



BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis

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Key words: vasculitis, guideline, management, cyclophosphamide, rituximab.

Scope and purpose

Background to vasculitis

The primary systemic vasculitides are heterogeneous, multisystem disorders characterized by inflammation and necrosis of small and medium blood vessels. Their aetiology is unknown. Three distinct clinico-pathological syndromes, often associated with ANCA, called ANCA-associated vasculitis (AAV), have been identified and collectively comprise the most common subgroup: granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (Churg Strauss/EGPA) and microscopic polyangiitis (MPA). Other forms of vasculitis (listed in Table 1) are usually ANCA negative and are defined by their clinico-pathological features.

There are no validated diagnostic criteria for AAV. The ACR devised classification criteria for different vasculitides, including GPA and EGPA but not MPA, and the Chapel Hill consensus conference (CHCC) in 1994 recommended definitions for GPA, EGPA and MPA [1–4]. The CHCC definitions were not intended for classification or diagnosis but provide a useful description of disease and include some features that have been used for classification purposes. The CHCC definitions were updated in 2012 to accommodate developments in knowledge about aetiopathogenesis and ANCA (CHCC 2012) [5]. Lanham *et al.* [6] reviewed EGPA in 1984 and provided a slightly different and mainly clinically oriented set of classification criteria when compared with the ACR for EGPA.



NICE has accredited the process used by the BSR to produce its guidance for the management of ANCA-associated vasculitis in adults. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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TABLE 1 Classification of the vasculitides adopted by the 2011–2012 international Chapel Hill Consensus Conference Nomenclature of the Vasculitides (CHCC2012)

Large-vessel vasculitis
Takayasu's arteritis
GCA
Medium-vessel vasculitis
Polyarteritis nodosa
Kawasaki disease
Small-vessel vasculitis
ANCA-associated vasculitis
Microscopic polyangiitis
Granulomatosis with polyangiitis
Eosinophilic granulomatosis with polyangiitis
Immune complex
Anti-GBM disease (Goodpasture's)
Cryoglobulinaemic vasculitis
IgA vasculitis (Henoch–Schönlein)
Hypocomplementaemic urticarial vasculitis (anti-C1q vasculitis)
Variable-vessel vasculitis
Behçet's disease
Cogan's syndrome
Single-organ vasculitis
Cutaneous leucocytoclastic angiitis
Cutaneous arteritis
Primary CNS vasculitis
Isolated aortitis
Others
Vasculitis associated with systemic disease
Lupus vasculitis
Rheumatoid vasculitis
Sarcoid vasculitis
Others
Vasculitis associated with probable aetiology
Hepatitis C virus-associated cryoglobulinaemic vasculitis
Hepatitis B virus-associated vasculitis
Syphilis-associated aortitis
Drug-associated immune complex vasculitis ^a
Drug-associated ANCA-associated vasculitis ^b
Cancer-associated vasculitis
Others

^aFor example, sulphonamides, penicillins, thiazide diuretics and many others. ^bTypically propylthiouracil, hydralazine and allopurinol with induction of MPO-ANCA. Adapted with permission from Jennette JC, Falk RJ, Bacon PA *et al.* 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2012;65:1–11. Copyright © 2013 by the American College of Rheumatology.

Diagnosis of vasculitis

In the early phases of the disease, the symptoms can be non-specific and a high index of suspicion is required to achieve an early diagnosis. Symptoms that should prompt consideration of a diagnosis of vasculitis are unexplained systemic disturbance, arthritis or arthralgia, cutaneous lesions, polymyalgia, episcleritis, neuropathy, microscopic haematuria, proteinuria, pulmonary infiltrates or nodules and maturity-onset asthma and persistent upper airways symptoms.

Once major organ involvement occurs the diagnosis usually becomes clear, although the presence of more advanced disease at diagnosis limits the potential benefit of therapy. Detailed clinical and laboratory assessment are very important to provide a full picture of the disease and assist in identifying the specific type of vasculitis in the majority of cases [7]. Laboratory and imaging studies are essential in helping to confirm a clinical diagnosis, but are of limited value in the absence of clinical signs when considering a diagnosis of systemic vasculitis and its differential diagnosis [8].

