Evidence Review:

Tocilizumab for Giant cell arteritis (adults)
NHS England

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Tocilizumab for Giant cell arteritis (adults)

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Prepared by Turnkey Clinical Evidence Review Team on behalf of NHS England Specialised Commissioning
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1. Introduction

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).

2. Summary of results

An evidence review was undertaken to identify the evidence available for the use of tocilizumab in the treatment of GCA and Takayasu arteritis (TAK). TAK 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 rheumatica. 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).

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.
## Appendix One

<table>
<thead>
<tr>
<th>Level</th>
<th>Study design and intervention</th>
<th>Outcomes</th>
<th>Reference</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Case series</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>16 patients</td>
<td>TCZ monotherapy for 6 patients (GCA patients). The remaining 16 patients received TCZ combined with other traditional synthetic immunosuppressive (anti-TNF) drugs: MTX (7 cases), mycophenolate mofetil (2 cases), and azathioprine (1 case) before TCZ initial dosage of 8mg/kg/iv, and a maintenance TCZ dosage ranging between 4-8mg/kg/4 weeks in 16 cases, and every 2 weeks in 1 case.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case series</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></td>
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</tr>
<tr>
<td></td>
<td>16 patients</td>
<td>Patients became asymptomatic or showed significant improvement, measured by CRP and ESR levels</td>
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<tr>
<td></td>
<td>16 patients</td>
<td>One patient suffered from a relapse TCZ treatment was discontinued for this patient due to severe neutropenia.</td>
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<td></td>
<td>Population: 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.</td>
<td>TCZ treatment was discontinued for 1 patient due to severe neutropenia</td>
<td>N/A</td>
<td></td>
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<tr>
<td></td>
<td>Comments: Single centre case series without clarity of methodology and patient selection. Complications were only reported on ad hoc basis.</td>
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</table>
3 Case series
Case series One relapse

<table>
<thead>
<tr>
<th>Case series</th>
<th>TCZ administered at 8 mg/kg/month, and MTX in some cases.</th>
<th>Clinical effectiveness of the intervention</th>
<th>TCZ treatment was administered to 8 female Colombian patients. 3 were naïve to treatment, both female patients received prednisone as part of their treatment, both female patients received prednisone, and MTX. The male patient received both TCZ and MTX induced remission of his disease activity.</th>
<th>Complication</th>
<th>One relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case series</td>
<td>N/A</td>
<td>TCZ at 8 mg/kg/month, with MTX in some cases.</td>
<td>Clinical effectiveness of the intervention</td>
<td>Clinical effectiveness was evaluated, objective (fever, fatigue, systemic symptoms and peripheral pulses), biological improvement (decrease in acute phase reactants) and improvements supported by radiology and imaging indices revealed normalisation post-treatment.</td>
<td>Complication</td>
</tr>
<tr>
<td>N/A</td>
<td>TCZ at 8 mg/kg/month and MTX induced remission of his disease activity.</td>
<td></td>
<td>TCZ treatment was administered to 8 female Colombian patients. 3 were naïve to treatment, both female patients received prednisone as part of their treatment, both female patients received prednisone, and MTX. The male patient received both TCZ and MTX induced remission of his disease activity.</td>
<td>Complication</td>
<td>One relapse</td>
</tr>
<tr>
<td>Systematic</td>
<td>N/A</td>
<td>TCZ at 8 mg/kg/month, with MTX in some cases.</td>
<td>Clinical effectiveness of the intervention</td>
<td>Clinical effectiveness was evaluated, objective (fever, fatigue, systemic symptoms and peripheral pulses) and radiological evaluations were assessed at baseline, at routine follow-up (1, 3, 6, and 9 months), and during a period of at least 1 year.</td>
<td>Complication</td>
</tr>
<tr>
<td>N/A</td>
<td>TCZ at 8 mg/kg/month and MTX induced remission of his disease activity.</td>
<td></td>
<td>TCZ treatment was administered to 8 female Colombian patients. 3 were naïve to treatment, both female patients received prednisone as part of their treatment, both female patients received prednisone, and MTX. The male patient received both TCZ and MTX induced remission of his disease activity.</td>
<td>Complication</td>
<td>One relapse</td>
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<tr>
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<td>Complication</td>
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</tbody>
</table>
### Case Series 1
**Population:** For a 16 year old female, a combined N/A 4 patients; 7 patients suffering from large vessel uncontrolled open label, consecutive patients, treated with TCZ. 5 were immediately naïve to GC treatment (range 3-7 months). Two patients were still taking GCs at study entry. GCs were tapered off the dosage of GCs administered. One patient (Case 3) achieved partial remission. In the two refractory patients who were still taking GCs at study entry, GCs were tapered off or the dosage was gradually decreased to 2.5 mg/day by the end of the study period. Mean follow up duration ranged from 7 - 11 months. Prednisone was withdrawn after 18 months. A 25 year old female patient showed remission and at 19 months, prednisolone dose was reduced from 40 to 5 mg/day. The 26 year old male showed rapid and marked symptomatic response following the introduction of biologic therapy, but complications subsequently occurred, cf. secondary outcome section. No individual data on CRP and ESR levels for the patients on TCZ were provided, but on average, these laboratory markers showed normalisation post-treatment.

