Evidence Review:

Tocilizumab for Takayasu arteritis (adults)
NHS England

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Prepared by Turnkey Clinical Evidence Review Team on behalf of NHS England Specialised Commissioning
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>3</td>
</tr>
<tr>
<td>Summary of results</td>
<td>3</td>
</tr>
<tr>
<td>Research Questions</td>
<td>5</td>
</tr>
<tr>
<td>Methodology</td>
<td>5</td>
</tr>
<tr>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>References</td>
<td>See appendix 1</td>
</tr>
<tr>
<td>Literature Search Terms</td>
<td>See appendix 2</td>
</tr>
</tbody>
</table>
1. Introduction

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.

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

2. Summary of results

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

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

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

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.
Research question 1: 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 h; 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).

Research question 2: 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.

Research question 3: 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.

3. Research questions
Is tocilizumab clinically effective in the treatment of large vessel vasculitis?
Is tocilizumab cost effective in the treatment of large vessel vasculitis?
Is tocilizumab more clinically and/or cost effective in the treatment of large vessel vasculitis than sustained treatment with high dose glucocorticoids, cyclophosphamide or other biologics?

4. Methodology
A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results
A detailed breakdown of the evidence is included in the Appendix.
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<thead>
<tr>
<th>Level</th>
<th>Study design and intervention</th>
<th>Outcomes</th>
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<th>Other</th>
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<tr>
<td>3</td>
<td>Case series</td>
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<td>16 patients refractory to glucocorticoid (GC) treatment. 14 females, 2 males: Takayasu arteritis (TAK) (n=7 cases), giant cell arteritis (GCA) (n=7), relapsing polychondritis (RP) (n=1), and aortitis associated with retroperitoneal fibrosis (n=1). Ages ranged from 7-77 years. Comments: Single centre case series without clarity of methodology and patient selection. Complications were only reported on an ad hoc basis.</td>
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<td>TCZ monotherapy for patients (GCA patients). The remaining 10 patients received TCZ combined with other traditional synthetic immunosuppressive (anti-TNF) drugs: MTX (7 cases), mycophenolate mofetil (2 cases), and azathioprine (7 cases) before TCZ initial dosage of 8mg/kg/iv, and a maintenance TCZ dosage ranging between 4-8mg/kg every 2 weeks in 16 cases and every 2 weeks in 1 case.</td>
<td>Clinical effectiveness of the intervention: Improvement in clinical manifestations or in some cases patients became asymptomatic for chest and limb pain, fever, headache, claudication etc. (TAK patients); or jaw aethesia (muscle weakness), chest or scapular pain, headaches etc. (GCA patients). Laboratory tests: normalisation of CRP &lt;0.5 mg/dL, and ESR &lt;20mm/1st hour (women) or 25mm/1st hour (men).</td>
<td>Llorca, Javier; Blanco, Ricardo; Castañeda, Santos; Humbria, Alicia; Ortego-Cantu, Norberto; Narváez, Javier; Mata, Cristina; Melchor-Shell, Aurococcus, Elena; Cacho-Allén, Jaime; Uch, Pac Mol, Concepción; Minguez, Mauricio; Hernández-Baumont, Gabriel; Bravo, Beatriz; Rubio, Esteban; Freixa, Mercedes; Peñi, Enrique; González-Vila, Carmen; Rueda-Gotor, Javier; Pina, Trinitario; Palou, Fontanas, Natalia; Calvo-Río, Vanesa; Ortiz, Serpa, Francisco; González-Gay, Miguel Ángel. Tocilizumab in refractory aortitis: study on 16 patients and literature review. Clin. Exp. Rheumatol. 2014;32(3 Suppl 82):S79-89.</td>
<td>N/A</td>
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<td>Patients became asymptomatic or showed significant improvement, measured by CRP and ESR levels.</td>
<td>Complication: One patient suffered from a relapse TCZ treatment was discontinued for this patient due to severe neutropenia.</td>
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### Case series 1

**Patients:** 8 female Colombian patients. 3 were naïve to treatment, TCZ monotherapy 2 newly diagnosed GCA patients, azathioprine taken as an adjunctive. In 2 patients received combined therapy with GCs, with or without methotrexate, infliximab or tocilizumab taken as an adjunctive. In 2 newly diagnosed GCA patients biotherapy treatment for improved biological, clinical and radiological outcomes after TAK patients received TCZ treatment at the standard dose of 8mg/kg/month over a minimum of one year.

