Clinical Commissioning Policy: Tocilizumab for Takayasu arteritis (adults)

Reference: NHS England: 16056/P

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Clinical Commissioning Policy: Tocilizumab for Takayasu arteritis (adults)

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Policy Statement

NHS England will commission tocilizumab for Takasayu arteritis (adults) in accordance with the criteria outlined in this document. In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources. This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About takayasu arteritis

Takayasu arteritis (TAK) is a form of 'large vessel vasculitis' (LVV) - a swelling in the vessel walls of the aorta (the major blood vessel running from the heart to the rest of the body) and the main arteries. Without successful treatment, TAK can lead to:

- organ failure
- damage to the blood vessels – and patients may need surgery to re-construct the damaged vessels.

About current treatment

Current treatment includes steroids and immuno-suppressants - both of these types of medicine reduce the body's immune response and can help to reduce swelling (inflammation). However, they do not always work well enough and can have side effects.

About the new treatment

Tocilizumab belongs to a group of medicines known as ‘monoclonal anti-bodies’.

- It is a biological medicine that works by ‘targeting’ specific proteins (receptors) on the surface of cells relevant to the cause of the disease.
- Tocilizumab attaches to the receptor for a ‘messenger’ called interleukin-6 – which is involved in causing swelling (inflammation).

Tocilizumab can help to reduce swelling in the blood vessels for patients with TAK.

What we have decided

NHS England has carefully reviewed the evidence to treat takayasu arteritis with tocilizumab. We have concluded that there is enough evidence to consider making the treatment available.

1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission tocilizumab in the treatment of adults with Takayasu arteritis (TAK).

TAK 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, giant cell arteritis (GCA) and TAK, of which the latter is under consideration of this policy proposition.

Treatment involves three phases: remission induction, remission maintenance and treatment of relapse. All individuals with TAK 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, TAK can lead to organ failure, irreversible ischaemia from large vessel stenosis or aneurysm requiring potentially hazardous large vessel reconstruction. The likelihood of relapse is high, with up to 84% of patients failing to respond to steroids.

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 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 has been designed to recognise and attach to antigens in the body. It is an interleukin‑6 (IL-6) inhibitor, meaning it decreases the inflammatory response. It is licensed for use in rheumatoid arthritis (EMA/502328/2014).

2 Definitions

Vasculitis is the inflammation of the blood vessels. It leads to swollen blood vessel walls and narrowed blood vessels.

TAK is an inflammatory disease of the large arteries. TAK particularly affects the aorta and the pulmonary artery. The major arteries that arise from the aorta may also be affected. These include the subclavian arteries that supply the arms, renal arteries to the kidneys, coronary arteries in the heart and carotid arteries in the head and brain. In some patients, widening of the aorta results in failure of the aortic valve in the heart, necessitating replacement. In 90% of patients one or more of these arteries become narrowed or blocked, hence TAK is also known as "pulseless disease". In 25% of patients part of an artery may swell, forming an aneurysm.

A monoclonal antibody is an antibody 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 IL-6. This messenger is involved in causing inflammation. By preventing IL‑6 attaching to its receptors, tocilizumab reduces inflammation.

Disease-modifying anti-rheumatic drugs (DMARDs) are a group of medications commonly used in patients with rheumatoid arthritis. They work to slow down disease

progression and include azathioprine, ciclosporin, leflunomide, methotrexate and mycophenolate mofetil. These agents, also commonly referred to as immunosuppressive therapies are also widely used in a variety of other inflammatory conditions including vasculitis.

3 Aims and Objectives

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

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

4 Epidemiology and Needs Assessment

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

TAK has an estimated incidence of 0.7-1.5 per million per annum in Europe, and an average age of onset of 23 years (Mohammed et al, 2015).

Consensus of clinical opinion is that an estimated 50% of patients with TAK will develop treatment resistant disease and may benefit from a biologic agent, as a result of which they would reduce their daily steroid.