Vasculitic syndromes should be considered in the differential diagnosis of patients with multisystem illness or pyrexia of unknown origin. However, there are a number of specific conditions that can mimic vasculitis, including infections, non-infectious inflammatory diseases, malignancy, drugs and factitious illnesses. Disorders such as atrial myxoma, cholesterol emboli and catastrophic APS may mimic vasculitic disorders. Vasculitis occurs in the context of other autoimmune rheumatic diseases such as SLE and RA [9, 10].

Investigations

Investigations are aimed at confirming the diagnosis, excluding secondary causes of vasculitis, assessing organ involvement and disease severity. Acute phase reactants such as CRP and ESR are typically elevated in the acute phases of most vasculitides. Urinalysis should be performed as soon as a diagnosis of vasculitis is suspected because renal involvement in particular may progress silently and be a source of confirmatory histology. Full blood count (FBC) should be measured, looking for anaemia, leucocytosis and eosinophilia. It is essential to investigate critical organ function, including renal, cardiac, pulmonary and neurology assessments, with appropriate organ-specific tests (creatinine clearance, urine protein/creatinine ratio, urinary red cell casts, echocardiography, pulmonary function tests, electromyography, etc.).

Autoantibodies including ANCA are useful in the appropriate clinical setting. It is important to recognize that a negative ANCA (by IIF and antigen-specific assay) does not exclude vasculitis and a positive ANCA does not necessarily prove vasculitis [8]. ANCA specificity is important, with the presence of PR3 ANCA being strongly suggestive of a diagnosis of GPA, especially in Caucasian populations [11]. MPO ANCA is less specific, but is most frequently associated with MPA and EGPA. One third of cases with EGPA or localized GPA may be ANCA negative.

Other useful tests include ANA (to exclude SLE, although it can be difficult to interpret the presence of pANCA in the presence of ANA), RF, complement levels (may be raised as part of an acute phase response but lowered in immune complex-mediated essential mixed cryoglobulinaemia, bacterial infections and SLE), cardiolipin antibodies and lupus anticoagulant for APS and cryoglobulins. Cryoglobulinaemia may occur in isolation or in association with other autoimmune diseases. In essential mixed cryoglobulinaemia associated with small vessel

vasculitis, the cryoglobulins may be associated with internal organ damage and may require aggressive therapy.

Infection should be excluded by blood culture and appropriate serology (including parvovirus, hepatitis B, hepatitis C and HIV) because the treatment for AAV involves intense immunosuppression. A tissue diagnosis should be obtained wherever possible. The choice of biopsy site is dependent on the clinical features, but skin and renal are often helpful for diagnosis. It is important to recognize that very early in the disease process the classical histological features of vasculitis may be absent. Upper airway biopsy frequently shows changes compatible with the diagnosis, but rarely classical granulomatous vasculitis. The treatment should not be delayed solely to get a biopsy or while awaiting the ANCA result if there are strong clinical grounds to make a diagnosis of vasculitis.

Imaging investigations, including angiography, should be carefully considered in appropriate cases. Magnetic resonance angiography and 18-fluorodeoxyglucose (FDG) PET CT are particularly valuable in assessing large vessel vasculitis such as giant cell arteritis. Coeliac axis and renal contrast angiography should be considered in situations where PAN is strongly suspected, such as patients with severe abdominal pain, frank haematuria and/or HBV infection.

Need for guidelines

AAV has an annual incidence of 20/million (GPA 11/million, MPA 6/million, EGPA 1–2/million), a prevalence of 200/million and a peak age of onset of 60–70 years in the white Caucasian population in the UK [12, 13]. AAV may be less common in non-Caucasian populations. Treatment has evolved over the last 20–30 years and a number of new treatments are now available [14]. This document updates the previous British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHRP) guideline published in 2007 in view of emerging evidence in the field of AAV and highlights where there is an evidence base for treatment protocols and where treatment is based on individual preference [15]. The BSR Standards, Audit and Guidelines Working Group (SAGWG) protocol for producing and updating existing guidelines was followed for developing this guideline.

Objective of the guideline

The aim of this document is to provide a guideline for the management of adults with AAV, especially the induction and maintenance of remission.

Target audience

The target audience is rheumatologists, nephrologists, general physicians and other specialists (e.g. chest physicians, ENT surgeons, ophthalmologists, dermatologists) who may come across vasculitis in the course of their work. We are also aiming the guidance towards specialist registrars in training and nurse practitioners dealing with vasculitis. The information will also be of value to primary care physicians to increase their understanding of these unusual conditions.

