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Swedish Society of Rheumatology 2018 guidelines for investigation, treatment, and follow-up of giant cell arteritis

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REVIEW

Swedish Society of Rheumatology 2018 guidelines for investigation, treatment, and follow-up of giant cell arteritis

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Objective: To develop evidence-based guidelines for the management of giant cell arteritis (GCA) as a complement to guidelines in other areas of rheumatology, issued by the Swedish Society of Rheumatology.
Methods: A working group selected key areas for recommendations, reviewed the available evidence, and wrote draft guidelines. These were discussed and revised according to standard procedures within the Swedish Society of Rheumatology, including a one-day meeting open to all members. For key recommendations, the quality of evidence was assessed according to GRADE. The final guidelines were approved by the Society board in March 2018.
Results: The guidelines include recommendations on diagnostic procedures, pharmacological treatment, follow-up, and adjuvant treatment. Ultrasonography is complementary to temporal artery biopsy (TAB) in the diagnostic work-up. Other imaging techniques (magnetic resonance imaging and positron emission tomography/computed tomography) are important in evaluating large-vessel involvement. Glucocorticoids (oral, or intravenous in cases with ischaemic complications) remain the first line treatment for GCA. Addition of tocilizumab is recommended for patients with relapsing disease who meet five criteria, representing active disease that has been objectively verified by TAB or imaging. Tocilizumab may also be considered in patients with newly diagnosed GCA who are at major risk of severe glucocorticoid side effects. Based on current evidence, tocilizumab treatment for > 1 year cannot be recommended.
Conclusion: These guidelines are based on current evidence and consensus within Swedish rheumatology. Following major developments in diagnostics and treatment of GCA, such guidelines are important for clinical practice, and should be updated on a regular basis.

Giant cell arteritis (GCA) is a primary systemic vasculitis of unknown aetiology that usually affects large and medium-sized arteries. The temporal artery is the most commonly affected artery; hence the previous name temporal arteritis.

GCA is very rare before the age of 50 years and occurs mainly after the age of 60, with an incidence that increases with age (1). Women are afflicted with the disease two to three times more often than men. The highest incidence has been observed in Scandinavia (2). Common symptoms are headache, jaw claudication, and soreness of the temporal arteries (3). Symptoms of polymyalgia rheumatica (PMR), fever, and malaise are also common. PMR can also be a disease on its own, but the treatment guidelines for PMR are not included in this document. Blindness is the most feared complication of GCA (4). Approximately 15% of patients have complications from major vessels, that is, inflammation of the aorta and its branches (5), and neurological symptoms with stroke affect about 10% (6).

The aim of these guidelines is to briefly summarize the current principles for pharmacological treatment of GCA based on the evidence in the literature, or, if such evidence is lacking, on consensus. Related issues on

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diagnostics and follow-up are also covered. The Swedish Society of Rheumatology approved these guidelines in March 2018.

Methods: development of clinical guidelines

Since 2002, the Swedish Society of Rheumatology has issued treatment guidelines on key areas of rheumatology. From 2008 onwards, guidelines on the treatment of rheumatoid arthritis (RA) and other conditions have been updated on an annual basis.

In March 2017, the board of the Swedish Society of Rheumatology decided that guidelines for the management of GCA should be developed. A working group, chaired by Dr Ann Knight, was appointed by the Society board. Working group members were selected based on expertise and regional representation. All group members submitted a declaration of conflict of interest to the Society board.

The development of guidelines followed standard procedures in the Swedish Society of Rheumatology. At a meeting, the working group identified important areas that should be covered by the guidelines. Based on separate literature searches, the evidence in each area was reviewed and draft summaries with recommendations were written. These were discussed within the working group, and a draft guideline document was formulated, based on consensus within the group. For selected recommendations, the evidence was graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (7). The quality of evidence is described as high, moderate, low, or very low, where high is the highest grade of evidence.

The draft guidelines were sent to the Society board and to the Swedish Society of Rheumatology College of Professors, which includes all professors in rheumatology in active clinical practice in Sweden. Based on comments by the board and the college, a revised version of the guidelines was written. This version was sent to the Society board, the College of Professors, all chairs at rheumatology units in Sweden, and all members of the Swedish Society of Rheumatology who had registered for the annual Society one-day meeting on guidelines and recommendations. Following further discussions at this meeting, the guidelines were again revised by the working group, and the revised version was sent to the Society board for final approval.

Swedish Society of Rheumatology 2018 guidelines for investigation, treatment, and follow-up of GCA

The guidelines were approved by the board of the Swedish Society of Rheumatology in March 2018. The following represents an English translation, which has been modified for the review format. The main recommendations in the guidelines are summarized in Table 1.

