SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND
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tocilizumab, 162mg solution for injection in pre-filled syringe and pre-filled pen (RoActemra®) SMC2014

Roche Products Limited

10 August 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

tocilizumab (RoActemra®) is accepted for restricted use within NHSScotland.

Indication under review: the treatment of Giant Cell Arteritis (GCA) in adult patients

SMC restriction: treatment with tocilizumab is subject to a 12 month clinical stopping rule.

A phase III study of patients with recently diagnosed or relapsed GCA reported superiority of tocilizumab plus 26-week glucocorticosteroid taper over placebo plus 26-week glucocorticosteroid taper for obtaining a sustained glucocorticosteroid-free remission of GCA at week 52.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of tocilizumab. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Chairman,
Scottish Medicines Consortium

Published 10 September 2018

Indication

The treatment of Giant Cell Arteritis (GCA) in adult patients.[1]

Dosing Information

The recommended dose is 162mg subcutaneously (SC) once every week in combination with a tapering course of glucocorticosteroids. Tocilizumab can be used alone following discontinuation of glucocorticosteroids.

Tocilizumab monotherapy should not be used for the treatment of acute relapses. Based upon the chronic nature of GCA, treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of GCA.[1]

Product availability date

January 2018

Tocilizumab meets SMC orphan equivalent criteria

Summary of evidence on comparative efficacy

Tocilizumab binds to, and inhibits signalling through soluble and membrane bound interleukin (IL)-6 receptors, preventing the pro-inflammatory effects of the cytokine IL-6, including; T-cell activation, immunoglobulin secretion, increase of hepatic acute phase protein synthesis and stimulation of haematopoiesis.[1] The diminishing of these inflammatory pathways is considered to lessen the pathological process causing GCA and support the maintenance of remission. GCA, sometimes known as temporal arteritis, is the most common type of inflammatory vasculitis, and affects medium and large arteries, primarily of the head and neck.[1, 2] Tocilizumab has previously been accepted for use within NHSScotland for the treatment of groups of patients with rheumatoid arthritis (RA) and systemic Juvenile Idiopathic Arthritis.

The Giant-Cell Arteritis Actemra (GiACTA) study is a two-part study: part 1 was a multicentre, randomised, double-blind, placebo-controlled, phase III study with a 52-week duration; part 2 is an ongoing open-label extension study with a 104-week duration.[2, 3] To be included in the study patients were required to be ≥50 years of age and have a recorded erythrocyte sedimentation rate (ESR) ≥50mm/hour or a C reactive protein (CRP) ≥2.45mg/dL associated with GCA, unequivocal cranial symptoms of GCA and / or symptoms of polymyalgia rheumatica (PMR), temporal artery biopsy with features of GCA and / or evidence of large cell vasculitis by angiography or cross-sectional imaging, active GCA within six weeks of baseline visit (defined as the presence of clinical signs and symptoms and ESR ≥30mm/hour or CRP ≥1mg/dL). A raised ESR or CRP were not required if active GCA had been confirmed by positive temporal artery biopsy within six weeks of the baseline visit. Patients could be classified as new-onset (diagnosis of GCA within six weeks of baseline visit) or relapsing active disease (diagnosis of GCA >six weeks before baseline visit and previous treatment with ≥40mg/day prednisone [or equivalent] for at least two consecutive weeks at any time). Patients were randomised in a 2:1:1:1 ratio to receive; weekly tocilizumab 162mg subcutaneously (SC) for 52 weeks plus a 26-week prednisone taper (weekly tocilizumab group, n=100); fortnightly tocilizumab 162mg SC for 52 weeks

plus a 26-week prednisone taper (fortnightly tocilizumab group, n=50); weekly placebo SC plus a 26-week prednisone taper (placebo plus 26-week taper group, n=50); or weekly placebo SC plus a 52-week prednisone taper (placebo plus 52-week taper group, n=51). Randomisation was stratified by baseline glucocorticosteroid dose: ≤30mg/day and >30mg/day of prednisone or equivalent.[2, 3] The fortnightly tocilizumab dose has not been licensed for GCA and will not be discussed any further.