The areas the guideline does not cover

The guideline does not cover the management of other systemic vasculitides, e.g. GCA, Takayasu's arteritis, cutaneous vasculitis, PAN, cryoglobulinaemic vasculitis, IgA vasculitis (Henoch–Schönlein) or the treatment of children. However, although the guideline and evidence refer to AAV only, it is appropriate to apply the same principles in the management of these other types of systemic vasculitis, although the references to clinical studies supporting the use of CYC for these conditions have not been included in this document.

Stakeholder involvement

Names and roles of members of the multidisciplinary team

Coordination team

The chair of the team was Dr Richard Watts, Consultant Rheumatologist, Ipswich Hospital NHS Trust, Senior Lecturer, Norwich School of Medicine, University of East Anglia, Norwich, UK. The clinical fellow was Dr Eleana Ntatsaki, Specialist Registrar in Rheumatology, Norfolk and Norwich University Hospitals NHS Foundation Trust, Clinical Teaching Fellow, Medical School, University College London, London, UK.

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Allied health care professional representatives

Janice Mooney, Senior Lecturer, School of Nursing and Midwifery, University of East Anglia, Norwich

Names and affiliations of users on the working party

John Mills, Chair, Vasculitis UK, Matlock

Involvement and affiliations of other people or organization including user representative organization and pharmaceutical companies in the development of the guideline

Vasculitis UK is a registered charity that offers support to people with vasculitis and their family and friends. John

Mills, the chair of Vasculitis UK, is a member of the working party.

Conflict of interest statement

Any conflicts of interest among members of the working party were fully declared. The declared conflicts of interest are included at the end of the article.

Rigor of development

Statement of scope of the literature search and strategy employed

The general search strategy was to look for all relevant evidence in the Cochrane library, MEDLINE (Ovid and PubMed) and EMBASE. The MEDLINE database was also searched for randomized controlled trials (RCTs) and non-randomized trials. The reference lists of identified papers and previous reviews were also searched. A manual search of abstracts presented at the annual meetings of the European League Against Rheumatism (EULAR) and BSR from 2009 to 2012 was also performed. (Details of the literature search strategy are provided in the Appendix.)

Statement of extent of Cochrane, NICE, RCP, SIGN, BSR and EULAR guidelines

Two Cochrane reviews have been published with relevance to AAV since the previous literature review [16, 17]. There are no National Institute for Health and Care Excellence (NICE), Royal College of Physicians (RCP), Scottish Intercollegiate Guidelines Network (SIGN) guidelines for the treatment of AAV.

There are previous BSR and BHPR (2007) and EULAR (2009) guidelines for the treatment of AAV in adults [15, 18]. The current guideline comprises a revision and update of the previously published BSR and BHPR (2007) guideline in view of more recent evidence in the area of AAV management. NICE is currently developing guidance for the use of rituximab (RTX) in AAV (<http://guidance.nice.org.uk/TAG/334>). The National Commissioning Board for NHS England has produced guidance on the provision of RTX for AAV [19].

Statement of any limits of the search

The search was conducted in September 2012. The search was limited to a specific time frame (1 January 2005 to 1 October 2012) and to the English language and human adult subjects. Each paper was reviewed and included if one or more of the focus themes identified in the modified Delphi exercise were studied (see Appendix and Table 2). Case reports and publications with insufficient outcome data and duplicate entries were discarded. Identified papers were categorized and the level of evidence graded according to international criteria (see Tables 3 and 4).