Diagnosis

The diagnosis of GCA is based on the medical history and clinical findings supported by laboratory parameters and, in the best case, a positive biopsy from the temporal artery. The American College of Rheumatology (ACR) classification criteria from 1990 (8) are used for classification in, for example, research contexts. They are not diagnostic criteria but may provide support when making a diagnosis. New, revised classification criteria are being discussed, partly to include newer diagnostic possibilities in, for example, imaging (9) (Table 2).

Table 1. Summary of recommendations for the treatment of giant cell arteritis (GCA).

Recommendation number	Summary statement
1	Glucocorticosteroids remain first line for the treatment of GCA.
2	It is vital not to delay treatment, for example while waiting for a temporal artery biopsy.
3	The recommended initial dose of prednisolone is 40–60 mg for 4 weeks, thereafter gradually tapered.
4	If vision is impaired or there are other signs of serious vascular involvement, intravenous methylprednisolone 1000 mg once daily for 3 days may be considered, followed by oral treatment as above.
5	The rationale for treating GCA with tocilizumab is primarily its glucocorticoid-sparing effect over time. Tocilizumab is recommended as a supplement to prednisolone treatment in patients with recurrent or active illness during glucocorticoid treatment, providing the criteria set in the guidelines are met.
6	In cases of newly diagnosed GCA, tocilizumab may be considered when there is a great risk of future side effects of glucocorticoids, and pronounced clinical and laboratory signs of vascular inflammation.
7	Treatment with tocilizumab should be discontinued after 1 year. Longer periods of treatment cannot be recommended with our present state of knowledge. If inflammation persists after 1 year of treatment with tocilizumab, an individual assessment must be made by the treating physician.

Table 2. Current and proposed classification criteria for giant cell arteritis (GCA).

Original criteria, ACR 1990 (8)	Proposal for new, extended criteria* (9)
Age at onset of disease ≥ 50 years	Age at onset of disease ≥ 50 years
New headache or new type of localized pain in the head, visual symptoms, loss of sight, PMR, constitutional symptoms, and/or jaw claudication	Any of the following: new headache of new type and localization, chewing, and/or jaw claudication
Tenderness at palpation or low pulse at the temporal artery	Tenderness at palpation or low pulse at the temporal artery and/or extracranial arteries
ESR ≥ 50 mm/h	ESR ≥ 50 mm/h and/or CRP ≥ 10 mg/L
Positive temporal artery biopsy (granulomatous arteritis or arteritis with mononuclear cells, giant cells)	Positive temporal artery biopsy (granulomatous arteritis or arteritis with mononuclear cells, giant cells) and/or imaging diagnostics using ultrasonography findings, MRI, and/or FDG-PET.

*These criteria are based on opinions and should not be used in clinical practice or in clinical studies. A patient has GCA if three out of five criteria are met, provided the biopsy is positive and/or the imaging diagnostics results are compatible with a GCA diagnosis. ACR, American College of Rheumatology; PMR, polymyalgia rheumatica; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; MRI, magnetic resonance imaging; FDG-PET, [^{18}F]fluorodeoxyglucose-positron emission tomography.

Imaging diagnostics for GCA

Cranial GCA. Doppler ultrasound (US) is a complement to temporal artery biopsy (TAB), which, for the present, is the gold standard for diagnosis of GCA. Oedema in vessel walls (halo phenomenon) is the typical US finding in GCA (10, 11). The advantage of this method is that it is non-invasive and easily available; the disadvantage is that it requires an experienced sonographist to be reliable. Magnetic resonance imaging (MRI) is another good method; in comparison with US, there is equal sensitivity (69% and 67%, respectively) and specificity (both 91%) (11). When there are reliable findings using US or MRI, in certain situations it is possible to dispense with biopsy (12). Positron emission tomography/computed tomography (PET/CT) has no part in the diagnosis of cranial GCA owing to the proximity of the central nervous system (CNS) (the high glucose metabolism in the CNS makes assessment difficult).

Extracranial GCA. PET/CT is primarily of value for diagnosing large-vessel vasculitis and for differential diagnosis regarding malignancy and other inflammatory conditions (13). MRI is another reliable and often more easily available method for diagnosing aortitis. So far, MRI and PET/CT have shown comparable sensitivity. New technology in which MRI technology and PET are combined gives even more information and is very promising for the future. US works less well when investigating the major vessels and is a less reliable method in cases of large-vessel GCA (14).

