NHS England

Evidence Review:

Tocilizumab for Giant cell arteritis (adults)

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Contents

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 rheumatic. These manifestations disappeared after 3 months of TCZ therapy. A corticosteroid sparing effect was also reported (27.3±17.6 mg/day of prednisone at TCZ onset to 4.2±3.8 mg/day at last visit). TCZ had to be discontinued in one patient because of severe neutropenia.

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

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

In a small case series involving 10 difficult to treat TAK patients in India with active disease in spite of treatment with steroids and second line agents for a median duration of 27 months, TCZ led to a significant clinical response with Indian Takayasu Arteritis Score (ITAS) falling to zero (from average 4.5 prior to treatment) and reduction in acute phase reactants in all 10 patients by the fourth infusion (8 mg/kg/day with maximum of 600 mg/infusion). There was significant reduction in steroid dosage Six patients (60%) maintained clinical response up to the sixth infusion and only two patients maintained stable disease state after discontinuation of therapy (Goel et al, 2013).

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

Level	Study design and intervention				Outcomes				Reference	Other		
Level of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
3	Case series	16 patients. Interventional case series, open-label, uncontrolled	TCZ monotherapy for 6 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 (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	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 asthenia (muscle weakness), chest or scalpular pain, headaches etc. (GCA patients). Laboratory tests: normalisation of CRP <0.5 mg/dL, and ESR <20mm/1st hour (women) or 25mm/1st hour (men)	Patients became asymptomatic or showed significant improvement, measured by CRP and ESR levels	Complication	One patient suffered from a relapse TCZ treatment was discontinued for this patient due to severe neutropenia	Loricera, Javier; Blanco, Ricardo; Castañeda, Santos; Humbría, Alicia; Ortego-Centeno, Norberto; Narváez, Javier; Mata, Cristina; Melchor, Sheila; Aurrecoechea, Elena; Calvo-Alén, Jaime; Lluch, Pau; Moll, Concepción; Mínguez, Mauricio; Herrero-Beaumont, Gabriel; Bravo, Beatriz; Rubio, Esteban; Freire, Mercedes; Peiró, Enriqueta; González-Vela, Carmen; Rueda-Gotor, Javier; Pina, Trinitario; Palmou-Fontana, Natalia; Calvo-Río, Vanesa; Ortiz-Sanjuán, 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.	TCZ treatment was discontinued for 1 patient due to severe neutropenia	N/A	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. Comments: Single centre case series without clarity of methodology and patient selection. Complications were only reported on an ad hoc basis.

