%, 95% CI 36-94; p=0.0010). The mean survival-time difference to stop glucocorticoids was 12 weeks in favour of tocilizumab (95% CI 7-17; p<0.0001), leading to a cumulative prednisolone dose of 43 mg/kg in the tocilizumab group versus 110 mg/kg in the placebo group (p=0.0005) after 52 weeks.[19]
Adverse effects (AEs)	Seven (35%) patients in the tocilizumab group and five (50%) in the placebo group had serious adverse events.[19]

ESTIMATED COST and IMPACT

COST

Tocilizumab is already marketed in the UK for the treatment of rheumatoid arthritis and active systemic juvenile idiopathic arthritis, and is currently being appraised by NICE for the treatment of Giant Cell Arteritis;

- 1 x 80mg/4ml concentrate for solution for infusion vial has an NHS indicative price of £102.40,
- 1 x 200mg/10ml concentrate for solution for infusion vial has an NHS indicative price of £256.00,
- 1 x 400mg/20ml concentrate for solution for infusion vial has an NHS indicative price of £512.00.[20]

A Patient Access Scheme is available.

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

☐ 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: *reduced use of secondary care/specialist services*

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

REFERENCES

[1]Electronic Medicines Compendium. *RoActemra 162 mg Solution for Injection in Pre-Filled Syringe.* Available from: https://www.medicines.org.uk/emc/product/5357 [Accessed 26 January 2018]

[2]ClinicalTrials.gov. *Tocilizumab for patients with giant cell arteritis: NCT01450137.* Available from: https://clinicaltrials.gov/ct2/show/NCT01450137 [Accessed 28 November 2017]

[3]Specialist Pharmacy Services. *Tocilizumab.* Available from: https://www.sps.nhs.uk/medicines/tocilizumab/ [Accessed 27 October 2017]

[4] Global Data. *RoActemra.* Available from: https://pharma.globaldata.com/ProductsView.aspx?ProductType=0,1&ProductID=2547 [Accessed 27 October 2017]. Login required

[5] GlobalData. *OpportunityAnalyzer: Vasculitis - Opportunity Analysis and Forecast to 2024.* Available from: https://pharma.globaldata.com/Reportsview.aspx?DocID=48831 [Accessed 1 December 2017]. Login required

[6] National Institute for Health and Care Excellence. *Single Technology Appraisal: Tocilizumab for treating giant cell arteritis, Committee papers.* Available from: https://www.nice.org.uk/guidance/gid-ta10172/documents/committee-papers [Accessed 26 January 2018]

[7] Vasculitis UK. *About Vasculitis*. Available from: http://www.vasculitis.org.uk/about-vasculitis/giant-cell-arteritis-temporal-arteritis [Accessed 28 November 2017]

[8] Polymyalgia Rheumatica & Giant Cell Arteritis UK. *What is Giant Cell Arteritis (GCA) or Temporal Arteritis (TA)?* Available from: http://www.pmrgca.co.uk/content/gca [Accessed 28 November 2017]
[9] Arthritis UK. *Who gets giant cell arteritis (GCA)?* Available from: https://www.arthritisresearchuk.org/arthritis-information/conditions/giant-cell-arthritis/who-gets-it.aspx [Accessed 28 November 2017]
[10] Arthritis UK. *What are the symptoms of giant cell arteritis (GCA)?* Available from: https://www.arthritisresearchuk.org/arthritis-information/conditions/giant-cell-arthritis/symptoms.aspx [Accessed 28 November 2017]
[11] NIHR Signal. *Ultrasound could help diagnose giant cell arteritis.* February 2017. Available from: https://discover.dc.nihr.ac.uk/portal/article/4000712/ultrasound-could-help-diagnose-giant-cell-arteritis [Accessed 28 November 2017]
[12] Polymyalgia Rheumatica & Giant Cell Arteritis UK. *Frequently Asked Questions.* Available from: http://www.pmrgca.co.uk/content/living/faqs [Accessed 28 November 2017]
[13] Office for National Statistics. *Population Estimates for UK, England and Wales, Scotland and Northern Ireland: mid-2016.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2016#main-points [Accessed 24 November 2017]
[14] NHS Choices. *Giant cell arteritis.* Available from: https://www.nhs.uk/conditions/giant-cell-arteritis/ [Accessed 28 November 2017]
[15] National Institute for Health and Care Excellence. *Final scope for the appraisal of tocilizumab for treating giant cell arteritis.* Available from: https://www.nice.org.uk/guidance/gid-ta10172/documents/final-scope [Accessed 28 November 2017]
[16] UKPharmaScan. *Technology Summary (644994).* Available from: https://www.ukpharmascan.org.uk/HS/technology/644994 [Accessed 28 November 2017] Login required
[17] Royal College of Physicians. *Diagnosis and management of giant cell arteritis.* August 2010. Available from: https://www.rcplondon.ac.uk/guidelines-policy/diagnosis-and-management-giant-cell-arteritis [Accessed 28 November 2017]
[18] National Institute for Health and Care Excellence. *Clinical Knowledge Summary: Giant cell arteritis*. Available from: https://cks.nice.org.uk/giant-cell-arteritis#!scenario [Accessed 1 December 2017]
[19] Villiger PM, Adler S, Kuchen S et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *The Lancet*. 2016 May 7-13;387(10031):1921-1927. Available from: https://doi.org/10.1016/S0140-6736(16)00560-2 [Accessed 1 December 2017]
[20] British National Formulary. *Tocilizumab*. Available from: https://bnf.nice.org.uk/medicinal-forms/tocilizumab.html [Accessed 1 December 2017]