EULAR recommendations for the management of primary small and medium vessel vasculitis

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ABSTRACT

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

Methods: An expert group (consisting of 10 rheumatologists, 3 nephrologists, 2 immunologists, 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 using a modified Delphi technique. In accordance with standardised EULAR operating procedures, recommendations were derived for the management of small and medium vessel vasculitis. In the absence of evidence, recommendations were formulated on the basis of a consensus opinion.

Results: In all, 15 recommendations were made for the management of small and medium vessel vasculitis. The strength of recommendations was restricted by low quality of evidence and by EULAR standardised operating procedures.

Conclusions: On the basis of evidence and expert consensus, recommendations have been made for the evaluation, investigation, treatment and monitoring of patients with small and medium vessel vasculitis for use in everyday clinical practice.

The primary systemic vasculitides produce inflammation of blood vessels resulting in occlusive, stenotic or aneurysmal change leading to ischaemic or haemorrhagic events. They are classified as small, medium or large vessel vasculitis depending on the calibre of the vessels involved.[1] This paper addresses the management of the adult spectrum of medium and small vessel vasculitis, which includes Wegener granulomatosis (WG), microscopic polyangiitis (MPA), Churg–Strauss syndrome (CSS), essential cryoglobulinemic vasculitis and polyarteritis nodosa (PAN). We present 15 recommendations from expert clinicians experienced in the management of these uncommon and difficult-to-treat conditions.

METHODS

These recommendations have been developed according to standardised operating procedures, as developed by the European League Against Rheumatism (EULAR) standing committees.[2]

This guidance is termed "recommendations" as opposed to "guidelines" or "points to consider" as it can provide guidance but needs to be tailored to meet individual requirements. It is intended for use by healthcare professionals, medical students and specialist trainees, and 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). CM was appointed as the clinical fellow in charge of the literature search.

A modified Delphi 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, "Wegener Granulomatosis"[Mesh] AND ("Epidemiologic Study Characteristics"[Mesh] OR "Evaluation Studies"[Mesh] OR "Study Characteristics" [Publication Type]) NOT "Case Reports" [Publication Type]. For the other conditions, the name of each specific disease was inserted in place of "Wegener Granulomatosis" to generate a list of citations. Microscopic polyangiitis is not a medical subject heading in PubMed and was inserted as free text in "all fields". To identify papers that may have been indexed as ANCA-associated vasculitis, an additional search using the terms "Antibodies, Antineutrophil Cytoplasmic"[Mesh] AND "Vasculitis"[Mesh] was performed. All identified papers were 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 a management outcome as identified in the modified Delphi exercise was studied. Duplicate datasets were discarded. The identified papers were then categorised and given a level of evidence according to internationally accepted criteria (table 1).[2] The evidence was assimilated to form 15 statements. Each statement was then voted on by the members of the steering committee according to internationally agreed criteria, (table 2)[2] and we present the median vote for each statement.

RESULTS

The modified Delphi exercise

The committee decided to limit this set of recommendations to the spectrum of vasculitis in adults. Henoch–Schönlein purpura and Kawasaki disease were excluded. We agreed to limit our evaluation of evidence for the viral-associated vasculitides to hepatitis B-associated PAN and hepatitis C-associated cryoglobulinemic vasculitis. 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, for example issues regarding fertility, pregnancy, renal protection; may not have an evidence base to formulate recommendations.

Literature search

The results of the literature search are as in table 4. A Cochrane review added three further studies. The manual search of the abstract of meetings in 2006–2007 did not add any studies.

Statements

1. We recommend that patients with primary small and medium vessel vasculitis be managed in collaboration with, or at centres of expertise (level of evidence 3, grade of recommendation D)

The rarity of primary systemic vasculitis makes it difficult to maintain expertise in their management.[3–6] Assessment of these patients requires expert guidance to differentiate activity from damage and to consider differential diagnoses. Patients with vasculitis may require interventions by specialists with an expertise in vasculitis, such as injection of subglottic stenosis,[7 8] specialised radiography[9 10] or renal transplantation.[11] For patients with refractory disease, sometimes the best option may be consideration of enrolment into a clinical trial. Vasculitis may relapse years after remission is achieved, even in previously unaffected organ systems.[12 13] Patients may develop complications from the treatment after many years of discontinuation.[14] Long-term follow-up is necessary for all patients with vasculitis and patients should have rapid access to specialist services.

