NHS England

Clinical Commissioning Policy Proposition:

Tocilizumab for Giant cell arteritis (adults)

Version Number: NHS England A13X12/01

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Plain Language Summary

This policy proposition sets out NHS England's proposed commissioning approach to the use of tocilizumab in the treatment of adults with Giant cell arteritis.

Giant cell arteritis (GCA) is a form of large vessel vasculitis (LVV); a swelling in the vessel walls of the aorta (the main blood vessel running from the heart to the rest of the body) and the main arteries. There are two forms of LVV, with this policy proposition considering giant cell arteritis (GCA).

Without successful treatment, GCA can lead to organ failure, blindness and damage to the blood vessels that may require reconstructive surgery. Current treatment includes steroids and immunosupressants (drugs that reduce the body's immune response), however both of these therapies have limited effectiveness and can have side effects.

Tocilizumab is a monoclonal antibody (a type of protein) that has been designed to recognise and attach to a specific structure (called an antigen) that is found in the body. Tocilizumab has been designed to attach to the receptor for a messenger molecule or ‘cytokine’ in the body called interleukin-6. This messenger is involved in causing inflammation (swelling).

NHS England has concluded that there is insufficient evidence to support a proposal for the routine commissioning of tocilizumab in the treatment of adults with Giant cell arteritis.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission tocilizumab in the treatment of adults with Giant cell arteritis.
For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether tocilizumab for Giant cell arteritis will be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. Proposed Intervention and Clinical Indication

Giant cell arteritis (GCA) is a form of large vessel vasculitis (LVV); a swelling of the blood vessel walls which affects the aorta and the main arteries. There are two forms of LVV, GCA and Takayasu arteritis (TAK), of which the former is under consideration of this policy proposition.

Treatment involves three phases: remission induction, remission maintenance and treatment of relapse. All individuals with GCA should be reviewed at regular intervals to formally assess and define disease activity and damage status using a formal instrument, predominantly with non-invasive imaging. This is essential to ensure that an accurate ascertainment of remission, refractory disease or relapse can be documented in every patient.

Without treatment, GCA can lead to organ failure, irreversible ischaemia from large vessel stenosis or aneurysm requiring potentially hazardous large vessel reconstruction. Up to 25% of patients with GCA suffer from blindness. The likelihood of relapse varies.

Relapse and poor response carry a risk that additional, critical ischaemic damage will occur, leading to irreversible deterioration in health. Relapse is also associated with hospitalisation, the need for major surgical reconstruction of greater vessels and infection risk from steroids and immunosuppression of remission re-induction.

Not everyone responds to standard treatment - on average, 70% of those treated will be in remission at two years. Increasing age and ischaemic symptoms at diagnosis are poor prognostic factors and glucocorticoid toxicity, particularly in older patients, causes major adverse events in 85%. Patients with refractory disease are also at higher risk of complications to standard of care therapy.

Complications of the disease and standard treatment (high doses of glucocorticoid therapy) can result in significant chronic morbidity. Specific complications include the risk of visual loss and the incidence of steroid related toxicity and the need for surgical intervention.

The current standard of care of high dose glucocorticoids with or without immunosuppressives is complicated by toxicity and limited efficacy.

Tocilizumab is an interleukin-6 (IL-6) inhibitor, which decreases the inflammatory response and is licensed for use in rheumatoid arthritis (EMA/502328/2014).

3. Definitions

Vasculitis (plural: vasculitides) means 'inflammation of the blood vessels'. It leads to swollen blood vessel walls and narrowed blood vessels.

Giant cell arteritis (GCA) is an inflammation of the lining of the arteries. Most often, it affects the arteries in the head and neck, especially those in the temples. For this reason, giant cell arteritis is sometimes called temporal arteritis. Giant cell arteritis frequently causes headaches, scalp tenderness, jaw pain and vision problems. If left untreated, it can lead to stroke or blindness.

A monoclonal antibody is an antibody (a type of protein) that has been designed to recognise and attach to a specific structure called an antigen that is found in the body. Tocilizumab has been designed to attach to the receptor for a messenger molecule or 'cytokine' in the body called interleukin-6 (IL-6). This messenger is involved in causing inflammation. By preventing IL-6 attaching to its receptors, tocilizumab reduces inflammation.

4. Aim and Objectives

This policy proposition aims to define NHS England's commissioning position on tocilizumab as part of the treatment pathway for adult patients with Giant cell arteritis.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults with Giant cell arteritis.

5. Epidemiology and Needs Assessment

Although the cause of GCA is unknown; T cells, cytokine-primed monocytes and macrophages are recognised to have an important role in disease pathogenesis.

GCA is much more common, especially in older people, with an incidence of 220 new cases per million per annum. Peak age of onset is between the ages of 70- 80 years [1] and can result in permanent loss of sight in up to 37% of cases [2].