**Clinical effectiveness of the intervention:**
- Clinical improvement (visually normalisation of acute phase reactants)
- Decrease in dosage of GCs (decrease on acute phase reactants)
- In the 13 patients together 9 patients, only 3 were on biologic drugs - the target of the authors’ intended analysis. Of these 9 patients, only 5 were on the biologic therapy, but complications subsequently occurred.
- Detailed evidence for improved biological, clinical and radiological outcomes after TAK patients received TCZ treatment for the 13 patients together

**Complication:** None.

**Outcome:** One relapse was observed.

**Comments:** The paper was more a review than a systematic review. All in all, the 13 patients together presented as a case series. It had limited information on patient selection criteria. It demonstrated evidence for improved biological, clinical and radiological outcomes after TAK patients received TCZ treatment for the 13 patients together

### Case series 2

**Patients:** 2 female caucasian patients, and 1 male patient after 1 month post-biologic, 40 to 5 mg/day. The 26 year old male patient received both and in addition to that mycophenolate and AZA. Mean age 22.3 years (range 16 - 28 years).

**Clinical effectiveness of the intervention:**
- Indian Takayasu arteritis activity (ITAS) and damage scores (TADs) calculated. The disease activity and damage indices used were the CRP level (normal<10 mg/l), ESR (normal<30mm/hr), MRA, computed tomographic angiography and high resolution ultrasound were used to assess disease progression. End-points: 1. Change in CRP from decision to start biological to 6 months post biological, 2. Change in arterial diameter post-dose of TCZ administered at 8mg/kg/month, and MTX induced remission responsiveness on patient selection criteria. It demonstrated evidence for improved biological, clinical and radiological outcomes after TAK patients received TCZ treatment for the 13 patients together

**Complication:** None.

**Outcome:** One relapse was observed.

**Comments:** This paper was set out to be a meta-analysis of 38 patients, but in reality only 9 patients were on biologic drugs - the target of the authors’ intended analysis. Of these 9 patients, only 5 were on the biologic therapy, but complications subsequently occurred.

### Case series 3

**Patients:** 6 patients with severe refractory Takayasu arteritis, open biologic, uncontrolled, and/or patients with systemic symptoms and peripheral pulses, biological improvement (decrease on acute phase reactants) and improvements supported by radiology.

**Clinical effectiveness of the intervention:**
- These results were supported by reduced levels of euthyroidism and normalization of acute phase reactants.
- Imaging by PET and magnetic nuclear imaging. All patients received a much lower dose of prednisone (<10mg/day) until the most recent visit or biologic cessation. 4. Change in arterial injury, assessed by non-invasive angiography (new or worsening stenosis, occlusion, dilatation or aneurysm), from decision to start biological until the most recent visit or biologic cessation.

**Complication:** None.

**Outcome:** No individual data on CRP and ESR levels for the patients on TCZ were provided, but on average, these laboratory markers showed normalization post-treatment.

**Comments:** This is a summary of 8 case reports, presented as a case series. It had limited information on patient selection criteria. It demonstrated evidence for improved biological, clinical and radiological outcomes after TAK patients received TCZ treatment for the 13 patients together

### Systematic

**Patients:** 82 cases of large-vessel vasculitides. Curr Opin Rheumatol 2014;20(3):125-129.

**Clinical effectiveness of the intervention:**
- Normalisation of clinical and laboratory markers showed rapid and marked systemic symptoms. Prednisone dose was reduced from 8 mg/kg/month, with MTX induced remission responsiveness on patient selection criteria. It demonstrated evidence for improved biological, clinical and radiological outcomes after TAK patients received TCZ treatment for the 13 patients together

**Complication:** None.

**Outcome:** No individual data on CRP and ESR levels for the patients on TCZ were provided, but on average, these laboratory markers showed normalization post-treatment.

**Comments:** This paper was set out to be a meta-analysis of 38 patients, but in reality only 9 patients were on biologic drugs - the target of the authors’ intended analysis. Of these 9 patients, only 5 were on the biologic therapy, but complications subsequently occurred.

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### FOR PUBLIC CONSULTATION ONLY

**Patients:** 8 female Colombian patients. 3 were naïve to treatment, TCZ monotherapy 2 newly diagnosed GCA patients, azathioprine taken as an adjunctive. In 2 patients received combined therapy with GCs, with or without methotrexate, infliximab or tocilizumab taken as an adjunctive. In 2 newly diagnosed GCA patients biotherapy treatment for improved biological, clinical and radiological outcomes after TAK patients received TCZ treatment at the standard dose of 8mg/kg/month over a minimum of one year.
### Case series 1

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<th>Case series</th>
<th>Patients</th>
<th>Open label, uncontrolled</th>
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<td>7 patients</td>
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Treatment with TCZ at dosage of 29.5 mg/day. Follow up range: 7 - 11 months.