Follow-up of GCA

Assessment of the effects of treatment should be based on clinical evaluation: the medical history and clinical assessment of possible GCA symptoms combined with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and blood counts. Remission is defined as a lack of signs, symptoms, and laboratory tests indicating active inflammation; relapse is defined as the return of typical clinical signs and symptoms and laboratory tests indicating inflammation. During treatment with the interleukin-6 (IL-6) inhibitor tocilizumab, CRP cannot be used as an effective measurement; instead, clinical evaluations and to a certain extent other laboratory tests indicating inflammation should give guidance, but ESR, haemoglobin, and platelets may also be affected by tocilizumab.

In studies, remission has been defined as the absence of glucocorticoid treatment, absence of symptoms, and absence of elevated inflammatory parameters in laboratory tests (15).

The recommended safety tests during tocilizumab treatment for GCA are the same as for the treatment of RA. (Regarding safety aspects, see recommendations from the Swedish Society of Rheumatology, www.http://svenskreumatologi.se/srfs-riktlinjer; in Swedish.) In brief, complete blood counts and liver enzymes should be followed on a regular basis: monthly during the first 6 months, then usually every 3 months. Lipids should be tested at baseline and after 3 months, and thereafter at individualized intervals.

There is no standard procedure for imaging (US, MRI, CT, and PET) in the follow-up and assessment of disease activity after treatment, and such imaging therefore cannot generally be recommended. However, known aortic dilatation caused by GCA should be followed up, e.g. with CT angiography (12).

Pharmacological treatment of GCA

Glucocorticoids. Treatment of GCA consists primarily of glucocorticoids. Early treatment with effective doses of glucocorticoids may have a protective effect on the

development of comorbidities, in particular eye complications (16). There are no studies on the ideal effective doses of glucocorticoids; all available data are based on previous experience and published treatment recommendations, based in turn on expert opinion and consensus (17, 18). The only randomized study which has investigated dosage and tapering of glucocorticoids is the GiACTA study, which studied the use of the IL-6 receptor blocker tocilizumab in GCA (19). As yet, there are no data on long-term follow-up of GiACTA which allow definite conclusions to be drawn regarding optimal dosage. Side effects of glucocorticoids are well known, and include osteoporosis and serious infections (20, 21). Finding the balance between such side effects and the risk of undertreating vasculitis is difficult. When loss of sight has already occurred, however, it is usual permanent. It is therefore never justifiable to omit treatment with glucocorticoids when waiting for a TAB.

Based on published data and experience, we make the following suggestions for suitable doses of glucocorticoids in the treatment of GCA. However, we would emphasize that an individual assessment should be made according to the patient's age, existing comorbidities, and clinical manifestations, e.g. visual complications and extracranial vascular involvement.

Oral glucocorticoids. In cases of uncomplicated GCA (without jaw claudication or visual complications), an initial dose corresponding to 40–60 mg of prednisolone should be given daily.

There is no steroid-tapering regimen that suits all patients and all clinical scenarios. An example is provided in Table 3.

Intravenous glucocorticoids. There is one small randomized controlled trial (RCT) showing favourable effects using intravenous glucocorticoids in GCA (22). This study, which was based on 27 individuals, showed that intravenous glucocorticoids in doses of 15 mg/kg for three consecutive days initially resulted in more patients in this group having sustained remission (after treatment with prednisolone) at week 78, compared with the control (saline-injected) group. In addition, the cumulative median dose of prednisolone was significantly lower in the intravenous group than in the control group (5636 g and 7860 g, respectively).

When there are serious ischaemic manifestations, especially ongoing or threatening visual complications such as diplopia, amaurosis fugax, or blurred vision, we recommend methylprednisolone as an intravenous pulse treatment of 1000 mg daily for three consecutive days. This should be followed by oral glucocorticoids as described above.

Tocilizumab for GCA. Tocilizumab – a humanized monoclonal antibody that binds to the IL-6 receptor – was registered in 2009 for the treatment of RA. Since September 2017, tocilizumab has been approved in Europe for the treatment of GCA. The label for tocilizumab does not include any limitations of the indications for this diagnosis. The recommended dose is 162 mg subcutaneously once a week in combination with decreasing the dose of glucocorticoids.

The effects of treatment with tocilizumab have been evaluated in two randomized, placebo-controlled studies, both with a 52 week follow-up.

A phase II study compared the effects of tocilizumab, given intravenously 8 mg/kg every 4 weeks, with placebo for patients who were being treated with prednisolone (which was reduced from 1 mg/kg to 0.1 mg/kg after 12 weeks, and thereafter with 1 mg per month) (23). In the treatment group (20 patients), 85% achieved sustained remission for 1 year, compared with 20% in the placebo group (10 patients).