Consensus of clinical opinion is that an estimated 10% of all new patients with GCA will develop treatment resistant disease and may benefit from a biologic agent, as a result of which they would reduce their daily steroid use to below 15mg per day.

6. Evidence Base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of tocilizumab in the treatment of adults with Giant cell arteritis.

An evidence review was undertaken to identify the evidence available for the use of tocilizumab in the treatment of GCA and TAK. TAK is a different form of large vessel vasculitis and is the subject of a separate policy proposition.

Is tocilizumab more clinically and/or cost effective for the treatment of the above mentioned conditions compared to sustained treatment with high dose glucocorticoids, cyclophosphamide or other biologics?

SUMMARY

The overall evidence for tocilizumab (TCZ) for the treatment of large vessel vasculitis, specifically Giant Cell Arteritis (GCA) and Takayasu Arteritis (TAK) is limited and low level, composed exclusively of single-arm observational studies with few patients and one systematic review with meta-analysis of low quality studies. Overall, the current evidence appears to indicate that TCZ therapy could lead to disease remission in patients with refractory GCA and TAK with relapse rates of 16-18%. TCZ also appears to cause potentially serious adverse events in a significant proportion of patients which could be similar to that observed with other biological-targeted treatments.

Clinical effectiveness: Is tocilizumab (TCZ) clinically effective for the treatment of large vessel vasculitis, specifically Giant Cell Arteritis (GCA) and Takayasu Arteritis (TAK)?

In the studies reviewed, clinical effectiveness of tocilizumab was reported in terms of reduction of clinical symptoms, normalisation of inflammatory markers and imaging (PET/CT) findings. There was limited clarity on the amount of glucocorticoids/ corticosteroids (CS) dose reduction that could be considered clinically significant and most studies reported variable amount if dosage reduction. Standard tocilizumab dose was 8mg/kg/IV/4 weeks across the studies.

The best evidence for clinical effectiveness of TCZ was from a systematic review and meta-analysis by Osman et al (2014) investigating the role of biological agents in the management of large vessel vasculitis. Out of a total of 25 studies shortlisted, 5 case series with 19 total GCA patients and 4 case series with a total of 11 TAK patients were specific to TCZ. There were only 3 RCTs and none of which involved TCZ. In the meta-analysis, all 19 GCA patients treated with TCZ achieved disease remission. There was corticosteroid (CS) dose reduction for all patients and total discontinuation of steroids in 9 (47%) patients. Pooled mean CS dose reduction was 16.55 mg per day (95% CI -26.24 to -6.86).

For 11 patients with TAK who received TCZ, 10 achieved remission (90%). All patients had a reduction of CS use with 4 (36%) discontinuing corticosteroids. Overall relapse rate in both groups was 16-18%. No adverse events were reported with TCZ in all four studies involving TAK patients. However, 5/19 (26.3%) of GCA patients treated with TCZ were reported to have a transient, self-limited transaminitis. Some patients also developed leukopenia but did not have increased infection rates. One patient developed a post-operative myocardial infarction,

and autopsy demonstrated active GCA despite normal clinical, serological and radiographic values.

While Osman et al (2014) is a well conducted systematic review and meta-analysis, all the evidence for TCZ comes from small case series with relatively short follow-up period. Such observational studies suffer from inherent bias as well as difference between study populations and treatment protocols between studies. The wide confidence interval in the meta-analysis data could be due to this heterogeneity.

Loricera et al. (2014) included 16 GCA and TAK patients refractory to glucocorticoid treatment. The study reported effectiveness of TCZ monotherapy for 6 GCA patients. The remaining 10 patients received anti-TNF agents before TCZ. At a standard dose was 8 mg/kg/IV/4 weeks, most patients experienced clinical improvement at average one year follow-up. Mean erythrocyte sedimentation rate reduced from 43±36 mm/1st h to 5±4 mm/1st h. At TCZ onset, 25% of patients had fever and 19% polymyalgia rheumatic. These manifestations disappeared after 3 months of TCZ therapy. A corticosteroid sparing effect was also reported (27.3±17.6 mg/day of prednisone at TCZ onset to 4.2±3.8 mg/day at last visit). TCZ had to be discontinued in one patient because of severe neutropenia.

In a more recent study on 22 GCA patients with refractory disease and/or unacceptable side effects due to corticosteroids, 15 were asymptomatic after three months of TCZ therapy. At a median follow up of 9 months, there was reduction of serum CRP levels from 1.9 (1.2–5.4) to 0.2 (0.1–0.9) mg/dL; $p<0.0001$ and ESR values from 44 (20–81) to 12 (2–20) mm/1st hour; $p<0.001$ in the study population. Median prednisone dose was reduced from 18.75 to 5 mg/day at the last visit. Corticosteroids were tapered in 20 patients, and discontinued in 4. While this high response rates and good laboratory outcome was encouraging, it was also reported that 6 patients suffered TCZ-linked adverse events, including severe neutropenia and one death due to infectious endocarditis (Loricera et al., 2015).