5 Evidence base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of tocilizumab in the treatment of adult patients with TAK.

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

vasculitis and is the subject of a separate policy proposition (NHS England Clinical Commissioning Policy 16019/P).

Summary

The overall evidence for tocilizumab for the treatment of large vessel vasculitis, specifically GCA and TAK is 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 tocilizumab therapy could lead to disease remission in patients with refractory GCA and TAK with relapse rates of 16-18%. Tocilizumab 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 highest level evidence for clinical effectiveness of tocilizumab 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 tocilizumab. There were only 3 RCTs and none of which involved tocilizumab. In the meta-analysis, all 19 GCA patients treated with tocilizumab achieved disease remission. There was 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 tocilizumab, 10 achieved remission (90%). All patients had a reduction of CS use with 4 (36%) discontinuing CS. Overall relapse rate in both groups was 16-18%. No adverse events were reported with tocilizumab in all four studies involving TAK patients. However, 5/19 (26.3%) of GCA patients treated with tocilizumab 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 tocilizumab 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 tocilizumab monotherapy for 6 GCA patients. The remaining 10 patients received anti-TNF agents before tocilizumab. At a standard dose of 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 hour to 5±4 mm/1st hour. At tocilizumab onset, 25% of patients had fever and 19% polymyalgia rheumatic. These manifestations disappeared after 3 months of tocilizumab therapy. A corticosteroid sparing effect was also reported (27.3±17.6 mg/day of prednisone at tocilizumab onset to 4.2±3.8 mg/day at last visit). Tocilizumab 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 tocilizumab 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 rate and good laboratory outcome was encouraging, it was also reported that 6 patients suffered tocilizumab-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 tocilizumab, 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 tocilizumab 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, tocilizumab 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 GCA and TAK 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 tocilizumab. 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 tocilizumab 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 tocilizumab, it is difficult to draw any conclusions on comparative effectiveness of tocilizumab 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 tocilizumab to TNF-α antagonists (infliximab (n=44), etanercept (n=6), adalimumab (n=6)). Mekinian et al. reported promising results for tocilizumab 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.

6 Criteria for Commissioning

Tocilizumab will be prescribed for adult patients where attempts to control disease progression of TAK have failed despite a trial of first line treatment (steroids in addition to DMARD) and second line treatment (steroids in addition to cyclophosphamide or DMARD administered for a minimum of 6 months).

Inclusion criteria:

(i) Patient presents with symptoms of active TAK according to at least one Birmingham Vasculitis Activity Score (BVAS) or Indian Takayasu Arteritis Activity (ITAS) score or on MR/CT imaging; AND

(ii) Shows an incomplete response, has a contraindication to, or has significant adverse effects from first line treatment: steroids and a DMARD such as methotrexate, azathioprine, leflunomide, cyclosporine or mycophenolate mofetil; AND

(iii) Shows an incomplete response, has a contraindication to, or has significant adverse effects from second line treatment or re-treatment: steroids and trial of cyclophosphamide or another DMARD such as mycophenolate mofetil for a minimum of 6 months.

Exclusion criteria:

(i) Patients with active infection or as advised by manufacturer (defined in Summary of Product Characteristics).

Stopping criteria:

(i) Serious adverse effects (including all cancers apart from non-melanoma cancers, recalcitrant bacterial infections); OR

(ii) Shows incomplete response at 6 months as assessed by clinical examination according to MR/CT imaging and supported by BVAS/ITAS scores; OR

(iii) Shows adequate response at 12 months as assessed by clinical examination according to MR/CT imaging and supported by BVAS/ITAS scores; OR

(iv) Patient chooses to discontinue treatment; OR

(v) Evidence of non-compliance as indicated by clinical assessment, MR/CT imaging and supported by BVAS/ITAS scores.

