EULAR recommendations for the management of large vessel vasculitis

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ABSTRACT

Objectives: To develop European League Against Rheumatism (EULAR) recommendations for the management of large vessel vasculitis.

Methods: An expert group (10 rheumatologists, 3 nephrologists, 2 immunolgists, 2 internists representing 8 European countries and the USA, a clinical epidemiologist and a representative from a drug regulatory agency) identified 10 topics for a systematic literature search through a modified Delphi technique. In accordance with standardised EULAR operating procedures, recommendations were derived for the management of large vessel vasculitis. In the absence of evidence, recommendations were formulated on the basis of a consensus opinion.

Results: Seven recommendations were made relating to the assessment, investigation and treatment of patients with large vessel vasculitis. The strength of recommendations was restricted by the low level of evidence and EULAR standardised operating procedures.

Conclusions: On the basis of evidence and expert consensus, management recommendations for large vessel vasculitis have been formulated and are commended for use in everyday clinical practice.

The large vessel vasculitides affect the aorta and its branches and include giant cell arteritis and Takayasu arteritis, which are anatomically, epidemiologically and clinically distinct conditions. The estimated incidence of giant cell arteritis in Europe, in individuals aged over 50 years of age varies between 32 and 290/million/year, making it the commonest primary systemic vasculitis in adulthood.[1–10] There are few studies reporting the incidence of giant cell arteritis outside of Europe: 102/million/year in Jerusalem[11] and 188/million/year in Minnesota, USA.[12] Giant cell arteritis has a prevalence of 240–1354/million in Northern Europe in individuals over 50 years of age.[5 13] It has an affinity to affect the branches of the carotid artery, but subclinical involvement of the other cranial arteries and the wider arterial tree is not uncommon.[14 15] Takayasu arteritis is less common than giant cell arteritis. The annual incidence of Takayasu arteritis is 0.4–2/million/year and the frequency in an autopsy study from Japan was 0.033%.[1 16 17] These conditions present a challenge to diagnosis and management. This paper summarises seven evidence-based recommendations for the management of the large vessel vasculitides.

METHODS

These recommendations have been developed according to standardised operating procedures, as developed by the European League Against Rheumatism (EULAR) standing committees.[18]

This guidance is termed "recommendations" as opposed to "guidelines" or "points to consider" as the evidence base is strong to provide guidance but not in itself sufficient to answer the needs of the individual patient. They will need to be tailored to individual needs. These recommendations are intended for use by healthcare professionals who look after patients with primary systemic vasculitis, for the training of medical students and specialist trainees, and for pharmaceutical industries and drug regulatory organisations.

The committee was convened by RL (rheumatologist) and LG (internist) and consisted of nine rheumatologists (BD, KdG, WG, BH, PM, CaS, DS, RW, HY), three renal doctors (CoS, DJ, KW), two immunologists (CK, TH), one internist (MC), one clinical epidemiologist (HR) and one US Food and Drug Administration (FDA) representative (JW). The specialty of each author was self-declared. CM was appointed as the clinical fellow in charge of the literature search.

Prior to the literature search, a modified Delphi among the experts was carried out to identify the scope of the recommendations. The Delphi process identified 10 points to focus the literature search. Following the Delphi exercise, the committee agreed on the search string to identify the publications in PubMed: for example, "Takayasu's arteritis"[Mesh] AND ("Epidemiologic Study Characteristics"[Mesh] OR "Evaluation Studies"[Mesh] OR "Study Characteristics" [Publication Type]) NOT "Case Reports" [Publication Type]. For giant cell arteritis, the medical subject heading used in PubMed and the search string was "Temporal arteritis". All papers identified in Medline were then limited to manuscripts indexed for adult patients and those having abstracts. The search was not limited to a time frame or by language. The Cochrane library was searched using the disease specific keywords. A manual search of abstracts presented at the annual meetings of the British Society for Rheumatology and the European League Against Rheumatism for the year 2007 and the American College of Rheumatology (ACR) for the year 2006 was performed.

Each paper was reviewed and included if it contained a management outcome as identified in the modified Delphi exercise. Duplicate datasets

Table 1 Determination of level of evidence: the data from studies was graded according to internationally accepted criteria

Category	Evidence
1A	From meta-analysis of randomised controlled trials
1B	From at least one randomised controlled trial
2A	From at least one controlled study without randomisation
2B	From at least one type of quasi-experimental study
3	From descriptive studies, such as comparative studies, correlation studies, or case–control studies
4	From expert committee reports or opinions and/or clinical experience of respected authorities

Trial methodology and other uncontrolled results from any of the studies (including randomised controlled trials) were awarded a lower level of evidence.

were discarded. The identified papers were then categorised and given a level of evidence according to internationally accepted criteria (table 1).[18] The evidence was assimilated into seven statements. Each statement was voted on by the members of the steering committee according to internationally agreed criteria (table 2)[18] and we present the median vote for each statement. In the absence of evidence some statements are based on expert opinion and the level of evidence reflects the same.