TABLE 2 Results of the Delphi exercise to assess the need for guideline revision

Recommendation	Vote
Remission induction treatment	Major 6 Minor 3 No change 1
Recommendation for patients with generalized/threatened organ involvement	Major 4 Minor 5 No change 1
Recommendation for patients with localised/early systemic disease (without threatened vital organ involvement)	Major 2 Minor 3 No change 5
Recommendation severe/life-threatening disease	Major 0 Minor 7 No change 3
Maintenance of remission	Major 4 Minor 6 No change 0
Assessment/monitoring disease activity	Major 0 Minor 7 No change 3
Damage	Major 0 Minor 5 No change 5
Patient function and quality of life	Major 0 Minor 6 No change 4
ANCA measurements	Major 0 Minor 6 No change 4
Detection and prevention of potential adverse effects of immunosuppressive therapy CYC-induced bladder toxicity	Major 1 Minor 4 No change 5
Infection with <i>Pneumocystis jiroveci</i>	Major 0 Minor 6 No change 4
Fungal infections	Major 0 Minor 2 No change 8
<i>Staphylococcus aureus</i> suppression	Major 0 Minor 3 No change 7
Cervical intraepithelial neoplasia	Major 0 Minor 4 No change 6
Infertility	Major 0 Minor 4 No change 6
Osteoporosis	Major 0 Minor 5 No change 5
<i>Mycobacterium</i> infection	Major 0 Minor 2 No change 8
Vaccinations	Major 0 Minor 5 No change 5
Cardiovascular risk	Major 0 Minor 5 No change 5
Thromboembolic risk	Major 0 Minor 4 No change 6

TABLE 3 Level of evidence

Category	Evidence
Ia	From meta-analysis of randomized controlled trials (RCTs)
Ib	From at least one RCT
IIa	From at least one controlled study without randomization
IIb	From at least one type of quasi-experimental study
III	From descriptive studies such as comparative studies, correlation studies, or case-control studies
IV	From expert committee reports or opinions and/or clinical experience of respected authorities

TABLE 4 Determination of recommendation strength

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

Delphi exercise to establish the extent of revision necessary

A Delphi exercise was conducted to assess the extent to which revision of the 2007 guideline was required. Members of the working group were provided with a questionnaire asking them to assess the need for revision for each of the management recommendations in the 2007 guideline. They were asked to comment whether they required minor revision, major revision or no revision at all. The results of the Delphi exercise are shown in [Table 2](#).

Level of evidence

Conventional classification for levels of evidence and strength of recommendation was used [20] ([Tables 3](#) and [4](#)).

Development of recommendation

The working group met on a single occasion to determine the recommendations. Each suggested recommendation was subjected to a vote relating to the wording and strength of the evidence. An 80% agreement was taken as indicative of consensus.

Following review from the wider community, the final draft guideline was circulated to all members of the working party for a vote on the levels of agreement with each recommendation. Voting was performed with possible levels of agreement ranging from 1 (total disagreement) to 5 (total agreement). All recommendations received a mean score ≥ 4 ($\geq 80\%$ strength of agreement). All

recommendations were accepted with a consensus of agreement of $\geq 80\%$.

Presentation of recommendations

The recommendations statements are presented stating the level of evidence followed by the strength of the recommendation in a bold capital letter, e.g. 1a/A means the level of evidence for this recommendation is 1a and the strength of the recommendation is A.

Next to each recommendation there is a percentage showing the level of the final consensus of agreement within the guidelines working committee; e.g. final consensus 90% means that 9 of 10 authors accepted the recommendation.

A recommendation may have more than one statement. Each recommendation is followed by a rationale, which includes the key references relevant to that recommendation.

The guideline

Eligibility criteria

Patients with disease consistent with the definitions of AAV as defined by the CHCC 2012 ([Table 5](#)) are eligible for treatment and use of this guideline.

This guideline is mainly based on evidence and data from clinical trials in GPA and MPA, therefore the advice relates mainly to those two conditions. EGPA is often treated using the same approach as for GPA and MPA, but very few EGPA patients have been included in most of the clinical trials. The majority of patients in these trials have been Caucasians from Europe or North America.

Exclusion criteria

For a diagnosis of AAV, it is important to consider other causes of systemic illness as outlined below, which must be excluded as far as possible.

- (i) Malignancy.
- (ii) Systemic infection—especially bacterial endocarditis.
- (iii) Drugs—known to be associated with vasculitis (e.g. propylthiouracil, allopurinol, hydralazine, cocaine, levamisole).
- (iv) Secondary forms of vasculitis associated with primary connective tissue disease such as RA or SLE.
- (v) Other vasculitides, including Behçet's syndrome, Takayasu's arteritis, giant cell arteritis, Kawasaki disease, cryoglobulinaemia, IgA vasculitis (Henoch-Schönlein) and polyarteritis nodosa.
- (vi) Vasculitis mimics, e.g. APS, cholesterol embolism, calciphylaxis and atrial myxoma.