7 Patient Pathway

Steroids (prednisolone) is the standard therapy for TAK, however, 50% of patients will need further treatment to achieve disease control. The first line treatment for TAK is steroids with DMARDs (methotrexate, azathioprine, leflunomide, cyclosporine or mycophenolate mofetil). The standard second line treatment is steroids with cyclophosphamide or DMARDs not previously trialled. Tocilizumab would be considered as a third line treatment if adequate disease control was still not achieved.

A small minority will not respond and will continue to have active or progressive disease that is refractory to conventional treatment. It is also noted that cyclophosphamide has significant cumulative side effects including gonadal toxicity inducing premature failure, bone marrow depression and infection, haemorrhagic cystitis, and an increased risk of future uroepithelial (bladder) cancer. As a consequence, any new treatments that can potentially limit exposure to cyclophosphamide and avoid its chemotherapy side effects should be considered

especially for people who have not completed their family (see patient pathway diagram below).

Tocilizumab is first given intravenously (at 8mg/kg), followed by 162mg given as a subcutaneous injection every 7 days (starting 28 days after the infusion).

In the absence of toxicity, treatment with tocilizumab should be continued for 6 months in the first instance.

For non-responders, defined as either:
(1) Development of >1 new stenosis of ≥50% lumen diameter in a large vessel, or limited dilatation ≤50% lumen diameter (without definite aneurysm formation) on MR or CT angiography studies: OR
(2) No increase, or up to 50% reduction in arterial wall PET enhancement of the arterial tree, treatment would be discontinued at 6 months.

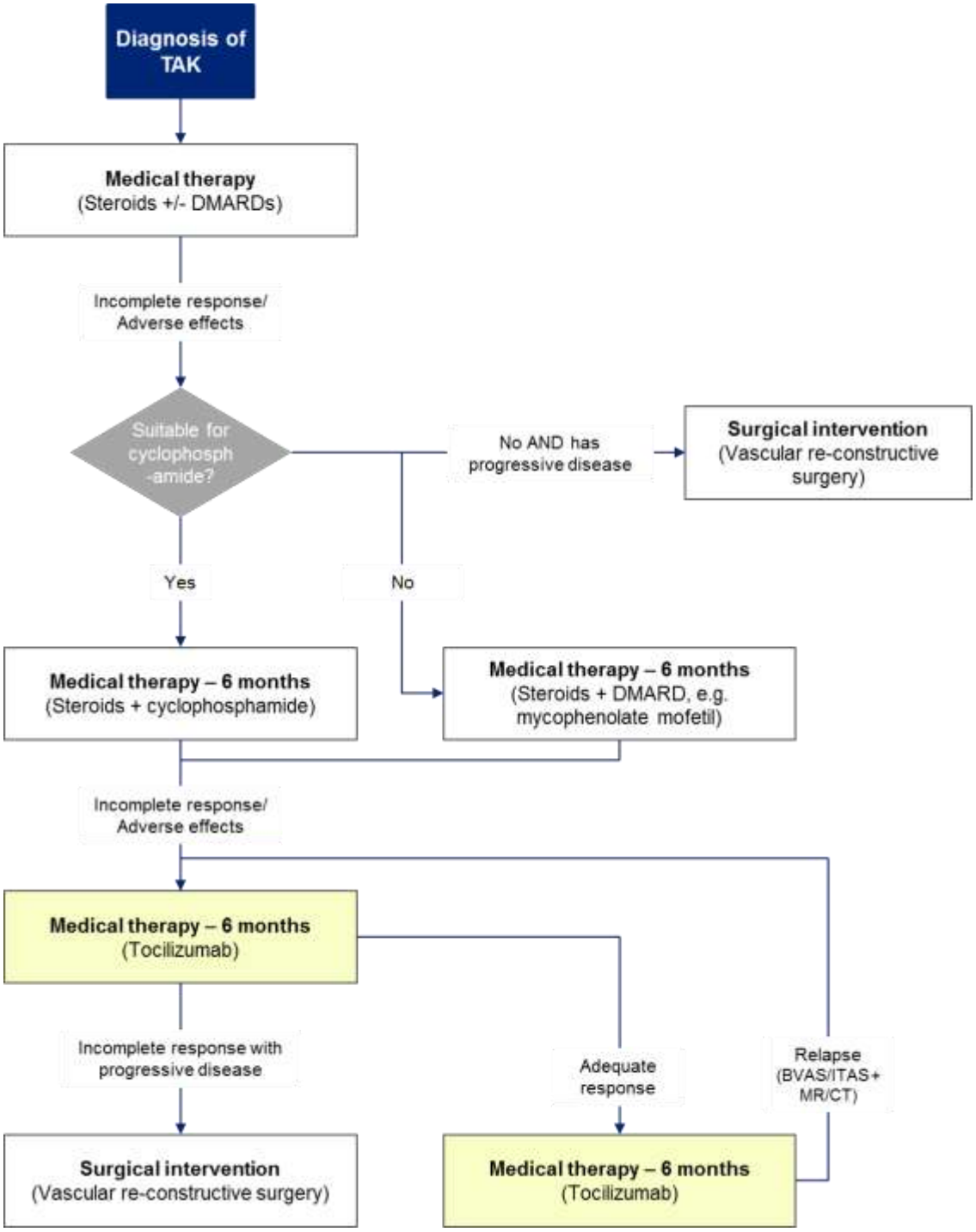
For non-responders who have active or progressive disease, surgical intervention to perform vascular re-constructive surgery is considered.