2. We recommend that anti-neutrophilic cytoplasmic antibody (ANCA) testing (including indirect immunofluorescence and ELISA) should be performed in the appropriate clinical context (level of evidence 1A, grade of recommendation A)

ANCA testing should be performed by indirect immunofluorescence to detect the labelling characteristic (cytoplasmic or perinuclear). The international consensus statement on testing for ANCA recommends testing all serum samples positive for ANCA by immunofluorescence for proteinase 3 (PR3) and myeloperoxidase (MPO).[15] A positive test for cytoplasmic (C) ANCA targeted to PR3, or perinuclear (P) ANCA against MPO has a high sensitivity and specificity for the diagnosis of ANCA-associated vasculitis.[16 17] We stress that the absence of a positive test does not rule out a diagnosis; and patients with less severe disease, especially those with isolated granulomatous disease of the upper or lower respiratory tract, may not have a positive ANCA.[18 19] ANCA testing should be performed in accredited laboratories that participate in external quality control programmes and undergo regular review of laboratory management and staff performing the assays.[20]

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.

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

3. A positive biopsy is strongly supportive of vasculitis and we recommend the procedure to assist diagnosis and further evaluation for patients suspected of having vasculitis (level of evidence 3, grade of recommendation C)

Histopathological evidence of vasculitis, for example fibrinoid necrosis, or pauci-immune glomerulonephritis, remains the gold standard for the diagnosis of vasculitis. The diagnostic yield of biopsies demonstrating either granuloma or vasculitis (or glomerulonephritis in a kidney sample) is over 70%;[19 21 22] but the yield of the biopsy will vary according to the organ sampled, the skill of the operator and the method of sampling.[19 21–25] Renal biopsy in patients with Wegener granulomatosis and active renal disease shows segmental necrosis in more than 85% of cases and extracapillary proliferation in more than 90%.[25] A biopsy is especially helpful in patients with a negative ANCA test.[21] The optimal biopsy site must be determined on individual assessment. In certain situations, for example renal involvement, repeated biopsies may be necessary to ascertain treatment response, disease relapse and chronic damage. Biopsies also help to rule out other differential diagnoses.

4. We recommend the use of a structured clinical assessment, urine analysis and other basic laboratory tests at each clinical visit for patients with vasculitis (level of evidence 3, grade of recommendation C)

Multiorgan involvement is common in primary systemic vasculitis. It is therefore important that a structured clinical assessment is conducted in all patients with a suspicion of vasculitis. This examination may be facilitated by the use of clinical tools that form a checklist of common items affecting various systems in vasculitis.[26–28] Such a structured examination should be carried out at each clinic visit to detect new organ involvement, which may develop at any time in the disease course.[13] Urine analysis should be performed on each patient at each visit to screen for infection, renal relapse or response, as well as bladder complications in patients treated with cyclophosphamide.[14 29 30] Inflammatory markers and renal functions should be performed periodically (every 1–3 months) to monitor disease evaluation and response. A full blood count and liver functions should be performed at similar intervals to screen for

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.

drug toxicity.[31 32] An acute fall in white cell count or a progressive leucopoenia may require reduction or discontinuation of immunosuppressive drugs. Similarly a declining renal function may necessitate dose adjustment or alteration of immunosuppressive agent. Patients should have periodic assessment of their blood sugar while on glucocorticoid therapy.

5. We recommend that patients with ANCA-associated vasculitis be categorised according to different levels of severity to assist treatment decisions (level of evidence 2B, grade of recommendation B)

The collaborative clinical trials conducted by the European Vasculitis Study (EUVAS) group have demonstrated that patients with different levels of disease severity respond to different treatment protocols.[31 33–35] The categories are shown in table 5. Treating doctors need to be aware that patients may change their disease category and treatment decisions will need to be modified accordingly. For example, it is appropriate to treat a patient with early systemic ANCA-associated vasculitis (AAV) with methotrexate, but this patient will need cyclophosphamide if he or she develops an organ or life-threatening disease manifestation.[33 34 36]

6. We recommend a combination of cyclophosphamide (intravenous or oral) and glucocorticoids for remission induction of generalised primary small and medium vessel vasculitis (level of evidence 1A for WG and MPA, grade of recommendation A; level of evidence 1B for PAN and CSS, grade of recommendation A)