RESULTS

The modified Delphi exercise

The items of the modified Delphi search on which there was agreement, are given in table 3. It was recognised that some of the items may not have an evidence base to formulate recommendations.

Literature search

The results of the literature search are as in table 4. Cochrane reviews added no further studies. The manual search of the abstract of meetings in 2006 did not reveal any abstracts with enough details of management outcomes to warrant inclusion.

Statements

1. We recommend a thorough clinical and imaging assessment of the arterial tree when a diagnosis of Takayasu arteritis is suspected (level of evidence 3, strength of recommendation C)

In the absence of a gold standard for the diagnosis and monitoring of patients with Takayasu arteritis, a clinical suspicion of vasculitis should trigger a thorough clinical examination of the arterial tree.[19–24] Magnetic resonance angiography or positron emission tomography can assist diagnosis and document the extent of the arterial involvement, but these modalities require formal validation.[25–28] They are not widely available and remain operator dependent. In their absence, conventional angiography should be considered. Takayasu arteritis should be managed at an expert centre because of the rarity of the disease, the limited availability of specialist imaging, specialist vascular surgery and the difficulty associated with treating this condition.[19 20 29 30]

2. A temporal artery biopsy should be performed whenever a diagnosis of giant cell arteritis is suspected, but this should not delay the treatment; a contralateral biopsy is not routinely indicated (level of evidence 3, strength of recommendation C)

A biopsy of the affected temporal artery should always be attempted whenever possible. Histopathological evidence is the gold standard for the diagnosis of giant cell arteritis. It is not a sensitive procedure and the presence of skip lesions may render the test negative.[31–36] Routine biopsy of both temporal arteries is not recommended because this does not add significantly to the diagnostic yield; although it may be of value in selected individuals.[37–39] An adequate sample length is important when a biopsy is carried out and we suggest a biopsy length of at least 1 cm to enable the pathologist to look at multiple sections of the artery over a wide area.[40–42] Due to the possibility of a false negative result, and the risk of irreversible ocular involvement, treatment with high-dose glucocorticoids should be commenced on strong clinical suspicion of giant cell arteritis, prior to the biopsy to be carried out.[43–46] Treatment prior to biopsy is unlikely to affect the result of the test, but the biopsy should not be delayed beyond 1–2 weeks of commencing glucocorticoid therapy.[47 48]

Raised inflammatory markers are highly sensitive for the diagnosis of giant cell arteritis. A normal erythrocyte sedimentation rate or C-reactive protein should raise suspicion for an alternative diagnosis.[49 50] In a meta-analysis of studies, ultrasonography of the temporal artery was 88% sensitive and 97% specific for diagnosing temporal arteritis.[51] It can demonstrate changes thought to be due to vessel wall oedema. This test awaits multicentre reproducibility.

3. We recommend early initiation of high-dose glucocorticoid therapy for induction of remission in large vessel vasculitis (level of evidence 3, strength of recommendation C)

Early intensive therapy with high-dose glucocorticoid induces remission in patients with large vessel vasculitis.[19 52 53] Visual loss in one eye is prevalent in 18% of patients at diagnosis.[54] It is usually irreversible and pulsed intravenous methylprednisolone may be of benefit to some patients who present early following the onset of visual symptoms.[45 55–59] The initial dose of prednisolone is 1 mg/kg/day (maximum 60 mg/day) and the initial high-dose should be maintained for a month and tapered gradually.[19 21 52 54 60] The taper should not be in the form of alternate day therapy, as this is more likely to lead to a relapse of vasculitis.[60] At 3 months, the glucocorticoid dose in clinical trials has been between 10–15 mg/day.[53 54 61 62] The duration of glucocorticoid therapy for patients with giant cell arteritis is variable and can extend to several years, but some patients may not be able to tolerate complete discontinuation of glucocorticoid therapy due to recurrent disease or secondary adrenal insufficiency.[52] All patients should have bone protection therapy in the absence of contraindications in accordance with local guidelines.[63]