Another recent case series by Mekinian et al (2015) on 49 patients with resistant TAK from multiple centres in France treated between 2001-2013 compared patients treated with tocilizumab (n=14) with those receiving TNF-α antagonists (n=56). This study reported that the proportion of complete or partial responses did not differ at 3, 6, and 12 months for the two groups (75% for TCZ, 83% for TNF- α A). 3-year relapse-free survival in patients on tocilizumab (85.7%) was statistically similar to patients on TNF-α A (91%) (P=0.81). CRP levels and the prednisone daily dose tended to be lower at 12 months in TAK patients treated with tocilizumab. While 21% of the 14 patients undergoing TCZ treatment had adverse events, including severe asymptomatic neutropenia, severe bacterial infections and breast cancer (with family history), no significant difference in terms of safety was observed between the various biological-targeted treatments, with up to 20% side effects in the entire treatment group (Mekinian et al., 2015).

In a small case series involving 10 difficult to treat TAK patients in India with active disease in spite of treatment with steroids and second line agents for a median duration of 27 months, TCZ led to a significant clinical response with Indian Takayasu Arteritis Score (ITAS) falling to zero (from average 4.5 prior to treatment) and reduction in acute phase reactants in all 10 patients by the fourth infusion (8 mg/kg/day with maximum of 600 mg/infusion). There was significant reduction in steroid dosage Six patients (60%) maintained clinical response up to the sixth infusion and only two patients maintained stable disease state after discontinuation of

therapy (Goel et al, 2013).

Cost effectiveness: Is tocilizumab cost effective for the treatment of large vessel vasculitis, specifically Giant Cell Arteritis (GCA) and Takayasu Arteritis (TAK)?

There were no studies identified that specifically addressed the clinical and cost effectiveness of tocilizumab for the treatment of large vessel vasculitis, specifically Giant Cell Arteritis (GCA) and Takayasu Arteritis compared to sustained treatment with high dose glucocorticoids, cyclophosphamide or other biologics.

Relative clinical and cost effectiveness: Is tocilizumab more clinically and/or cost effective for the treatment of the above mentioned conditions compared to sustained treatment with high dose glucocorticoids, cyclophosphamide or other biologics?

Overall, there is poor quality and inconclusive evidence on comparative effectiveness of TCZ. The systematic review and meta-analysis by Osman et al (2014) analysed data from 25 studies on different biological agents in the management of large vessel vasculitis. The results of three randomised control trials included in the review show that anti-TNF agents (infliximab, etanercept and adalimumab) are not effective in inducing remission or in reducing CS doses in patients with GCA. On the other hand, results from case series of patients with GCA and TAK suggested that TCZ may be of some benefit for the maintenance of remission, and for the reduction of CS use. Case series results also suggest that infliximab may be beneficial in the maintenance of remission and possibly reducing the amount of CS use in TAK patients. As the RCTs did not include TCZ, it is difficult to draw any conclusions on comparative effectiveness of TCZ with other biologics.

Only one study compared tocilizumab directly to other biologics in the treatment of TAK. Mekinian et al. (2015) conducted a retrospective, observational study that compared the efficacy of TCZ to TNF-α antagonists (infliximab (n=44), etanercept (n=6), adalimumab (n=6)). Mekinian et al. reported promising results for TCZ use in TAK patients, with superior outcomes at 6 months compared to TNF-α antagonists. This included higher response rates (90% vs. 68%), improved CRP levels (2 mg/L vs 6 mg/L.) and lowered prednisone doses (10mg/d vs. 14 mg/d). The authors of the study reported no significant difference in safety between TNF-α antagonists (side effects in 13 of 56 patients, 23.2%) and tocilizumab (side effects in 3 of 14 patients, 21.4%; P>0.05).However, due to the small sample size of patients treated with etanercept and adalimumab, no statistical correlations could be meaningfully drawn for these two drugs. Furthermore, the retrospective, observational nature of the study meant that treatment options were assigned without randomisation.

7. Documents That Have Informed This Policy Proposition

[1] Smeeth L, Cook C, Hall AJ. Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990-2001. Ann Rheum Dis. 2006 Aug;65(8):1093-8. Epub 2006 Jan 13.

[2] Patil P, Williams M, Maw WW, Achilleos K, Elsideeg S, Dejaco C, Borg F, Gupta S, Dasgupta B. Fast track pathway reduces sight loss in giant cell arteritis: results of a longitudinal observational cohort study. Clin Exp Rheumatol. 2015 Mar-Apr;33(2 Suppl 89):S-103-6.

8. Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016).