Definition of disease states

Remission

There is no uniformly accepted definition of remission that has been used in clinical trials. We have defined two states of disease remission to encompass patients who have well-controlled disease but remain on therapy and

TABLE 5 The Chapel Hill Consensus Conference definitions for ANCA-associated vasculitis

Definitions for AAV	
AAV	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e. capillaries, venules, arterioles and small arteries), associated with MPO-ANCA or PR3-ANCA. Not all patients have ANCA. Add a prefix indicating ANCA reactivity, e.g. PR3-ANCA, MPO-ANCA, ANCA-negative.
GPA	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract and necrotizing vasculitis affecting predominantly small to medium vessels (e.g. capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is common.
EGPA	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract and necrotizing vasculitis predominantly affecting small to medium vessels and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present.
MPA	Necrotizing vasculitis with few or no immune deposits predominantly affecting small vessels (i.e. capillaries, venules or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.

AAV: ANCA-associated vasculitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; MPA: microscopic polyangiitis. Adapted from Jennette JC, Falk RJ, Bacon PA *et al.* 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2012;65:1–11. Copyright © 2013 by the American College of Rheumatology.

those who have been successfully weaned off all treatment for vasculitis:

- (i) On drug remission is defined as a prednisolone dose ≤ 10 mg/day and a BVAS ≤ 1 for ≥ 6 months.
- (ii) Drug-free remission is defined as ≥ 6 months off all treatment for vasculitis

(4/D). Final consensus 90%.

Relapsing disease

Relapsing is disease that has been previously well controlled with or without drugs and has become active.

Minor relapse

A minor relapse is defined as an increase in at least one new or worse minor item and no major BVAS items.

Major relapse

A major relapse is an increase in at least one major BVAS item (4/D). Final consensus 100%.

In certain circumstances, if at least two systems are involved (not including the presence of systemic features alone, which may be present or absent), a patient can be considered to have a major relapse in the absence of any major items. This definition is deliberately unclear because physician discretion is required in these cases.

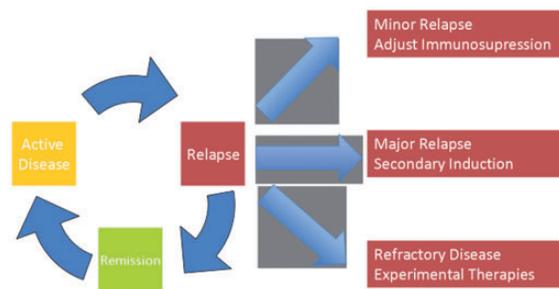
Refractory disease

Refractory disease is progressive disease that is not fully responsive to current therapy, i.e. remission is not achieved (4/D). Final consensus 80%.

The continuum between the different disease states and the recommended management principles are illustrated in Fig. 1.

Treatment

All patients with AAV should be considered to have severe potentially life- or organ-threatening disease.

Fig. 1 The continuum of disease activity in AAV

Final consensus 80%.

Treatment regimens are divided into induction, maintenance and long-term follow-up (Fig. 2). Patients who relapse may require a further course of induction therapy (secondary).

The essential principles of management are

- (i) Rapid diagnosis.
- (ii) Rapid initiation of treatment.
- (iii) Early induction of remission to prevent organ damage.
- (iv) Maintenance of remission with the aim of eventual drug withdrawal.
- (v) Prevention of drug toxicity.