Combination therapy with oral cyclophosphamide 2 mg/kg/day (max 200 mg/day) and prednisolone 1 mg/kg/day (max 60 mg/day) has been used for remission induction of ANCA-associated vasculitis since the 1970s.[12] A meta-analysis[37] of three randomised controlled trials[38–40] concluded that pulsed cyclophosphamide was more likely to result in remission than continuous oral therapy, and with a lower risk of side effects. However, pulsed therapy may be associated with a higher risk of relapse.[27] In the meta-analysis, the trials were not readily comparable because they had different therapeutic regimens. The EUVAS group have designed and tested a regimen of intravenous cyclophosphamide at a dose of 15 mg/kg (max 1.2 g) every 2 weeks for the first 3 pulses, followed by infusions every 3 weeks for the next 3–6 pulses.[39 41] The results of a larger randomised controlled trial are awaited.[41 42] Dose adjustments have been made for renal function and age in clinical trials.[43 44] For continuous oral low-dose cyclophosphamide, the dose has been reduced by 25% for >60 years of age and by 50% for >75 years of age.[43] For pulsed high-dose cyclophosphamide dose adjustment has been as in table 6.

In patients with PAN and CSS, the combination of cyclophosphamide and glucocorticoid achieves better control of disease as compared to glucocorticoid alone but the long-term survival remains unchanged.[45] This combination therapy also produces sustained remission of greater than 18 months.[46] Pulsed intravenous cyclophosphamide has been used in PAN and CSS[47 48] with equal efficacy and a lower incidence of adverse events compared to daily oral low-dose cyclophosphamide.[48] These data are not easy to interpret because the trial comparing the two modes of administration[48] included patients who would currently be classified as having MPA.[1]

Antiemetic therapy should be routinely administered with intravenous cyclophosphamide. Cyclophosphamide metabolites are toxic to the urothelium and can cause haemorrhagic cystitis in the short term and malignancy in the long term.[14 29 30] Patients should be encouraged to drink plenty of fluids, or given intravenous fluids on the day of the infusion to dilute the

Table 4 Results of the literature search: number of papers identified in PubMed

Keyword used in search string	No. of identified citations	Restricted to "adult" and "abstract"	Unique citations
Wegener granulomatosis	560	332	332
Microscopic polyangiitis	152	106	63
Churg–Strauss syndrome	131	84	53
Polyarteritis nodosa	284	133	75
Cryoglobulinemia	304	201	197
Antibodies, antineutrophil cytoplasmic AND vasculitis	420	247	89
Total no of identified citations			809

Table 5 European Vasculitis Study (EUVAS) disease categorisation of anti-neutrophilic cytoplasmic antibodies (ANCA)-associated vasculitis

Category	Definition
Localised	Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms
Early systemic	Any, without organ-threatening or life-threatening disease
Generalised	Renal or other organ threatening disease, serum creatinine <500 μmol/litre (5.6 mg/dl)
Severe	Renal or other vital organ failure, serum creatinine >500 μmol/litre (5.6 mg/dl)
Refractory	Progressive disease unresponsive to glucocorticoids and cyclophosphamide

metabolites in the urine. Patients receiving pulse cyclophosphamide should also be given oral or intravenous 2-mercaptoethanesulfonate sodium (Mesna), which binds to acrolein, a toxic metabolite of cyclophosphamide, rendering it non-toxic.[13] Mesna also retards the degradation of 4-hydroxymetabolites, further reducing the toxic acrolein products in the urine. Mesna may also be beneficial in patients receiving continuous oral cyclophosphamide.[12 13 49]

Monitoring for cyclophosphamide should be as per standard protocols.[32] In both modalities of administration, dose changes or discontinuation of cyclophosphamide may be necessary in the event of an acute leucopoenia or a gradual fall over time. In the event of a stable leucopoenia, it may be possible to maintain the level of immunosuppression with a closer level of blood monitoring.

We encourage prophylaxis against *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) in all patients being treated with cyclophosphamide; with trimethoprim/sulphamethoxazole (800/160 mg on alternate days or 400/80 mg daily), where not contraindicated.[50–52] The use of pentamidine in the event of an adverse reaction or contraindication to trimethoprim/sulphamethoxazole is not cost-effective.[50]

7. We recommend a combination of methotrexate (oral or parenteral) and glucocorticoid as a less toxic alternative to cyclophosphamide for the induction of remission in non-organ threatening or non-life threatening ANCA-associated vasculitis (level of evidence 1B, grade of recommendation B)