A phase III study, which comprised a total of 251 patients, compared the effects of tocilizumab 162 mg subcutaneously every week or every other week with a placebo (19, 24). Prednisolone was administered according to a tapering schedule for 26 weeks (both tocilizumab arms and a placebo arm) or for 52 weeks (a placebo arm). All the study personnel were blinded for CRP, but the evaluators who were responsible for

Table 3. Example of schedule for reducing glucocorticosteroid treatment for giant cell arteritis.

Step	Recommendation
1	40–60 mg prednisolone/day for approximately 4 weeks (until ESR and CRP have been normalized, and signs and symptoms have improved
2	Thereafter, reduction of the dose by 10 mg every other week to 20 mg daily
3	Thereafter, reductions of 2.5 mg with 2–4 week intervals to 10 mg daily
4	If there are no signs of relapse, the dose may be reduced by 1 mg every month or every other month.
Follow-up and treatment modification	After every dose reduction, the patient's ESR and CRP are checked and the return of signs and symptoms is also checked. If signs and symptoms of active disease return, the dose of prednisolone should be increased to the latest effective dose.

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

safety were informed about the ESR. The percentages of sustained remission from 12 weeks after the beginning of treatment until the 1 year follow-up were 56% (tocilizumab every week) and 53% (tocilizumab every other week) in the treatment arms, and 14% (prednisolone reduction schedule for 26 weeks) and 18% (prednisolone reduction schedule for 52 weeks) (19).

There were also significant differences in the cumulative prednisolone dose which favoured tocilizumab (19, 23), and a major improvement in patient-reported results [health-related quality of life, measured with the 36-item Short Form Health Survey (SF-36)] and the patients' global assessment of disease activity in those who were treated with tocilizumab in the phase III study (19).

These studies of tocilizumab in GCA included both patients who had newly diagnosed disease and those who had a recurrence of GCA (19, 23). All patients had active disease at randomization. In an analysis limited to patients with relapse, significant differences were observed in comparison with placebo only in the group that was treated with tocilizumab every week (19). There was no corresponding difference between the doses for newly diagnosed patients. Serious adverse events occurred to a lesser extent in the patients who were treated with tocilizumab (14% and 15% for tocilizumab every other week and weekly, respectively), in comparison with placebo (22% and 25% for prednisolone reduction schedules of 26 and 52 weeks, respectively) in the phase III study (19).

To conclude, treatment with tocilizumab combined with prednisolone (initial dose 20–60 mg) has a greater probability of sustained remission (moderate quality of evidence) and a lower cumulative prednisolone dose (moderate quality of evidence) compared with prednisolone alone. There are limited data concerning safety when treating GCA with tocilizumab. The data available from clinical trials do not indicate an increased risk of serious adverse events. There is a lack of information about treatment for periods longer than 1 year.

Treatment of GCA with tocilizumab should be followed by a specialist in rheumatology.

Tocilizumab is recommended as an addition to treatment with glucocorticoids for patients who meet all five criteria listed in Table 4.

In newly diagnosed GCA, tocilizumab may be considered as an addition to treatment with glucocorticoids in patients with pronounced clinical or laboratory signs of inflammation and a high risk of side effects in future treatment with glucocorticoids (e.g. severe, uncontrolled diabetes, manifest osteoporosis, mental illness with deterioration after previous treatment with glucocorticoids, or severe, unstable heart disease). For patients with newly diagnosed GCA, the efficacy of tocilizumab 162 mg every other week appears to be similar to that of the recommended dose (19).

This proposed limitation for the use of tocilizumab is based on consensus in the Swedish Society for Rheumatology.

With concomitant treatment with tocilizumab, glucocorticoid treatment should be reduced to 15 mg of prednisolone daily at week 8. Thereafter, the aim should be to reduce the glucocorticoid treatment completely within 26 weeks after the start of treatment, e.g. in accordance with the schedule used in the GiACTA study (Table 5).

Treatment with tocilizumab should be stopped after 1 year for patients who have achieved sustained remission. These patients should be followed by a specialist for at least 6 months after the completion of treatment.

To enable the follow-up of effects and safety in patients who have been treated with tocilizumab in clinical practice, all Swedish patients who start tocilizumab treatment with GCA indication should be registered and followed up in the national Swedish Rheumatology Quality Register (SRQ).