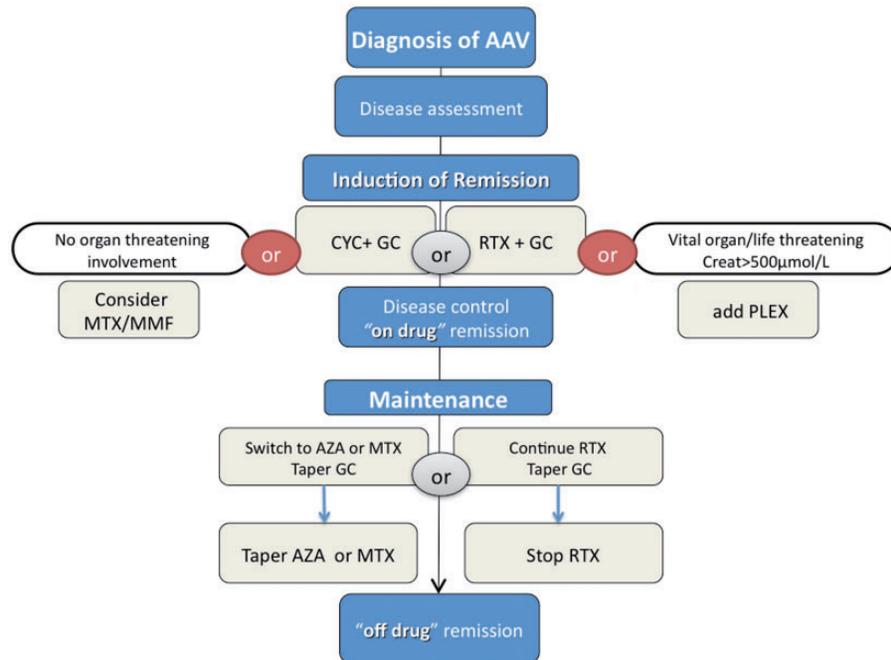
Primary induction of remission

Recommendation

All patients with newly diagnosed AAV should be considered as having a potentially severe life- or organ-threatening disease and therefore should be assessed for treatment with glucocorticoids (GCs) and pulsed i.v. CYC or RTX (1a/A). Final consensus 100%.

Organ involvement and function should be systematically assessed in all patients and those with no evidence of organ damage may be considered for alternative

Fig. 2 Algorithm of the treatment guideline for AAV



Final consensus 90%.

induction therapy with MTX or MMF (1b/A for MTX and 2a/B for MMF). Final consensus 90%.

Rationale

Treatment has conventionally been stratified according to disease severity (early, systemic, generalized), with different approaches to induction therapy, with the use of non-CYC-based regimens for mild disease. The drive for this approach has been the desire to reduce cumulative CYC exposure and avoidance of toxicity. However, long-term data from the Non-renal Wegener's Granulomatosis Treated Alternatively with Methotrexate (NORAM) study, which compared MTX with CYC in patients with no or minimal renal disease, demonstrated that the median time to relapse was longer in CYC-treated patients during the 18 months of the trial and the cumulative relapse-free survival was higher in the CYC group [21]. Therefore all patients should be considered to have severe potentially life- or organ-threatening disease. Patients with no evidence of organ damage may be considered for alternative induction therapy with MTX. In patients intolerant of MTX, MMF may be an alternative, as there is evidence from small studies to support its use in remission induction, while full results from an RCT [Mycophenolate Versus Cyclophosphamide in ANCA Vasculitis (MYCYC) trial] are awaited [22–25]. Preliminary data from the MYCYC trial suggest that MMF is not non-inferior to CYC for primary remission induction [26].

We have not provided an exhaustive list of definitions of organ damage. However, patients with ENT or retro-orbital disease are often considered to have less severe

disease; those without evidence of bone destruction on MRI or CT may be considered to have mild disease.

Cyclophosphamide

Recommendation

CYC should be given by i.v. pulses initially at 2-week intervals and then every 3 weeks, following the CYCLOPS trial regimen (1a/A). Final consensus 90%.

Lifetime exposure to CYC should not exceed 25 g (3/C). Final consensus 90%.

Rationale

The use of CYC and other immunosuppressive agents has transformed the prognosis of AAV from fulminant conditions to chronic relapsing diseases requiring long-term follow-up and treatment. The natural history of untreated GPA and MPA is of a rapidly progressive, usually fatal disease. In 1958 Walton observed a mean survival of 5 months, with 82% of patients dying within 1 year and >90% dying within 2 years in patients with GPA [27]. The introduction of CYC combined with prednisolone resulted in a significant improvement in the mortality of GPA, with a 5-year survival rate of 82%, although there remains considerable morbidity associated with both disease and treatment [28].

Induction therapy with CYC combined with GCs is effective in 90% of AAV patients [29]. The CYCLOPS study showed that there was no difference in remission rates between the pulsed i.v. and continuous low-dose oral CYC regimens [30]. Pulsed i.v. CYC regimens use a lower cumulative dose of CYC than oral regimens; while this is associated with lower rates of neutropenia, it may be associated

TABLE 6 Pulsed CYC reductions for renal function and age

Age, years	Creatinine, <300 µmol/l	Creatinine, 300–500 µmol/l
<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

with a higher long-term risk of relapse [31]. The lower rate of neutropenia may be associated with a lower infection rate. Because of the lower toxicity with pulsed i.v. CYC, the CYCLOPS i.v. CYC regimen is preferred.