For responders, defined as improvement or stability of imaging findings, including either:
(1) Failure to develop further increases in arterial wall thickness, stenosis or dilatation/aneurysm, based on MR or CT angiography studies; OR
(2) Resolution of PET enhancement without anatomical progression of arterial disease, the treatment should continue for another 6 months before the patient is gradually stepped down to non-biological agent maintenance therapy (which could include any or all of the following: low dose glucocorticoids, conventional DMARDs such as methotrexate, azathioprine, leflunomide or mycophenolate mofetil).

If the patient is deteriorating during step-down, as assessed by BVAS/ITAS scores or on MR/CT imaging, tocilizumab should be indicated for 12 months to maintain remission.

Consensus of clinical opinion is that approximately 50% of patients with TAK will require a biologic agent, as a result of which they would reduce their daily steroid.

See illustrative patient pathway below.


Diagnosis of TAK
Medical therapy
(Steroids +/- DMARDs)
Incomplete response/
Adverse effects
Suitable for cyclophosph -amide?
No AND has progressive disease
Surgical intervention
(Vascular re-constructive surgery)
Yes
No
Medical therapy – 6 months
(Steroids + cyclophosphamide)
Medical therapy – 6 months
(Steroids + DMARD, e.g. mycophenolate mofetil)
Incomplete response/
Adverse effects
Medical therapy – 6 months
(Tocilizumab)
Incomplete response with progressive disease
Adequate response
Relapse
(BVAS/ITAS+ MR/CT)
Surgical intervention
(Vascular re-constructive surgery)
Medical therapy – 6 months
(Tocilizumab)

8 Governance Arrangements

All cases must be managed by a clinician or clinicians experienced in managing TAK, as well as a radiologist. Networked care arrangements between local and specialist centres to be put in place to provide clinical support in cases where clinicians manage a small number of patients.

9 Mechanism for Funding

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team.

10 Audit Requirements

Patients receiving these agents will be invited to join the UKIVAS registry, in order to review longer term efficacy and safety. Where patients choose not to join, patient data will be reported to local network of specialist centres and presented at regional level.

Treatment centres will use a decision support tool to track and audit use of tocilizumab, in order to ensure it is administered according to the Criteria for Commissioning.

11 Documents which have informed this Policy

Tocilizumab in the treatment of Giant Cell Arteritis. (NHS England Clinical Commissioning Policy 16019/P).

12 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

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