Methotrexate (20–25 mg/week, oral or parenteral) can be used as an alternative to cyclophosphamide in patients with less severe disease and in whom renal function is normal.[13 33 36 53–58] It should be commenced at a dose of 15 mg/week and escalated to 20–25 mg/week over the next 1–2 months, if tolerated. In a randomised controlled trial, it has been shown to be equal to cyclophosphamide in its capacity to induce remission.[33] It may take longer to achieve remission with methotrexate as compared with cyclophosphamide in patients with pulmonary involvement.[33] Patients on methotrexate may benefit from supplementation with folic acid or folinic acid. Methotrexate should be monitored according to standard protocols.[32]

8. We recommend the use of high-dose glucocorticoids as an important part of remission induction therapy (level of evidence 3, grade or recommendation C)

There are no clinical trials examining the role of glucocorticoid therapy but every clinical trial or cohort study conducted has used glucocorticoid therapy in combination with immunosuppressive therapy. It is common practice to commence prednisolone or prednisone at 1 mg/kg/day as in recent clinical trials.[31 33 56] The initial high dose should be maintained for 1 month, and should not be reduced to less than 15 mg/day for the first 3 months.[42 59] The glucocorticoid dose should then be tapered to a maintenance dose of 10 mg/day or less during remission.[31] When a rapid effect is needed, intravenous pulsed methylprednisolone may be used in addition to the oral prednisolone as part of remission induction therapy.[40] Local guidelines for the prevention of glucocorticoid-induced osteoporosis should be followed in all patients.[60]

9. We recommend plasma exchange for selected patients with rapidly progressive severe renal disease in order to improve renal survival (level of evidence 1B, grade of recommendation A)

Plasma exchange improves renal survival in patients with severe renal disease (serum creatinine >500 μmol/litre or 5.65 mg/dl) when used as an adjunct to daily oral cyclophosphamide and prednisolone.[34] It has not been shown to improve overall survival and it is not known whether or not it benefits patients with less severe disease.[61 62] The effect of plasma exchange on extra-renal manifestations has not been well studied.

10. We recommend remission-maintenance therapy with a combination of low-dose glucocorticoid therapy and, either azathioprine, leflunomide or methotrexate (level of evidence 1B for azathioprine, grade of recommendation A; level of evidence 1B for leflunomide, grade of recommendation B; level of evidence 2B for methotrexate, grade of recommendation B)

Long-term cyclophosphamide therapy has been used to maintain remission in patients with AAV.[12] The toxicity of long-term cyclophosphamide makes it an unattractive option.[14 29 30] Azathioprine (2 mg/kg/day) is safer than oral cyclophosphamide, but as effective at 18 months in preventing relapse.[31 63] Methotrexate (20–25 mg/kg/week) has been effectively used for maintenance therapy after induction of remission with cyclophosphamide (if the serum creatinine is <130 μmol/litre or 1.5 mg/dl).[64 65] Leflunomide (20–30 mg/day) may be more effective than methotrexate in remission maintenance, but is associated with more adverse effects.[66]

Remission maintenance therapy should be continued for at least 18 months (especially in WG).[31] Recently published guidelines by the British Society for Rheumatology recommend therapy for at least 24 months.[67] Early cessation of therapy is associated with an increased risk of relapse.[33] The role of serial ANCA testing to guide therapy is controversial.[68–70] Some studies have shown that patients in whom the ANCA titres persist, rise fourfold or become positive have a higher incidence of relapse,[63 68] while other studies have not shown this association.[70]

Table 6 Dose modification of pulsed cyclophosphamide as used in a randomised controlled trial comparing the efficacy of daily oral versus pulsed cyclophosphamide for renal vasculitis (http://www.vasculitis.org/protocols/CYCLOPS.pdf)

Pulsed CYC dose reductions for renal function and age		
	Creatinine (μmol/litre)	
Age, years	<300	300–500
<60	15 mg/kg/pulse	12.5 mg/kg/pulse
60–70	12.5 mg/kg/pulse	10 mg/kg/pulse
>70	10 mg/kg/pulse	7.5 mg/kg/pulse

The trial did not include a separate regimen for patients with a creatinine of <150 μmol/litre.
CYC, cyclophosphamide.