At baseline, the initial prednisone dose taken orally had to be between 20mg and 60mg per day. The prednisone dose was reduced weekly in all the study patients as determined by the study protocol. Doses ≥20mg/day were administered in an open-label manner; when patients' prednisone dose was <20mg/day, doses were administered in a double-blind manner. Once prednisone was reduced from 1mg/day to 0mg/day, placebo tablets were used to maintain blinding.[3] In the study, flare was defined as the recurrence of signs and symptoms of GCA and / or an ESR ≥30mm/hour which required an increase in prednisone dose. Patients who had a GCA flare or could not adhere to the prednisone taper during the study period switched to open-label escape therapy with prednisone but continued to receive the randomly assigned treatment: tocilizumab or placebo. These patients were considered to have treatment failure in terms of the primary outcome.[3] Calcium, vitamin D, bisphosphonates, anti-platelet therapy, methotrexate and lipid-lowering agents were allowed as concomitant medication.[2]

The primary analysis was conducted in the intention-to-treat population and patients with missing data at week 52 were imputed as non-responders.[2] The study met its primary endpoint with 56% (56/100) of patients in the weekly tocilizumab plus 26-week prednisone tapering group and 14% (7/50) of patients in the placebo plus 26-week prednisone tapering group achieving a sustained prednisone-free remission at week 52, estimate of difference in response rate was 42% (99.5% confidence interval [CI] 18 to 66%), p<0.001 (statistical significance threshold for superiority was p<0.005 for the primary outcome). Important secondary outcomes are detailed in table 1 below.

Table 1. Primary and important secondary outcomes of the GiACTA study[2, 3]

	Weekly tocilizumab plus 26-week prednisone taper (n=100)	**Placebo plus 26-week prednisone taper (n=50)**	**Placebo plus 52-week prednisone taper (n=51)**
Proportion of patients with a sustained response (relapse-free) at week 52, %	56%	14%	18%
	p<0.001*		
Median actual cumulative prednisone dose to week 52 (range)	1,862mg (630 to 6,602)	3,296mg (932 to 9,778)	3,818mg (822 to 10,698)
	p<0.001 for both comparisons		

*the p value for the comparison against placebo plus 26-week prednisone taper indicates superiority, and for the comparison against placebo plus 52-week prednisone taper indicates non-inferiority

Sensitivity analyses of the primary efficacy outcome included; excluding the requirement for normalised CRP (<1mg/dL) from the definition of sustained response, disregarding adherence to the prednisone tapering regimen and including only patients that completed the study and were compliant with the study medicine: all results of the sensitivity analyses were in line with the primary analysis. A *post-hoc* analysis indicated superiority for weekly tocilizumab treatment over placebo plus 52-week prednisone taper and sensitivity analyses produced results in line with this analysis. [2, 3]

Weekly tocilizumab was associated with a statistically significant lower median actual cumulative prednisone dose over the study period than both placebo groups.

For both the subgroups of patients who had relapsing disease and newly diagnosed disease at baseline; weekly tocilizumab plus 26-week prednisone taper was associated with a lower risk of GCA flare than treatment with placebo plus 26-week prednisone tapering and treatment with placebo plus 52-week prednisone taper.[1, 3] The study was not powered to show a difference between these subgroups and the results have not been adjusted for multiplicity.

Quality of life data was collected in the GiACTA study using the patient global visual analogue scale, the Short-Form 36 (SF-36) tool and the EuroQol 5-dimensions (EQ-5D) tool. In the physical component on the SF-36 tool there was a statistically significant difference between the weekly tocilizumab group and the placebo plus 52-week taper group indicating an improvement in quality of life with tocilizumab treatment. No other significant differences were reported. [1-3]

Part 2 of the GiACTA study is a 104-week open-label extension (OLE) / long term follow-up that is due for completion in 2018. The primary objective of the OLE is to further evaluate safety and the efficacy of tocilizumab beyond 52 weeks. If a patient was in remission at the end of part 1 of the GiACTA study their tocilizumab or placebo SC injections were stopped and they were observed during part 2 of the study. An interim OLE analysis included 88 patients that had reached at least the week 100 visit of the overall study, 45 of these patients had met the primary endpoint of part 1 of the study. The relapse proportions for patients that were responders in part 1 were; 33% (8/24) in patients treated with weekly tocilizumab in part 1, and 20% (1/5) for both of the placebo plus 26-week taper and placebo plus 52-week taper patients in part 1. Most of the relapses occurred more than 12 weeks after patients had completed part 1 and finished treatment with tocilizumab or placebo.[2]