#### Clinical effectiveness of the intervention

Rapid and complete remission in all patients following the introduction of biologic therapy, but complications were noted such as a transient increase in liver enzymes.

#### Clinical symptoms

Stupor, myalgia, constitutional symptoms, headache).

#### Clinical findings

Magnetic resonance angiography (MRA) was performed to monitor local inflammation.

#### Relapse or health insurance company not supporting the off label use of TCZ

One relapse; one patient could not secure health insurance for a combination of GCs plus methotrexate.

### Case series 2

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<thead>
<tr>
<th>Case series</th>
<th>Patients</th>
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<td>7 patients</td>
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Treatment with TCZ at 8mg/kg/2 weeks for the first month, followed by monthly administration thereafter. Mean follow up time was 4.3 months (range 3-7 months). Two patients were resistant to GC treatment, and one with TAK was immediately treated with TCZ. 5 patients were receiving a mean prednisone dosage of 29.5 mg/day.

#### Clinical effectiveness of the intervention

Complete remission, defined as normalisation of clinical indices, inflammatory markers and PET/CT findings.

#### Clinical symptoms

Stupor, myalgia, constitutional, headache).

#### Clinical findings

Magnetic resonance angiography (MRA) was performed to monitor local inflammation.

#### Relapse or health insurance company not supporting the off label use of TCZ

None; N/A

### Comments

This was a well-conducted study, albeit limited by the small patient sample size and a short follow-up duration.

### References


Salvarani, Carlo; Magnani, Lucia; Catapano, Mariangela; Pipitone, Nuccio; Versari, Annibale; Dardani, Lucia; Pugliai, Lia; Melicori, Riccardo; Boiardi, Luigi; Facciotumacchi a novel therapy for patients with large vessel vasculitis. Rheumatology 2011;50(1):w13156.
3 Case series 22 Tocilizumab administered at 8 mg/kg/4 weeks (20% of patient sample).

Clinical effectiveness of the intervention:

- 3 patients were asymptomatic after three months of TCZ therapy. All had a median follow-up of 9 months; reduction of severe CRP levels (from 38, 1.25 to 0.9, 0.8 mg/dL, p=0.001) and ESR values (from 44 to 20-81) to 12 (2-20) mm/1st hour; p=0.001. 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.

- Llorente, Javier, Blanco, Ricardo; Hernández, José L.; Castañeda, Santos; Mercado, Antonio; Pérez-Pampín, Eva; Frank, Enric; Hambrecht, Alicia; Calvo-Añón, Jaime; Aurnocaschell, Elena; Navarro, Javier; Sánchez-Añón, Amalia; Vela, Paloma; Diaz, Blanca; Melé, Cristina; Lluch, Paco; Moll, Concepcion; Hernández, Begoña; Calvo-Rio, Vanesa; Ortiz-Sanjín, Francisco; González-Vela, Carmen; Pina, Trinitario; González-Gay, Miguel A. Tocilizumab in gran cell arteritis: Multicenter open-label study of 32 patients. Semin. Arthritis Rheum. 2015;44(4):717-723.

- 3 instances of adverse events during TCZ therapy. TCZ had to be discontinued in 3 patients due to sepsis, recurrent pneumonia, and cytomegalovirus infection. Moreover, 1 patient died after the second infusion of TCZ due to a stroke in the setting of an infectious endocarditis.

Population: Median age 42 years (range 20–55 years). Takayasu arteritis patients refractory to disease-modifying antirheumatic drugs (DMARDs). 80% female.

Comments: Authors concluded that whilst TCZ was effective at bringing about response rates in GCA patients with refractory disease and/or unacceptable side effects, there were safety concerns that need to be taken into account. The study design has limitations in that it is observational and retrospective. Although the study has a large sample size for a new disease like GCA, 22 patients is overall still a small number.

Population: Median age 42 years (range 20–55 years). Takayasu arteritis patients refractory to disease-modifying antirheumatic drugs (DMARDs). 80% female.