3	Case series	8 Colombian patients with severe and/or refractory Takayasu arteritis, open label, uncontrolled	TCZ administered at 8 mg/kg/month, and clinical, laboratory, and radiological analyses were assessed at baseline, at routine follow-up (1, 3, 6, and 9 months), and during a period of at least 1 year. TCZ treatment was continued until the last follow up. 3 patients received intravascular interventions and high dosages of corticosteroids and immunosuppresants before TCZ treatment	Clinical effectiveness of the intervention	Clinical improvement (visually evaluated), objective (fever, fatigue, systemic symptoms and peripheral pulses), biological improvement (decrase on acute phase reactants) and improvements supported by radiology	These results were supported by reduced levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as well as imaging by PET and mangetic nuclear imaging. All patients received a much lower dose of prednisone (<10mg/d) post-treatment, with 3 patients on combination therapy with an immunosuppresant, e.g. MTX or AZA.	Complication	One relapse	Cañas, Carlos Alberto; Cañas, Felipe; Izquierdo, Jorge Hernan; Echeverri, Andrés-Felipe; Mejía, Mauricio; Bonilla-Abadía, Fabio; Tobón, Gabriel J.. Efficacy and safety of anti-interleukin 6 receptor monoclonal antibody (tocilizumab) in Colombian patients with Takayasu arteritis. J Clin Rheumatol 2014;20(3):125-129.	One relapse was observed	N/A	Population: 8 female Colombian patients. 3 were refractory to multiple treatments, including glucocorticoids, 3 were naïve to immunosuppressive drugs and 2 were previously treated with anti-TNF (IFX without control of disease). Average age 31 years (range 12 - 43 years). 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 results after TAK patients received TCZ treatment at the standard dose of 8mg/kg/month over a minimum of one year.
3	Case series	N/A	TCZ at 8mg/kg/month, with MTX in some cases	Clinical effectiveness of the intervention	Indian Takayasu arteritis activity (ITAS) and damage scores (TADs) calculated. The disease activity indices used were the CRP level (normal <5 mg/L), ESR (normal <30mm/hr). MRA, computerised tomographic angiography and high resolution ultrasound were used to ases disease progression. End-points: 1. Change in CRP from decision to start biologic to 6 months post-biologic, 2. Change in daily prednisolone dose from biologic start time to the current dose or last dose prior to cessation of biologic, 3. Change in ITAS and TADS from decision to start biologic 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 biologic until the most recent visit or biologic cessation	For the 16 year old female, a combined therapy of TCZ at 8mg/kg/month and MTX induced sustained remission, manifested by normalisation of acute phase inflammatory markers and and significant improvement of constitutional symptoms. Prednisone was withdrawn after 18 months. The 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 outome 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.	Complication	TCZ treatment was discontinued for the male patient after 1 dose of TCZ because he developed severe necrotising pancreatitis two weeks after infusion.	Youngstein, Taryn; Peters, James E.; Hamdulay, Shahir S.; Mewar, Devesh; Price-Forbes, Alec; Lloyd, Mark; Jeffery, Rachel; Kinderlerer, Anne R.; Mason, Justin C.. Serial analysis of clinical and imaging indices reveals prolonged efficacy of TNF-α and IL-6 receptor targeted therapies in refractory Takayasu arteritis. Clin. Exp. Rheumatol. 2014;32(3 Suppl 82):S11-18.	See secondary outcomes	N/A	Population: 2 female caucasian patients, and 1 male asian patient, all suffering from TAK. Prior to TCZ treatment, both female patients received prednisone and MTX. The male patient received both and in addition to that mycophenolate and AZA . Mean age 22.3 years (range 16 - 26 years). Comments: This paper was set out to be a meta-analysis of 98 patients, but in reality only 9 patients were on biologic drugs - the target of the authors' intended analysis. Of these 9 patients, only 3 were on TCZ, making this paper of limited use. The small sample size meant that no meaningful statistics could be conducted for TCZ treatment. Luckily, case reports for each TCZ-treated patient was provided.
3	Systematic	N/a	TCZ at 8mg/kg/4 weeks for all studies except for Nisimoto et al. 2008, which administered TCZ once every 3 weeks. Follow up ranged from 3 months to >60 months	Clinical effectiveness of the intervention	Normalisation of clinical and biological infloammatory markers (ESR and CRP); remission and decrease in dosage of GCs required to maintain remission post-treatment	TCZ is effective in achieving remission for both GCA and TAK patients on combined therapy with GCs, with or without methotrexate, Infliximab or azathioprine taken as an adjunctive. In 2 newly diagnosed GCA patients naïve to treatment, TCZ monotherapy was sufficient to maintain remission	N/A	N/A	Schäfer, Valentin S.; Zwerina, Jochen. Biologic treatment of large-vessel vasculitides. Curr Opin Rheumatol 2012;24(1):31-37.	N/A	N/A	Population: A total of 13 GCA patients and 3 TA patients were covered by the systematic review. Age range 20 - 79 years. Comments: The paper was more a review than a systematic review. All in all, the 13 patients together provide evidence to support the efficacy of TCZ as a treatment for GCA and TAK.