Treatment regimen and cumulative dose of CYC

Pulsed i.v. CYC regimen

The standard dose is 15 mg/kg, reduced for age and renal function (Table 6). The maximum i.v. CYC dose is 1500 mg. According to the protocol, the patient should receive pre-hydration (e.g. 1 l normal saline) and should be encouraged to consume plenty of oral fluids for 3 days (e.g. 3 l/day) after each infusion.

The first three pulses are usually given at intervals of 2 weeks and thereafter at 3-week intervals. Lifetime exposure to CYC should not exceed 25 g since the toxicity of CYC long term is determined by cumulative dose [21, 32]. Guidance on the safe administration of CYC has been provided in the UK. Although this was written for oncology units, the same principles apply to the administration of CYC for AAV [33].

Monitoring CYC treatment

Recommendation

Patients on CYC should be monitored regularly for leucopenia and the dose should be reduced if there is CYC-induced leucopenia/neutropenia (1b/B). Final consensus 100%.

Rationale

Pulsed i.v. CYC regimen monitoring protocol [30]. Between the first and second pulse, check the FBC on days 7 and 10 and the day of the pulse.

If the leucocyte nadir is $<3 \times 10^9/l$ and/or the neutrophil nadir is $<1.5 \times 10^9/l$ even if the white blood cell (WBC) count has recovered to $>4 \times 10^9/l$ and the neutrophil count is $2 \times 10^9/l$ on the day of the pulse, then reduce the dose of the next pulse by

- (i) Leucocyte nadir $1-2 \times 10^9/l$ or neutrophil nadir $0.5-1.0 \times 10^9/l$: reduce CYC dose by 40%.
- (ii) Leucocyte nadir $2-3 \times 10^9/l$ or neutrophil nadir $1-1.5 \times 10^9/l$: reduce CYC dose by 20%.

Before subsequent pulses check the FBC on the day of the pulse or the previous day.

If the WBC count prior to the pulse is $<4 \times 10^9/l$ and/or the neutrophil count is $<2 \times 10^9/l$, then postpone the pulse until the WBC count is $>4 \times 10^9/l$ and the neutrophil count is $>2 \times 10^9/l$ and check the FBC weekly until it has recovered. Reduce the CYC dose by 25%.

With any further episodes of leucopenia/neutropenia, make a further 25% reduction in dose from the planned dose.

Duration of CYC therapy

Recommendation

Each individual course of CYC should be a minimum of 3 months and should not exceed 6 months (1b/B). Final consensus 90%.

Rationale

Clinical trial evidence supports the transfer to maintenance therapy at 3–6 months where successful remission has been achieved and aims for a maximum duration of CYC therapy of 6 months. If remission has not been achieved, then the patient should be considered as refractory to therapy and referred to a tertiary centre [31].

Rituximab

Recommendation

RTX is as effective as CYC for remission induction of previously untreated patients (1b/A) and is preferable when CYC avoidance is desirable (infertility, infection) (1b/B). Final consensus 100%.

Rationale

The RTX for ANCA-associated vasculitis (RAVE) [34] and RTX versus CYC in ANCA-associated renal vasculitis (RITUXVAS) [35] trials examined the efficacy of B lymphocyte depletion therapy in the induction phase of treatment for AAV. Both RCTs showed that RTX was not inferior to CYC for remission induction in situations where disease is not directly life-threatening.

The RAVE and RITUXVAS trials did not demonstrate the expected benefit of RTX regarding the safety profile. The RAVE trial showed equivalent side-effect rates compared with oral CYC. Infection rates were similar in both arms in the RITUXVAS trial and mild to moderate infusion reactions were not uncommon.

Dose regimen for RTX

Recommendation

Both commonly used RTX protocols (375 mg/m²/week for 4 weeks; 1000 mg repeated after 2 weeks) appear equally effective for induction of remission (3/C). The licensed and recommended RTX dosing protocol for the treatment of AAV is 375 mg/m²/week for 4 weeks (1b/B). Final consensus 100%.