Summary of evidence on comparative safety

Tocilizumab SC is licensed for use in RA; the safety profile in GCA patients is comparable with the known safety profile in RA and no new safety concerns were highlighted.[2] From the GiACTA study, in the weekly tocilizumab group plus 26-week prednisone taper, the placebo plus 26-week prednisone taper group and placebo plus 52-week prednisone taper group respectively, the following were reported; treatment related adverse events (AEs): 68% (68/100), 64% (32/50) and 53% (27/51), serious AE: 15% (15/100), 22% (11/50) and 25% (13/51).[2, 3] The proportion of patients that withdrew from the study groups due to an AE were; 6% from the weekly tocilizumab group, 4% from the placebo plus 26-week taper and none (0%) from the placebo plus 52-week taper group.[3]

In the weekly tocilizumab group plus 26-week prednisone taper, the placebo plus 26-week prednisone taper group and placebo plus 52-week prednisone taper group respectively, the following were reported; serious infections: 7% (7/100), 4% (2/50) and 12% (6/51), infections and infestations: 75% (75/100), 76% (38/50) and 65% (33/51), peripheral oedema: 16% (16/100), 16% (8/50) and 12% (6/51), nasopharyngitis: 29% (29/100), 18% (9/50) and 25% (13/51), arthralgia: 13% (13/100), 22% (11/50) and 16% (8/51).[2] In the same groups, injection-site reactions were reported for 7% (7/100), 10% (5/50) and 2% (1/51), grade 3 elevation of alanine aminotransferase level: 2% (2/100), 0% (0/50) and 2% (1/51). Grade 3 neutropenia was reported for 4% (4/100) of patients in the weekly tocilizumab plus 26-week prednisone taper group.[3]

In terms of adverse events of interest, there were no serious bleeding AEs or serious myocardial infarctions; there was one serious stroke in the placebo plus 52 week taper group (2%); endocrine disorders were reported for 6% of patients in the weekly tocilizumab group, 2% in the placebo plus 26 week taper group, and 4% in the placebo plus 52 week taper group.[2] No deaths were reported during

part 1 of the GiACTA study. During part 2 of the study one patient died as a result of an aortic dissection.[2] It is not clear if this was considered to be treatment related.

Summary of clinical effectiveness issues

Immediate high dose glucocorticosteroid is the mainstay of treatment for symptomatic GCA in order to prevent visual and ischaemic complications. On induction of remission, glucocorticosteroids are slowly tapered down to avoid a relapse of disease signs and symptoms. Up to 50% of patients experience relapses during the tapering process.[2] Off label use of immunosuppressants including methotrexate may be considered as an adjuvant therapy in patients with recurrent relapse or when it is not possible to reduce the glucocorticosteroid dose.[4] Increased exposure to glucocorticosteroids is associated with an increased risk of developing a range of AEs with approximately 80% of patients treated with glucocorticosteroids experiencing AEs at 10 year follow-up. Patients with relapsing disease will have been exposed to a higher amount of glucocorticosteroid than newly diagnosed patients and therefore could be considered to be at higher risk of developing steroid associated AEs.[2, 3] The incidence of GCA is highest between 70 and 80 years of age, normally only occurs in patients over the age of 50, and it is three times more common in women.[5, 6] Tocilizumab is the first biological agent licensed for the treatment of GCA and meets SMC orphan equivalent criteria.

The primary outcome indicated that weekly tocilizumab plus 26-week steroid tapering was superior to placebo plus 26-week steroid tapering in terms of obtaining a sustained remission of GCA at week 52 and this is considered to be clinically meaningful. Tocilizumab plus 26-week steroid tapering was non-inferior to placebo plus 52-week steroid tapering. Patients in the placebo plus 26-week taper group and placebo plus 52-week taper group received approximately twice the median cumulative dose of prednisone compared to those in the weekly tocilizumab group.[2, 3]