Comments: Authors noted that the efficacy and safety profile of TCZ was very similar to TNF-α antagonists, measured by complete and partial response, relapse-free survival, vascular complications and the % of patients experiencing side effects. This study was retrospective and treatments were therefore given at the physicians discretion, lacking uniformity.
| 2 | Meta Analysis: | GCA, TAK (TCZ) | Biological therapies: anti-TNF agents (adalimumab, etanercept), anti-IL6R (tocilizumab), anti-CC02 (ustekinumab), anti-CD20 (rituximab), anti-IL12/23 p40 (ustekinumab), and the soluble CTLA4 receptor fusion protein (abatacept) | Anti-TNF agents were reported to be effective in cases of GCA and TAK, however, the role of biological agents in the management of large vessel vasculitis (LVV) is limited. The role of biological agents in the management of GCA and TAK is limited. | Adverse events: | 4/19 (26.3%) GCA patients treated with TCZ developed a transient, self-limited transaminitis. Some patients also developed leucopenia; however, they did not have increased infections. One patient developed a post-operative myocardial infarction, and autopsy demonstrated active GCA despite normal clinical, serological and radiographic values. | Refer to outcomes: | Population: GCA 58-85 years, TAK 28-30 years, 73-89% of patients were female. Comments: While this 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. There seems to be a wide confidence interval in the meta-analysis data indicating substantial heterogeneity. The results of the randomised control trials included in the review show that anti-TNF agents 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 suggested that infliximab may be beneficial in the maintenance of remission and possibly reducing the amount of CS use in TAK patients. Given the limitations of the evidence available for TCZ, the study was graded as Level 2. |

| 3 | Case series: | 10 | Six doses of monthly TCZ infusions (6 mg/kg/day with maximum of 600 mg/infusion) | Clinical effectiveness of the intervention: | Disease remission: 90% | Adverse events: | There was no major adverse event or death. | Refer to outcomes: | Population: GCA 58-85 years, TAK 28-30 years, 73-89% of patients were female. Comments: While this 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. There seems to be a wide confidence interval in the meta-analysis data indicating substantial heterogeneity. The results of the randomised control trials included in the review show that anti-TNF agents 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 suggested that infliximab may be beneficial in the maintenance of remission and possibly reducing the amount of CS use in TAK patients. Given the limitations of the evidence available for TCZ, the study was graded as Level 2. |
# Appendix Two

## Literature Search Terms

<table>
<thead>
<tr>
<th>Assumptions / limits applied to search:</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Original search terms:</strong></td>
<td></td>
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</table>
| Updated search terms - Population       | Large vessel vasculit*  
|                                        | LVV  
|                                        | Giant cell arteritis  
|                                        | GCA  
|                                        | Takayasu arteritis  
|                                        | Takayasu’s arteritis  
|                                        | TA  
|                                        | Aortitis |
| Updated search terms - Intervention     | (Tocilizumab) OR (Actemra) OR (RoActemra) OR (Atlizumab) OR (Monoclonal antibod* MRA) OR (Monoclonal antibod* IL*6) OR (IL*6*inhibit*) OR (Interleukin*6*inhibit*) OR (IL*6 block*)  
|                                        | Anti*interleukin 6) |
| Updated search terms - Comparator       | None |
| Updated search terms - Outcome          | None |
| **General inclusion criteria:**         | In order of decreasing priority, articles will be selected based on the following criteria.  
|                                        | 1. All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available)  
|                                        | 2. All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available)  
|                                        | >>>> If studies included reaches 30, inclusion stops here  
|                                        | 3. All relevant case control and cohort studies, that qualify after exclusion criteria  
|                                        | >>>> If studies included reaches 30, inclusion stops here  
|                                        | 4. All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria  
<p>|                                        | &gt;&gt;&gt;&gt; If studies included reaches 30, inclusion stops here |
| <strong>Specific inclusion criteria:</strong>        |      |</p>
<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td><strong>Title/Abstract</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Published date &lt;5 yrs, &lt;10 yrs RCTs, SRs, MAs</strong></td>
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<tr>
<td><strong>English language</strong></td>
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Additional articles were added per the request of the policy working group and stakeholder feedback:

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<td>Studies with the following characteristics will be excluded:</td>
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<tr>
<td>1. Does not answer a PICO research question</td>
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<tr>
<td>2. Comparator differs from the PICO</td>
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<td>3. &lt; 50 subjects (where studies with &gt;50 subjects exist)</td>
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<tr>
<td>4. No relevant outcomes</td>
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<td>5. Incorrect study type</td>
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<tr>
<td>6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with &gt; one surgeon/doctor or one clinical site exist)</td>
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<tr>
<td>7. Narrative / non-systematic reviews (relevant referenced studies to be included)</td>
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<tr>
<td><strong>Specific exclusion criteria</strong></td>
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