Other disease-modifying anti-rheumatic drugs in GCA. In several minor RCTs, methotrexate has been shown to have a certain glucocorticoid-sparing effect (25, 26). The patients included were started on methotrexate at diagnosis with a dose of 7.5–15 mg per week, and these patients required a lower cumulative dose of glucocorticoids than those on glucocorticoids without methotrexate. A meta-analysis (27)

Table 4. Criteria for addition of tocilizumab to treatment with glucocorticoids in patients with giant cell arteritis.

Number	Criterion
1	Relapse during glucocorticoid treatment or relapse after the completion of treatment with glucocorticoids
2	Large vessel arteritis that has at some point been verified with biopsy or with imaging of large vessels (MRI, PET-CT, or CT angiography)
3	Clinically active giant cell arteritis
4	Elevated CRP and ESR
5	Obvious side effects of glucocorticoid treatment or great risk of such side effects from future treatment with glucocorticoids

MRI, magnetic resonance imaging; CT, computed tomography; PET, positron emission tomography; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 5. Description of schedule for reduction of prednisolone in the GiACTA study (19).

Week	Prednisolone dose/day (mg)
1–7	Reduction from 20–60 mg to 20 mg after 7 weeks
8	15
9	12.5
10	12.5
11	10
12	9
13	8
14	7
15	6
16	6
17	5
18	5
19	4
20	4
21	3
22	3
23	2
24	2
25	1
26	1
27	0

of these studies found a moderate glucocorticoid-sparing effect and a lower risk of relapse (low quality of evidence) from adjunctive treatment with methotrexate. It should be pointed out that patients with a therapy-refractory or relapsing disease have not been studied in a randomized way. Addition of methotrexate in treating GCA may be considered in cases of late relapse without major inflammatory activity or with marked glucocorticoid side effects, when the patient does not meet the criteria for tocilizumab treatment (Table 4).

Three tumour necrosis factor inhibitors (infliximab, adalimumab, and etanercept) have been studied, but none of these showed any convincing efficacy (28).

Treatment with cyclophosphamide, administered in doses of 500 mg/m^2 body surface area, alternatively 500 mg, monthly, or every other week for 6 weeks followed by monthly treatment, has been reported in cases of glucocorticoid-dependent, refractory GCA to have a significant glucocorticoid-sparing effect (29), and to lead to long-term remission in more than 50% of patients. Its use, however, is limited by side effects. Cyclophosphamide should be considered in cases of intracerebral involvement of large-vessel disease.

Azathioprine had a weak glucocorticoid-sparing effect when given as a dose of 150 mg/day for 52 weeks, according to one RCT (with a small number of patients) (30). It is therefore seldom used in GCA.

Abatacept is a humanized fusion protein that modifies co-stimulation in antigen presentation, thereby inhibiting T-cell activity. Several experimental studies indicate that activated T cells play a role in the pathogenesis of GCA, and activated T cells have been found in arterial biopsies from GCA patients (31). Abatacept has been tested in a phase II study with 49 patients with either new or relapsing GCA, where it was given in combination with glucocorticoids (32). Relapse-free survival was significantly better and relapse frequency was lower in the abatacept group compared to the glucocorticoid-only group. The percentage of serious side effects was the same in both groups (32). To sum up, the addition of abatacept to glucocorticoid treatment results in a lower risk for relapse than with glucocorticoids alone (low quality of evidence). Treatment with abatacept may be considered when there are serious side effects from tocilizumab or when there is a contraindication for tocilizumab.

A phase III study with abatacept was planned to start in 2018, but it has been withdrawn by Bristol Myers-Squibb.

Adjuvant treatment in GCA

As treatment with glucocorticoid risks causing or worsening osteoporosis, preventive treatment with calcium and vitamin D for all patients, and sometimes bisphosphonate or other anti-resorptive therapy for patients with other risk factors, is recommended. Blood pressure and blood glucose should be monitored during treatment with glucocorticoids, especially during the introductory phase of treatment. There is some evidence from retrospective observation studies that acetylsalicylic acid (ASA) and anticoagulants reduce the risk of ischaemic complications (33), but there is a lack of RCTs (34). All in all, treatment with ASA in newly diagnosed GCA should be considered unless there are contraindications.

Conclusions

These guidelines were developed following major progress in diagnostic procedures and in the treatment of GCA. A key issue was the rational and evidence-based selection of patients with GCA for treatment with tocilizumab. The recommendations are based on current evidence and consensus within Swedish rheumatology. The draft guidelines were written by a small group of experts, but the development followed the standard procedures for such guidelines in Sweden, which ensure a broad discussion within the rheumatology community and are likely to contribute to their utility in clinical care. These standard procedures include regular updates, taking new evidence and growing clinical experience into account.

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