Tocilizumab was commenced up to six weeks after glucocorticosteroids were initiated for acute flare of GCA. The GiACTA study did not evaluate early disease control but assessed the value of tocilizumab in combination with tapering glucocorticosteroid, however, early flare control is the primary goal of disease management.[2] Patients tapered their prednisone dose according to the study protocol algorithm: over 26 weeks or 52 weeks, which may have resulted in patients tapering faster than would be seen in normal Scottish practice. The British Society for Rheumatology and the British Health Professionals in Rheumatology suggest glucocorticosteroid tapering regimens ranging from 54 to 108 weeks depending on symptoms at the time of flare, tolerability of glucocorticosteroids and of dose reductions.[4] An alternative suggested tapering regimen is over 124 weeks.[7] The more rapid tapering regimens used in the GiACTA study may have resulted in higher relapse rates and limit the generalisability to patients in Scotland. Although prednisolone is the most commonly used oral glucocorticosteroid in NHS Scotland, prednisone doses are equivalent and its use in the study is satisfactory.

There are limited long term data and there is uncertainty regarding the optimal duration of treatment: the marketing authorisation is for 12 months based on the pivotal study, but an interim analysis of the OLE suggests that tocilizumab may be associated with a higher rate of relapse following treatment withdrawal, but the OLE is ongoing and the patient numbers were small. A rebound effect following tocilizumab discontinuation cannot be excluded.[2]

Disparity between the treatment groups in the following factors may have biased the results. A smaller proportion of patients in the weekly tocilizumab group were treated with concomitant methotrexate than in the placebo plus 26-week taper group and placebo plus 52-week taper group (11%, 16% and 18% respectively); this may suggest that patients in the weekly tocilizumab group were less difficult to treat. Fewer patients in the weekly tocilizumab group compared with the placebo plus 26-week taper group

had ischaemic related vision loss at baseline (7% versus 14%), used concomitant analgesics (3% versus 16%), and patients in the weekly tocilizumab group had a shorter mean duration of GCA (307 days versus 365 days) and lower mean prednisone starting dose (79mg versus 105mg) compared with the placebo plus 26-week taper group. [2] No baseline data were recorded for relevant comorbidities such as cerebrovascular disease, cardiovascular disease, osteoporosis, and diabetes. No details were reported to reflect the severity of the flares in each of the treatment groups and patients reported outcomes may have been biased by the open label prednisone dosing in patients receiving ≥20mg daily. The exclusion of patients requiring steroids for other conditions or on long term steroids may reduce the generalisability of the study results.

Off-label immunosuppressive medicines such as methotrexate, mycophenolate mofetil and azathioprine are used to treat complicated GCA in Scottish practice but there is insufficient evidence to conduct an indirect treatment comparison including these medicines.

Tocilizumab provides an additional treatment option and may be of particular benefit to patients with poor tolerability of steroids as it could reduce steroid exposure and associated adverse events. Clinical experts consulted by SMC considered that tocilizumab is a therapeutic advancement. Patients will require training for self-administration or assistance if unable to self-administer the weekly treatment.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of tocilizumab, as an orphan equivalent medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- The symptoms of GCA such as severe headache, scalp tenderness, temporary and permanent sight loss, and features of polymyalgia are disabling and reduce patients' quality of life. These symptoms and overwhelming fatigue make socialising, employment and caring for someone challenging if not impossible.
- High dose steroids are the only treatment for GCA flare. Steroids can be difficult to tolerate due to the adverse effects, particularly for older patients. Adverse effects of high dose and prolonged steroid use include developing; psychosis, diabetes, osteoporosis, cataracts and increased susceptibility to infections. For patients in whom steroids are contraindicated there are no alternative treatments. Steroid dose reductions can be stressful as there is a risk of disease relapse and associated disability. Steroid treatment can be up to two years in most cases but longer for some patients and there is a lack of evidence for alternative steroid-sparing therapies currently used in practice.
- Tocilizumab is expected to improve quality of life, reduce steroid exposure time, reduce the risk of developing difficult to manage steroid associated AEs and support safe independent living. Families may benefit from restoration of normal life and financial income.
- Tocilizumab is associated with important adverse effects, however rheumatologists are familiar with the management of these.
- Tocilizumab is of value for all patients diagnosed with GCA following relapse on steroid taper or considered to be at risk from treatment with high dose steroids as determined by the treating rheumatologist; who are likely to be supported by local or national protocols for commencing, monitoring and withdrawing treatment.