4. We recommend that an immunosuppressive agent should be considered for use in large vessel vasculitis as adjunctive therapy (level of evidence 1A for giant cell arteritis, strength of recommendation B; level of evidence 3 for Takayasu arteritis, strength of recommendation C)

Giant cell arteritis requires long-term glucocorticoid therapy; 86% of patients suffer glucocorticoid-related adverse events at

Table 2 Determination of strength of recommendation

Strength	Directly based on:
A	Category 1 evidence
B	Category 2 evidence or extrapolated recommendations from category 1 evidence
C	Category 3 evidence or extrapolated recommendations from category 1 or 2 evidence
D	Category 4 evidence or extrapolated recommendations from category 2 or 3 evidence

Table 3 Results of the modified Delphi: 10 topics that the committee agreed to address

No.	Topic	Coverage
1	Diseases to be addressed	WG, MPA, CSS, PAN, cryoglobulinemic vasculitis, GCA, Takayasu arteritis
2	Initial assessment	Involvement of expert centres, structured clinical examination, role of ANCA, staging of disease, biopsy
3	Remission induction	Cyclophosphamide, methotrexate, high-dose glucocorticoids
		Doses, route of administration, regimen of intravenous use, prophylaxis against *Pneumocystis jiroveci* and osteoporosis, tapering of glucocorticoids, bladder protection, antiemetic therapy, monitoring for drug toxicity, plasmapheresis
4	Remission maintenance	Choice of immunomodulator, length of treatment, co-trimoxazole
5	Relapsing disease	Choice of immunomodulator, referral to expert centre
6	Refractory disease	Choice of immunomodulator, experimental therapies
7	Cryoglobulinemic vasculitis	Choice of therapy, antiviral therapy
8	Polyarteritis nodosa	Choice of therapy, antiviral therapy
9	Monitoring and follow-up	Structured clinical examination, blood test monitoring, urine analysis, vaccination, fertility and contraception
10	Complications of disease	Anaemia, hypertension, thromboprophylaxis, reconstructive surgery, renal protection

ANCA, anti-neutrophilic cytoplasmic antibodies; CSS, Churg–Strauss syndrome; GCA, giant cell arteritis; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa; WG, Wegener granulomatosis.

10-year follow-up.[52] In an effort to reduce the duration of glucocorticoid therapy, there have been three randomised controlled trials of methotrexate as adjunctive therapy to glucocorticoid.[54 62 64] A meta-analysis of these three trials demonstrates a modest role for methotrexate (10–15 mg/week) in reducing relapse rate and lowering the cumulative dose of glucocorticoid therapy.[65] The combination of infliximab and glucocorticoid therapy does not reduce the risk of relapse as compared to glucocorticoid monotherapy, and is not recommended in giant cell arteritis.[61]

Despite glucocorticoid therapy, Takayasu arteritis can remain active at a subclinical level.[66] Azathioprine (2 mg/kg/day) and methotrexate (20–25 mg/week) have been used as adjuncts to glucocorticoid therapy in patients with Takayasu arteritis.[21 67 68] The addition of these agents to glucocorticoid may help to improve disease control and facilitate reduction of the cumulative glucocorticoid dose. Cyclophosphamide has been used in adults with Takayasu arteritis resistant to glucocorticoids in a small open label study.[69]

5. Monitoring of therapy for large vessel vasculitis should be clinical and supported by measurement of inflammatory markers (level of evidence 3, strength of recommendation C)

There are no valid biomarkers for assessing response and diagnosing relapse in large vessel vasculitis. Clinical monitoring aided by inflammatory markers should inform the decision to alter therapy. For patients with Takayasu arteritis, periodic imaging with MRI may assist assessment of disease activity.[25 26] Positron emission tomography may also be of value for monitoring.[28] There is limited evidence for the use of carotid and subclavian ultrasonography for monitoring of Takayasu arteritis.[70–72] All the imaging modalities need formal validation for monitoring of vasculitis activity. All patients with Takayasu arteritis will need long-term monitoring.

For patients with giant cell arteritis, a relapse is usually associated with a rise in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Aortic imaging should be considered in giant cell arteritis, especially in patients with an aortic insufficiency murmur,[73] because subclinical involvement is common and may progress to form aneurysm or dissection in 9%–18% of patients.[14 73–76] In symptomatic patients, the presence of normal inflammatory markers should raise suspicion of an alternative diagnosis. Patients in clinical remission who have discontinued therapy and experience a relapse should be treated as per new patients. For those still on glucocorticoids, an increase of 5–10 mg/day may be sufficient to treat the relapse.[54] Increase to a full remission induction dose of glucocorticoid (1 mg/kg/day) is not usually necessary unless ocular or neurological symptoms recur.