3	Case series	4 patients; open label, uncontrolled	Treatment with TCZ at dosage 8mg/kg/month. Follow up ranged from 7 - 11 months.	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 end 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 normalisatin 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.	Salvarani, Carlo; Magnani, Luca; Catanoso, Mariagrazia; Pipitone, Nicolò; Versari, Annibale; Dardani, Lucia; Pulsatelli, Lia; Meliconi, Riccardo; Boiardi, Luigi. Tocilizumab: a novel therapy for patients with large-vessel vasculitis. Rheumatology (Oxford) 2012;51(1):151-156.	None	N/A	Population: For a 16 year old female, a combined therapy of TCZ at 8mg/kg/month and MTX induced sustained remission, manifested by normalisation of acute phase inflammatory markers and and significant improvement of constitutional symptoms. 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 outome 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.
3	Case series	7 consecutive patients, open label, uncontrolled	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 naïve to GC treatment were immediately treated with TCZ. 5 patients were receiving a mean prednisone dosage of 29.5 mg/day	Clinical effectiveness of the intervention	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 six out of seven patients after the first TCZ infusion - the acute phase response proteins (ESR and CRP serum levels) returned to normal. Completely normalisation was achieved in all patients after three months of treatment. Of the 5 patients who had LVV diagnosed by MRA, the angiograms showed improvement for the 2 TA patients and completely resolved for the 3 GCA patients the after 3 month period of treatment. In the 5 patients out of 7 who did not discontinue TCZ treatment, prednisone dosage could be reduced within 12 weeks to a mean of 2.5 mg/day (range 0–10 mg/day).	Relapse or health insurance company not supporting the off label use of TCZ	1 TA patient suffered from a relapse after 8 months when TCZ was given at 8mg/kg/4 weeks, and was put back on a combination of GCs, methotrexate and infliximab (5mg/kg/4 weeks). The patient who could not secure health insurance for off-label TCZ use reverted to a combination of GCs plus methotrexate	Seitz, Michael; Reichenbach, Stephan; Bonel, Harald M.; Adler, Sabine; Wermelinger, Felix; Villiger, Peter M.. Rapid induction of remission in large vessel vasculitis by IL-6 blockade. A case series. Swiss Med Wkly 2011;141():w13156.	One relapse; please see secondary outcome for details	N/A	Population: 7 patients suffering from large vessel vasculitis (LVV), either newly diagnosed (3 patients) or relapsing (4 patients). The 4 relapsing patients were resistent to GC treatment i.e. dosage could not be lowered to <7.5mg/day. 2 TAK and 5 GCA patients. Mean age of GCA patients: 70 years (range 63 - 79 years). Mean age of TAK patients: 33.5 years. Comments: Evidence from the 7 patients suffering from GC or TA support the efficacy of TCZ as a treatment for LVV. There are three limitations: the non-experimental study design, which does not allow efficacy to be inferred in the absence of a control group, the small number of patients, and the short observation time.

3	Case series	49	Tocilizumab at 8mg/kg/4 weeks (20% of patient sample)	Clinical effectiveness of the intervention	CRP levels, prednisone dosage after TCZ therapy.	CRP level (30 mg/L) [1–200 mg/L] at baseline versus 6 mg/L [0–100 mg/L] at 12 months; P<0.05), and daily prednisone dose (15 mg [4–75 mg] at baseline versus 7.5 mg [1–30 mg] at 12 months; P<0.05) significantly decreased after 12 months of biological targeting treatments	Overall response, Relapse free survival (RFS)	Overall response (ie, complete and partial) to biological targeted treatments at 6 and 12 months was 75% and 83%, respectively. The 3-year relapse-free survival was 90.9% (83.5%–99%) over the biological treatment period compared with 58.7% (43.3%–79.7%; P=0.0025) with disease-modifying antirheumatic drugs. No difference in efficacy was found between tumor necrosis factor-α antagonists and tocilizumab. After a median follow-up of 24 months (2–95 months), 21% of patients experienced adverse effects	Mekinian, Arsene; Comarmond, Cloé; Resche-Rigon, Mathieu; Mirault, Tristan; Kahn, Jean Emmanuel; Lambert, Marc; Sibilia, Jean; Néel, Antoine; Cohen, Pascal; Hie, Miguel; Berthier, Sabine; Marie, Isabelle; Lavigne, Christian; Anne Vandenhende, Marie; Muller, Géraldine; Amoura, Zahir; Devilliers, Hervé; Abad, Sébastien; Hamidou, Mohamed; Guillevin, Loïc; Dhote, Robin; Godeau, Bertrand; Messas, Emmanuel; Cacoub, Patrice; Fain, Olivier; Saadoun, David; French Takayasu Network. Efficacy of Biological-Targeted Treatments in Takayasu Arteritis: Multicenter, Retrospective Study of 49 Patients. Circulation 2015;132(18):1693-1700.	21% of patients experienced adverse events; 6.6% had treatments discontinued. Of the 14 TCZ-treated patients, 3 had side effects, including severe asymptomatic neutropenia, breast cancer and severe bacterial infection. The percentage of TCZ patients with side effects was not statistically different to patients taking TNF-α antagonists, however	-	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 physician's discretion, lacking uniformity.
3	Cohort	22	TCZ administered at 8mg/kg/4weeks	Clinical effectiveness of the intervention	C-reactive protein (CRP) levels, ESR and prednisone dosage after TCZ therapy	15 patients were asymptomatic after three months of TCZ therapy. At a median follow up of 9 months, 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]. 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.	-	-	Loricera, Javier; Blanco, Ricardo; Hernández, José L.; Castañeda, Santos; Mera, Antonio; Pérez-Pampín, Eva; Peiró, Enriqueta; Humbría, Alicia; Calvo-Alén, Jaime; Aurrecoechea, Elena; Narváez, Javier; Sánchez-Andrade, Amalia; Vela, Paloma; Díez, Elvira; Mata, Cristina; Lluch, Pau; Moll, Concepción; Hernández, Íñigo; Calvo-Río, Vanesa; Ortiz-Sanjuán, Francisco; González-Vela, Carmen; Pina, Trinitario; González-Gay, Miguel Á. Tocilizumab in giant cell arteritis: Multicenter open-label study of 22 patients. Semin. Arthritis Rheum. 2015;44(6):717-723.	6 instances of adverse events during TCZ therapy. TCZ had to be discontinued in 3 patients due to severe neutropenia, 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: 69 +/- 8 years. Giant cell arteritis (GCA) patients with refractory disease and/or unacceptable side effects due to corticosteroids Comments: Authors concluded that whilst TCZ was effective at bringing about response rates in GCA patients with refractory disease, there were safety concerns that need to be taken into account. The study design has limitations in that it is observational and restrospective. Although the study has a large sample size for a rare disease like GCA, 22 patients is overall still a small number