Additional Patient and Carer Involvement
We received a patient group submission from Polymyalgia Rheumatica and Giant Cell Arteritis Scotland (PMR-GCA Scotland). PMR-GCA Scotland is a registered charity and has not received any funding from pharmaceutical companies in the past two years. A representative from PMR-GCA Scotland participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of tocilizumab alongside a 26-week taper regimen for glucocorticosteroids for the treatment of GCA. The comparator was glucocorticosteroid treatment alone, with a 52 week taper regimen. In the analysis, patients received either weekly tocilizumab 162mg SC for a maximum of 52 weeks, in addition to glucocorticosteroids (at a starting dose appropriate to each patient and tapered in accordance with the protocol for the GiACTA study) or glucocorticosteroids alone tapered over a period of 52 weeks.

Response was defined as the absence of relapse / flare that would require escape glucocorticosteroid medication for one week prior to recommencing the tapering regimen. Patients entered the semi-Markov cost-utility model in a remission state and in each 7 day cycle length could move between the starting state of remission and on steroids (tapering) and remission and off steroids, on flare / relapse, on remission with maintenance steroids (escape) and death. The model assumes loss of response occurs upon first relapse / flare and that escape therapy is provided for one week.

The probabilities of steroid-related adverse events and GCA-related complications were also considered for relapse / flare states in the model, which was run over a lifetime time horizon of 30 years, given the mean age of patients as 73 years. A reduced 20 year time horizon was considered in the scenario analysis and a 40 year time horizon was also provided.

Utility data were taken from the GiACTA study informing the clinical effectiveness of tocilizumab with glucocorticosteroids versus glucocorticosteroids alone, which had collected utility data using the EQ-5D, to which standard UK tariffs were applied. Additional utilities required for the extrapolation of the utility values beyond the one year time-frame of the GiACTA study and disutilities associated with AEs, were taken from the literature.

Costs included in the model included the cost of medicines and concomitant medication, plus monitoring (blood test costs) and the costs of outpatient and primary care visits for the management of GCA. Additional costs for glucocorticosteroid-related adverse events were included as were the cost of dealing with GCA complications of vision loss and non-fatal stroke (the probability of fatal stroke was added to the background mortality from ONS life tables for the death state).

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

Results of the base case and probabilistic sensitivity analyses and key scenario analysis results are provided below.

Table 2. Economic base case and key scenario analysis

Base case - Total population						
PAS	**Treatment**	**Costs (£)**	**QALYs**	**Incremental Costs**	**Incremental QALYs**	**ICER (£/QALY)**
With PAS	Tocilizumab	£24,354	7.74	£3,904	0.14	£27,610
	GC alone	£20,450	7.60			
Base case - Newly diagnosed population						
With PAS	Tocilizumab	£24,036	8.18	£3,822	0.13	£30,486
	GC alone	£20,214	8.06			
Base case - Relapsed/refractory population						
With PAS	Tocilizumab	£24,528	7.32	£3,792	0.15	£24,561
	GC alone	£20,736	7.17			

GC = glucocorticosteroid, PAS = Patient Access Scheme, QALY = quality adjusted life year, ICER = incremental cost effectiveness ratio

Deterministic sensitivity analyses results were provided which showed the parameter with the greatest uncertainty, and the sole parameter where an ICER exceeding £30,000 per QALY gained, was the lower bound estimate for the cost of diabetes. However, the submitting company noted that the diabetes cost may be an underestimate, which would lower the ICER compared with the base case.

Probabilistic sensitivity analysis based on 1,000 iterations for the total population, newly diagnosed and relapsed / refractory populations gave ICERs (with PAS) of £26,950, £31,084 and £23,792 respectively. From this analysis the submitting company stated that 56% of the simulations (with PAS) fell below a threshold of £30,000 per QALY gained.

The sole scenario analysis whereby the (with PAS) ICERs exceeded £30,000 per QALY gained for the total population was the duration of tocilizumab treatment. This was assumed to be 12 months for the base case but was varied to 24, 36, 48 and 60 months and producing corresponding (with PAS) ICERs of £88,172, £143,242, £192,927 and £237,526 respectively.