Table 7 Alternative remission induction treatments in relapsing, refractory or persistent disease

Drug	Dose	Reference
Intravenous immunoglobulin	2 g/kg over 5 days	Muso *et al*, Jayne *et al*[77 78]
15-Deoxyspergualin	0.5 mg/kg/day till white cell count nadir of 3000/μl, then wait until the white cell count returns to ⩾ 4000/μl and repeat the dose for six cycles	Burke *et al*[79]
Anti-thymocyte globulin	2.5 mg/kg/day for 10 days adjusted according to lymphocyte count: no anti-thymocyte globulin if <150/μl, 1.5 mg/kg/day if 150–300/μl, full dose if >300/μl	Schmitt *et al*[35]
Infliximab	3–5 mg/kg/infusion every 1 to 2 months	Booth *et al*[80]
Mycophenolate mofetil	2 g/day	Koukoulaki *et al*, Stassen *et al*[74 81]
Rituximab	375 mg/m^2 body surface area weekly for 4 weeks	Keogh *et al*, Keogh *et al*, Stasi *et al*, Brihaye *et al*, Eriksson *et al*[82–86]

The addition of trimethoprim/sulphamethoxazole (800/160 mg twice daily) to standard remission maintenance can reduce the risk of relapse in WG.[71] Although trimethoprim/sulphamethoxazole has been used as the sole remission maintenance agent in half the patients of one randomised controlled trial,[71] trimethoprim/sulphamethoxazole monotherapy may not be effective for maintenance of remission.[72] In patients with nasal disease, treatment with topical antibiotics such as mupirocin may be considered in the presence of chronic carriage of nasal *Staphylococcus aureus*.[73]

The glucocorticoid dose should be tapered to a maintenance dose of 10 mg/day (or less) prednisolone during remission.[31] This can be reduced gradually after 6–18 months depending on patient response with the aim of discontinuing therapy.

Mycophenolate mofetil has been used in open label studies for remission maintenance.[74–76]

11. Alternative immunomodulatory therapy choices should be considered for patients who do not achieve remission or relapse on maximal doses of standard therapy: these patients should be referred to an expert centre for further management and enrolment in clinical trials (level of evidence 3, grade of recommendation C)

For patients who fail to achieve remission and have persistent low activity, intravenous immunoglobulin can be used to achieve remission.[77 78] Prior to therapy, serum immunoglobulin levels must be measured because patients with selective IgA deficiency may develop an anaphylactic reaction on receiving intravenous immunoglobulin (IVIG) or a pre-existing hyper-γ-globulinemia may become aggravated leading to a hyperviscosity state. For patients with progressive disease in spite of optimal therapy, alternative options include conventional immunosuppressants such as mycophenolate mofetil and 15-deoxyspergualin, and biological agents such as anti-thymocyte globulin, infliximab and rituximab (table 7).[35 74 79–86] In 5 open label trials of rituximab in refractory or relapsing AAV, 42/46 (91%) patients achieved remission within 6 months.[82–86] The use of rituximab in AAV is currently being tested in four separate clinical trials. (Clinical trials.gov identifiers NCT00104299, NCT00424749, NCT00307593 and EUDRACT No. 2005-003610-15, 2006-001859-35.)

12. We recommend immunosuppressive therapy for patients with mixed essential cryoglobulinemic vasculitis (non-viral) (level of evidence 4, grade of recommendation D)

There are no clinical trials conducted for the treatment of essential (hepatitis C negative) cryoglobulinaemic vasculitis. The consensus of the committee is that this disease should be treated in the same way as the other small vessel diseases discussed in these recommendations (WG, MPA and CSS), with immunomodulatory agents and glucocorticoids. Rituximab has been used in patients with hepatitis C-associated cryoglobulinaemic vasculitis, and may also be of benefit in non-viral-associated essential cryoglobulinaemic vasculitis.[87]

13. We recommend the use of antiviral therapy for the treatment of hepatitis C-associated cryoglobulinaemic vasculitis (level of evidence 1B, grade of recommendation B)

The use of different preparations of interferon (IFN)α to induce remission in hepatitis C-associated cryoglobulinemia is well documented.[88–92] Combination therapy with ribavirin and IFNα may be more beneficial than IFNα monotherapy.[93 94] However, relapse is common following the stopping of IFNα and these patients will need long-term therapy. They should be managed in conjunction with a hepatologist.

14. We recommend a combination of antiviral therapy, plasma exchange and glucocorticoids for hepatitis B-associated PAN (level of evidence 3, grade of recommendation C)

We suggest the use of high-dose glucocorticoid therapy tapered over 2 weeks followed by antiviral agents; this treatment combination accompanied by plasma exchange has been shown to have a high rate of remission induction.[95] There is limited data on the use of rituximab in refractory cases.[87] The treatment of this condition should be in conjunction with a hepatologist.