6. We recommend the use of low-dose aspirin in all patients with giant cell arteritis (level of evidence 3, strength of recommendation C)

Patients with giant cell arteritis are at an increased risk of developing cardiovascular and cerebrovascular events.[74 77] The addition of low-dose aspirin (75–150 mg/day) protects against such events and should be prescribed to all patients in the absence of contraindications.[78 79] Gastroduodenal mucosal protection should be considered when commencing aspirin. The use of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) does not seem to be influence the clinical profile or glucocorticoid requirement of patients with giant cell arteritis[80 81]

7. Reconstructive surgery for Takayasu arteritis should be performed in the quiescent phase of disease and should be undertaken at expert centres (level of evidence 3, strength of recommendation C)

Arterial reconstruction and bypass grafting may be necessary in up to 70% of patients with Takayasu arteritis to reverse some of the features of the disease, for example renovascular hypertension.[19–21 82] In expert hands, reconstructive surgery has a good outcome, but revision surgery is often needed.[19 29 30 83 84]

Table 4 Results of the literature search on 31/08/2007: number of papers identified in PubMed

Keyword used in search string	No. of identified citations	Restricted to "adult" and "abstract"	Unique citations
Temporal arteritis	508	371	371
Takayasu arteritis	274	207	195
Total no of identified citations			566

Table 5 The seven recommendations for the management of large vessel vasculitis with the level of evidence for each statement and the median strength of recommendation as per EULAR operating procedures

Statement	Level of evidence	Median final vote
We recommend a thorough clinical and imaging assessment of the arterial tree when a diagnosis of Takayasu arteritis is suspected	3	C
A temporal artery biopsy should be performed whenever a diagnosis of giant cell arteritis is suspected, but this should not delay the treatment; a contralateral biopsy is not routinely indicated	3	C
We recommend early initiation of high-dose glucocorticoid therapy for induction of remission in large vessel vasculitis	3	C
We recommend that an immunosuppressive agent should be considered for use in large vessel vasculitis as adjunctive therapy	1A for GCA	B for GCA
	3 for TAK	C for TAK
Monitoring of therapy for large vessel vasculitis should be clinical and supported by measurement of inflammatory markers	3	C
We recommend the use of low-dose aspirin in all patients with giant cell arteritis	3	C
Reconstructive surgery for Takayasu arteritis should be performed in the quiescent phase of disease and should be undertaken at expert centres	3	C

EULAR, European League Against Rheumatism; GCA, giant cell arteritis; TAK, Takayasu arteritis.

Angioplasty and stent insertion have a higher rate of restenosis than surgical reconstruction, but may be appropriate for some patients.[19 84–86] Elective procedures should be performed when disease is in remission.[19 30] These patients will need long-term follow-up.[30 87 88]

DISCUSSION

Application of these recommendations

Giant cell arteritis and Takayasu arteritis affect different age groups and have a different disease burden. Yet, many of the clinical manifestations and pathological findings in these disorders overlap. Furthermore, the principles of managing these two conditions are similar.

To produce these recommendations (table 5), we have performed a systematic review of literature and have applied internationally accepted grading criteria of clinical trials and studies.[18] The absence of many large clinical trials in these conditions prevents us from supporting some of the statements with stronger grades. For example, the use of glucocorticoid therapy in large vessel vasculitis is universally accepted but the lack of evidence based on clinical trials meant that the level of evidence could only be 3 (descriptive studies), leading to a grade of recommendation no higher than C. Our final recommendations represent the distillation of evidence and experience of an international group of doctors with an expertise in the management in these conditions. The project has also led to the committee to propose a research agenda for large vessel vasculitis (box 1). We hope that these recommendations will assist individual clinicians in the management of these conditions, and provide a tool for auditing their practice.

Box 1 Research agenda

- Validation of imaging techniques (ultrasound, magnetic resonance and positron emission tomography) for diagnosis and/or monitoring of large vessel vasculitis.
- Identification of a biomarker for diagnosis and monitoring of large vessel vasculitis.
- Development of diagnostic criteria for large vessel vasculitis.
- Adequately powered randomised controlled trials to assess the role of adjuvant therapy (conventional as well as biological) with glucocorticoid in large vessel vasculitis.
- The role of thromboprophylaxis for primary prevention of vascular outcomes in giant cell arteritis.
- Long-term clinical outcomes in treated large vessel disease: vascular surgery, osteoporosis, cardiovascular and cerebrovascular events.

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