2-	Meta Analysis	193 (19 GCA, 11 TAA on TCZ)	Biological therapies : anti-TNF agents (infliximab, adalimumab, etanercept), anti-IL6R (tocilizumab), anti-CD20 (rituximab), anti-IL-12/23 p40 (ustekinumab), and the soluble CTLA4 receptor fusion protein (abatacept)	Clinical effectiveness of the intervention	1. Disease remission 2. Reduction in corticosteroid use 3. Relapse	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 16.55 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 patients with TAK 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 (18%) achieved remission relapsed during the follow-up period.	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.	Osman, Mohammed; Pagnoux, Christian; Dryden, Donna M.; Storie, Dale; Yacyshyn, Elaine. The role of biological agents in the management of large vessel vasculitis (LVV): a systematic review and meta-analysis. PloS One 2014;9(12):e115026.	Refer to outcomes	Refer to outcomes	Population: GCA 58 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 suggest 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 evidnce available for TCZ, this study was graded as Level 2-.
3	Case series	10	Six doses of monthly TCZ infusions (8 mg/kg/day with maximum of 600 mg/infusion)	Clinical effectiveness of the intervention	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 immunosuppresants	Tocilizumab 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 toclizumab 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.	Goel, Ruchika; Danda, Debashish; Kumar, Sathish; Joseph, George. Rapid control of disease activity by tocilizumab in 10 'difficult-to-treat' cases of Takayasu arteritis. International Journal of Rheumatic Diseases 2013;16(6):754-761.	Refer to outcomes	Refer to outcomes	Population: 24.5 (13–53) years. Average disease duration 25.5 (1.5–60) months and Indian Takayasu Arteritis Score (ITAS) 4.5 (0–13), respectively. All patients had active disease with ITAS of ≥ 1 and/or they were angiographically active in spite of treatment with steroids and second line agents for a median duration of 27 (15–60) months. Difficult to treat TAK patients : All patients had active disease with ITAS of ≥ 1 and/or they were angiographically active in spite of treatment with steroids and second line agents for a median duration of 27 (15–60) months. Comments: This is a small case series with lack of clarity on the methdology for patients selection (for example it is not clear if these were consecutive cases versus selective cases where TCZ was offered to only those where a response was seen)

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	None
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: 1. Mekinian, et al. Efficacy of Biological-Targeted Treatments in Takayasu Arteritis: Multicenter, Retrospective Study of 49 Patients. Circulation 2015;132(18):1693-1700. 2. Loricera, et al. Tocilizumab in giant cell arteritis: Multicenter open-label study of 22 patients. Semin. Arthritis Rheum. 2015;44(6):717-723. 3. Osman, et al. The role of biological agents in the management of large vessel vasculitis (LVV): a systematic review and meta-analysis. PloS One 2014;9(12):e115026. 4. Goel, et al. Rapid control of disease activity by tocilizumab in 10 'difficult-to-treat' cases of Takayasu arteritis. International Journal of Rheumatic Diseases 2013;16(6):754-761.
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