Box 1 Research agenda

- Diagnostic criteria for primary systemic vasculitides.
- Identification of a biomarker for diagnosis and monitoring of primary systemic vasculitis.
- Adequately powered randomised controlled trials with disease specific subanalysis for alternatives to cyclophosphamide for remission induction.
- Biological agents in refractory and relapsing patients.
- Adequately powered randomised controlled trials for testing conventional agents in mixed essential cryoglobulinemic vasculitis.
- Long-term outcomes in treated vasculitis: for example cardiovascular, neoplasia, cerebrovascular, renal and metabolic abnormalities and strategies to prevent adverse outcomes.

Table 8 The 15 recommendations for the management of small and medium vessel vasculitis with the level of evidence for each statement and the median strength of recommendation as per European League Against Rheumatism (EULAR) operating procedures

Statement	Level of evidence	Median vote
1. We recommend that patients with primary small and medium vessel vasculitis be managed in collaboration with, or at centres of expertise	3	D
2. We recommend that ANCA testing (including indirect immunofluorescence and ELISA) should be performed in the appropriate clinical context	1A	A
3. A positive biopsy is strongly supportive of vasculitis and we recommend the procedure to assist diagnosis and further evaluation for patients suspected of having vasculitis	3	C
4. We recommend the use of a structured clinical assessment, urine analysis and other basic laboratory tests at each clinical visit for patients with vasculitis	3	C
5. We recommend that patients with ANCA-associated vasculitis be categorised according to different levels of severity to assist treatment decisions	2B	B
6. We recommend a combination of cyclophosphamide (intravenous or oral) and glucocorticoids for remission induction of generalised primary small and medium vessel vasculitis.	1A for WG and MPA	A for WG and MPA
	1B for PAN and CSS	A for PAN and CSS
7. We recommend a combination of methotrexate (oral or parenteral) and glucocorticoid as a less toxic alternative to cyclophosphamide for the induction of remission in non-organ threatening or non-life threatening ANCA-associated vasculitis	1B	B
8. We recommend the use of high-dose glucocorticoids as an important part of remission induction therapy	3	C
9. We recommend plasma exchange for selected patients with rapidly progressive severe renal disease in order to improve renal survival	1B	A
10. We recommend remission-maintenance therapy with a combination of low-dose glucocorticoid therapy and, either azathioprine, leflunomide or methotrexate	1B for azathioprine	A for azathioprine
	1B for leflunomide	B for leflunomide
	2B for methotrexate	B for methotrexate
11. Alternative immunomodulatory therapy choices should be considered for patients who do not achieve remission or relapse on maximal doses of standard therapy: these patients should be referred to an expert centre for further management and enrolment in clinical trials	3	C
12. We recommend immunosuppressive therapy for patients with mixed essential cryoglobulinemic vasculitis (non-viral)	4	D
13. We recommend the use of antiviral therapy for the treatment of hepatitis C-associated cryoglobulinaemic vasculitis	1B	B
14. We recommend a combination of antiviral therapy, plasma exchange and glucocorticoids for hepatitis B-associated PAN	3	C
15. We recommend the investigation of persistent unexplained haematuria in patients with prior exposure to cyclophosphamide	2B	C

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

15. We recommend the investigation of persistent unexplained haematuria in patients with prior exposure to cyclophosphamide (level of evidence 2B, grade of recommendation C)

The use of cyclophosphamide is strongly associated with the risk of bladder cancer.[14 29 30] The use of Mesna as an uroprotective agent lowers the risk but may not always protect against bladder toxicity.[13] The cancer can occur within months of commencement of cyclophosphamide or many years after its discontinuation.[14] Tobacco smokers are particularly susceptible and may develop the cancer at lower doses and earlier than non-smokers.[14] All patients must have a periodic urine analysis for the length of their follow-up. In the presence of non-glomerular haematuria, an urgent urology opinion must be sought.

DISCUSSION

Implementation of these recommendations

The recommendations (table 8) have been based on an extensive literature search. In the absence of evidence, the statements have been based on the opinion and practice of experts from nine countries (France, Germany, Italy, Spain, Sweden, Switzerland, The Netherlands, Turkey, the UK and USA). The application of internationally accepted grading criteria prevents us from supporting some of the statements with stronger grades.[2] The project has also led to the committee to propose a research agenda for small and medium vessel vasculitis (box 1). These recommendations provide a framework of practice that should apply to the majority of patients with small and medium vessel vasculitis. Each statement should be an opportunity for auditing clinical practice. Recommendations for clinical management need continuous updating and this group recommends that based on the many advances and on-going research in this field, an update of these recommendations should be conducted in 3 years.

Competing interests: None declared.

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