**Clinical symptoms** (claudication, myalgia, constitutional, headache), ESR, CRP and GC dosage to maintain remission. Magnetic resonance angiography (MRA) was performed to monitor local inflammation. Rapid and complete remission in 6 of seven patients after the first month of treatment. Of the 5 patients who had LVV diagnosed by MRA, the angiograms showed improvement for the 3 GCA patients the second month of treatment. Of the 5 patients out of 7 who did not resolve for the 3 GCA patients the second month of treatment. Of the 5 patients out of 7 who did not resolve for the 3 GCA patients the second month of treatment. In the two TA patients and completely resolved in both. (5mg/kg/4 weeks). The patient who was given at 8mg/kg/month and was put back on GCs at study entry, who were still taking GCs at study entry, GCs were tapered off or the dosage was gradually decreased to 2.5 mg/day by the end of the study period.

**Clinical effectiveness of the intervention**

- **Complete remission,** defined as normalisation of clinical indices, inflammatory markers and PET/CT findings. All patients had satisfactory clinical and laboratory response. 3 patients achieved the primary and point of complete response. PET/CT findings significantly improved in all 4 cases. No serious adverse events were noted. Only one patient had a transient increase in liver enzymes. Partial remission, defined as normalisation of clinical indices and laboratory parameters, but not of PET/CT findings. Decrease in dosage of GCs administered. One patient (Case 3) achieved partial remission. In the two refractory patients who were still taking GCs at study entry. GCs were tapered off or the dosage was gradually decreased to 2.5 mg/day by the end of the study period.

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

- One relapse; One patient (Case 3) achieved partial remission. In the two refractory patients who were still taking GCs at study entry. GCs were tapered off or the dosage was gradually decreased to 2.5 mg/day by the end of the study period.

**For Public Consultation Only**

| Case series | 7 patients; open label, uncontrolled | Treatment with TCZ at dosage b/w5mg/kg/month. Follow up ranged from 3-7 months | Clinical symptoms (claudication, myalgia, constitutional, headache), ESR, CRP and GC dosage to maintain remission. Magnetic resonance angiography (MRA) was performed to monitor local inflammation | Rapid and complete remission in 6 of seven patients after the first month of treatment. Of the 5 patients who had LVV diagnosed by MRA, the angiograms showed improvement for the 3 GCA patients the second month of treatment. Of the 5 patients out of 7 who did not resolve for the 3 GCA patients the second month of treatment. In the two TA patients and completely resolved in both. (5mg/kg/4 weeks). The patient who was given at 8mg/kg/month and was put back on GCs at study entry, who were still taking GCs at study entry, GCs were tapered off or the dosage was gradually decreased to 2.5 mg/day by the end of the study period. | One relapse; please see secondary outcome for details | N/A | None | N/A | Population: For a 15 year old female, a combined therapy of TCZ at b/w5mg/kg/month and MFT reduced sustained remission, manifested by normalisation of acute phase inflammatory markers and end significant improvement of constitutional symptoms. Prednisone was withdrawn after 19 months. A 25 year old female patient showed remission and at 19 months, prednisolone dose was reduced from 40 to 5 mg/day. The 26 year old male showed rapid and marked symptomatic response following the introduction of biologic therapy, but complications subsequently occurred, cf. secondary outcome section. No individual data on CRP and ESR levels for the patients on TCZ were provided, but on average, these laboratory markers showed normalisation post-treatment. Comments: This was a well-conducted study, albeit limited by the small patient sample size and a short follow-up duration. | 8 | 8 |
FOR PUBLIC CONSULTATION ONLY

