



Clinical Commissioning Policy Proposition: Tocilizumab for Takayasu arteritis (adults)

Reference: NHS England A13X06/01

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**Clinical Commissioning Policy Proposition:
Tocilizumab for Takayasu arteritis (adults)**

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Equality Statement

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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 Takayasu arteritis.

Takayasu arteritis (TAK) 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.

Without successful treatment, TAK can lead to organ failure and damage to the blood vessels that may require reconstructive surgery. Current treatment includes steroids and immunosuppressants (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). By suppressing the inflammatory response, tocilizumab may be suitable for the treatment of TAK, as it may reduce swelling in the blood vessels.

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

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.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanism.

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 Takayasu 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

Takayasu arteritis (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.

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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.

Takayasu Arteritis (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 (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.

Disease-modifying antirheumatic 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.

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 Takayasu arteritis.

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

5. 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.

Takayasu arteritis has an estimated incidence of 0.7- 1.5 per million per annum in Europe, and an average age of onset of 23 years [1].

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

6. 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 Takayasu arteritis.

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.

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).

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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).

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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. Proposed Criteria for Commissioning

Tocilizumab will be prescribed for adult patients where attempts to control disease progression of Takayasu arteritis 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, ciclosporin 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 (Summary of product characteristics, SPC).

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.

8. Proposed 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, ciclosporin 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

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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 dosage: 1st dose of 8mg/kg given intravenously, followed by 162mg given as a subcutaneous injection every 7 days (starting 28 days after the infusion).

Duration: 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 $\geq 50\%$ lumen diameter in a large vessel, or limited dilatation $\leq 50\%$ 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:

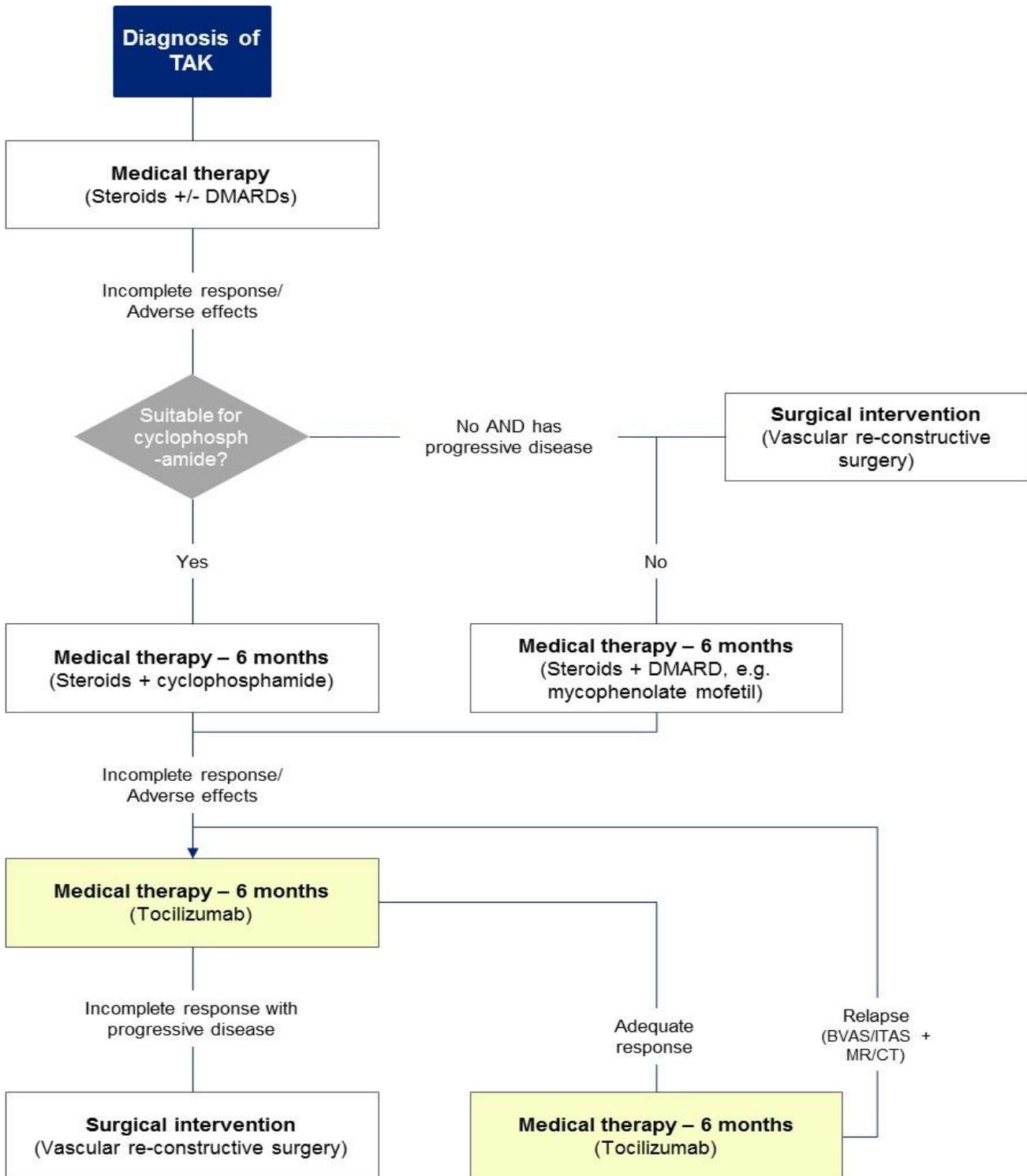
(1) Failure to develop further increases in arterial wall thickness, stenosis or dilatation/aneurysm, based on MR or CT angiography studies; OR

(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 Takayasu arteritis will require a biologic agent, as a result of which they would reduce their daily steroid.

Patient pathway
Illustrative diagram



9. Proposed 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.

10. Proposed Mechanism for Funding

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

11. Proposed 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 software systems to track and audit use of tocilizumab (Blueteq), in order to ensure it is administered according to the Criteria for Commissioning.

12. Documents That Have Informed This Policy Proposition

[1] Mohammad AJ, Mandl T. Takayasu arteritis in southern Sweden. J Rheumatol. 2015 May;42(5):853-8

13. 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).