The analysis had a number of limitations:

- A key limitation is the effect of extrapolation methods used on the resulting data and the likely substantial impact this has on results. Firstly the longer term extrapolation of time to first flare suggests a treatment effect of tocilizumab in preventing flare compared with glucocorticosteroids alone that lasts for the majority of the 30 year time horizon, following one year of therapy. This is uncertain given the absence of longer-term data. Secondly, the method of selecting data to model time to subsequent flare is less clear as is the mix of sources used to populate this, but the effect is that cumulative glucocorticosteroid dose is increased over the long term for the glucocorticosteroid group whereas it remains limited in the tocilizumab group over a sustained period for which there are no robust comparative clinical data.
- The justification for the different tapering schedules used is reasonable given the licensing for tocilizumab and current clinical practice in Scotland for tapering glucocorticoids, but by not including a 26 week tapered glucocorticosteroid only group it is more difficult to verify the appropriateness of model assumptions for the groups over the longer term. This is because the effect of tocilizumab

itself is expected to comprise both the ability to use a different tapering schedule and the overall effect on GCA side effects. In addition, since the extrapolation assumptions concerning glucocorticosteroid dose may be flawed, the implications of unstated assumptions behind lengthened tapering periods for the glucocorticosteroid arm in the scenario analysis are unclear. The submitting company clarified the doses assumed at 12, 60 and 120 months for both the scenario analyses but it would be useful to have further clarifications regarding the numbers affected by relapses, flares and both condition and steroid related AEs.

- AEs relating to tocilizumab are not incorporated into the model, and at present there are insufficient long-term data to indicate what the longer term clinical effectiveness profile looks like for the treatment. However, it is likely that the impact of including adverse events in the model would be minimal as the rate of adverse events was similar between the treatment arms in the study.

The Committee also considered the benefits of tocilizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in quality of life was satisfied. In addition, as tocilizumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted tocilizumab for restricted use in NHS Scotland.

Additional information: guidelines and protocols

The British Society for Rheumatology (BSR) and the British Health Professionals in Rheumatology (BHPR) published a management guideline titled 'BSR and BHPR guidelines for the management of giant cell arteritis' in 2010. The guidelines recommend the immediate use of high dose glucocorticosteroid in patients with a clinical suspicion of GCA. Different doses are recommended depending on the presence of jaw claudications and visual disturbances or loss. It is advised the patients receive bone protection while on steroid therapy and that gastrointestinal protection is considered. Only when signs, symptoms and laboratory results associated with a GCA flare have resolved should a tapering reduction of steroid be considered. The guideline includes the following suggested tapering regimen; prednisolone 40 to 60mg daily for at least three to four weeks or until GCA flare resolution, then a 10mg increment reduction in daily dose every two weeks until a dose of 20mg is reached, then a 2.5mg increment reduction in daily dose every two to four weeks until a daily dose of 10mg is reached and then a 1mg increment dose reduction every one to two months until patient has completed the course. Any flare during this tapering period would likely result in a change in the regimen. The addition of low dose aspirin should be considered for patients with no contra-indications to aspirin treatment.

The guideline also recommends the introduction of methotrexate or alternative immunosuppressing therapies should be considered when patients suffer recurrent relapses (should be commenced at the third relapse) or are unable to tolerate weaning of their steroid dose. This guideline precedes the licensing of tocilizumab for GCA.[4]

The European League Against Rheumatism (EULAR) published recommendations for the management of large vessel vasculitis in 2009. These recommendations were broadly in line with those of the BSR and BHPR.[9]

Additional information: comparators

Off-label methotrexate and other immunosuppressive agents may be used as an adjunct to glucocorticosteroid treatment.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
tocilizumab	**162mg SC weekly for 52 weeks only**	**11,871**
methotrexate	7.5mg to 20mg orally weekly	8 to 21

Doses are for general comparison and do not imply therapeutic equivalence. Costs from BNF online on 7 August 2018. Methotrexate use is off-label for this indication. The methotrexate dosing range is obtained from BMJ Best Practice.[5]

Additional information: budget impact

The submitting company estimated the number of patients eligible to receive tocilizumab was 1,589 people in year 1 rising to 1,670 in year 5 to which confidential uptake rates were applied.

*Other data were also assessed but remain commercially confidential.**

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This assessment is based on data submitted by the applicant company up to and including 15 June 2018.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of

Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.