### Case series

<table>
<thead>
<tr>
<th>Case Series</th>
<th>N</th>
<th>Treatment</th>
<th>Clinical effectiveness of the intervention</th>
<th>CRP levels, pre-treatment dose</th>
<th>Overall response, relapse-free survival (RFS)</th>
<th>Overall response to complete and partial control and mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>22</td>
<td>Tocilizumab at 4 mg/kg/4 weeks</td>
<td></td>
<td>CRP levels (mg/dL) at baseline; 50% of patients (40% of patients) had CRP at baseline</td>
<td></td>
<td>90% of patients had a complete and partial response</td>
<td></td>
</tr>
</tbody>
</table>
### Meta Analysis

**1.** For 19 GCA patients treated with TCZ plus prednisone in 5 case series, all achieved disease remission and a reduction of corticosteroid (CS) doses. Pooled mean dose reduction was 19.35 mg per day (95% CI: 26.24 to 6.86). Three GCA patients were treated with TCZ and no CS while nine completely discontinued CS by the end of the follow-up periods. Three (16%) patients treated with TCZ developed a relapse during the follow-up period.

**2.** For 11 TAK patients who received TCZ in 4 case series, 91% achieved remission including one with TCZ monotherapy. All patients had a reduction of CS use with 4 being CS-free (36%), and many discontinuing their other immunosuppressive medications. Two patients (19%) achieved remission relapsed during the follow-up period.

### Clinical effectiveness

**Response to therapy, defined as attainment of ITAS of 0 during follow-up visits, with normalization of inflammatory markers and stable disease on conventional angiography or other imaging modalities. In addition, reduction in dosage of steroids and second line immunosuppressors**

**Adverse events**

No adverse events were reported with TCZ in TAK patients (5/19 (26.3%)). GCA patients treated with TCZ were reported to have 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.

**Outcome**

Index: Mohamed, Pandu; Chitlani, Dryden, Donna M.; Stone, Dale; Yacoub, Elaine.


### Case series

**1.** TCZ infusions (6 mg/kg/day with maximum of 600 mg infusion) TCZ infusions led to a clinical response with ITAS of 0 and reduction in acute phase reactants (APR) in all 10 patients by the fourth infusion. Six patients (60%) maintained clinical response with radiologically stable disease and normal APR up to the sixth infusion. Two out of three patients (66%) with normal APR at baseline achieved and maintained stable disease state up to the last infusion, in contrast to 49.2% (4/7) responders in those with baseline high APR. Tocilizumab facilitated rapid reduction in steroid dose from 24 ± 15 to 5.4 ± 4.9 mg/day (P = 0.003). However, following discontinuation of tocilizumab therapy after six infusions, at a median follow-up of 8 months (range 3–14 months) only two patients maintained stable disease state.

**Adverse events**

There was no major adverse event or fatality.

**Outcome**


### Population

Population: GCA 38 to 85 years, TAK 28-30 years.

73-89% of patients were females.

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 was 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></th>
</tr>
</thead>
<tbody>
<tr>
<td>Original search terms:</td>
<td>None</td>
</tr>
</tbody>
</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  
   >>> If studies included reaches 30, inclusion stops here |
| Specific inclusion criteria |  |
### Inclusion criteria

- Title/Abstract
- Published date <5 yrs, <10 yrs RCTs, SRs, MAs
- English language

Additional articles were added per the request of the policy working group and stakeholder feedback:

### Exclusion criteria

#### General exclusion criteria

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

#### Specific exclusion criteria

None