Rationale

The optimum dose regimen for RTX in induction in AAV has not been determined. RTX regimens as used in protocols for the treatment of other conditions, such as

lymphoma and RA, have been tried in AAV. The lymphoma regimen uses a dose of 375 mg/m²/week for 4 consecutive weeks with a cumulative dose of 2.5–3 g. The RA regimen administers two infusions of 1 g RTX given with a 2-week interval. Both the RAVE and RITUXVAS trials used the lymphoma regimen. In a retrospective review of 65 patients the two regimens for AAV were compared and were found to be of equal efficacy [36]. There was no difference in the duration of B cell depletion or the therapeutic effect, despite the fact that the mean serum concentration after using the lymphoma regimen is higher than that achieved with the RA regimen. The latter results in a lower total dose of RTX over a shorter period of time, but is more convenient for patients and cheaper. However, the 375 mg/m²/week for 4 consecutive weeks regimen has been licensed and hence is recommended.

There are many unanswered questions regarding the optimum use of RTX, and because of this, consensus recommendations have recently been developed for its use in AAV [37]. There are, however, two groups in which the use of RTX is justified—young people at risk of infertility and those at high risk of infection.

RTX is not known to be associated with infertility and therefore should be considered for use in pre-menopausal woman >30 years of age in whom the risk of permanent infertility is high with CYC therapy.

The rates of infection are generally low in RTX-treated patients with RA [38]. Nevertheless, there are insufficient data on the risks of infection in other autoimmune diseases, vasculitis included, in patients receiving repeat cycles of RTX, taking other immunosuppressants and those with depleted B cells. The risks of infection with modern short-course CYC regimens may be as much related to GC use as to CYC. RTX may be justified in patients at high risk of infection. There is no clear evidence on whether repeat treatment should be pre-emptively given or whether re-treatment should be given on relapse. RTX is superior to CYC in relapsing patients (RAVE), who will also be those at greatest risk of cumulative CYC toxicity.

Mycophenolate and methotrexate

Recommendation

MTX (up to 25–30 mg once per week) and MMF (up to 3 g/day) are alternative remission induction agents for patients with evidence of low disease activity and not at risk of suffering organ damage as assessed by the BVAS (1b/A). Final consensus 100%.

MTX should not be used in patients with moderate or severe renal impairment (1b/B). MMF may be an alternative to MTX (2a/B). Final consensus 100%.

Rationale

MTX was used as the alternative arm to CYC in the NORAM study [39]. In this study of patients with no or minimal renal disease, MTX was as effective as CYC at inducing remission over a 12-month period. Long-term follow-up has indicated that these patients remain at high risk of relapse [21]. Patients in this group are often

those with disease restricted to the upper airways and are PR3-ANCA positive and have a high relapse rate. MTX should only be considered for primary induction therapy in patients with no evidence of organ-threatening involvement; in the upper airways this means no evidence of bone destruction or tracheal involvement. In the NORAM study, treatment was stopped as per protocol at 12 months, but this does not reflect usual clinical practice. MTX should be avoided in patients with moderate or severe acute renal impairment but can be used cautiously in patients with mild renal impairment with increased frequency of monitoring. Neither MTX nor MMF induce sustained remission.

Preliminary data from the MYCYC trial failed to demonstrate that MMF is non-inferior to CYC for primary induction [26]. A recommendation on the use of MMF for primary induction must await the publication of the full trial results and long-term follow-up.

Plasma exchange

Recommendation

Patients with AAV presenting with severe renal failure (creatinine >500 µmol/l) should be treated with pulsed CYC and GCs, with plasma exchange (PLEX) in a centre experienced in its use (1a/B). Final consensus 100%.

Treatment with PLEX should also be considered in those with other life-threatening manifestations of disease such as pulmonary haemorrhage (3/C). Final consensus 100%.

Rationale

Patients presenting in advanced renal failure have a much worse prognosis. The use of PLEX improves renal survival but does not affect mortality [40, 41].

The use of PLEX for other manifestations of severe disease, especially pulmonary haemorrhage, has not yet been confirmed with an RCT but is widely practiced [42]. The use of PLEX is being investigated in the PEXIVAS study (<http://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/renal/pexivas/index.aspx>).

There is also some evidence for the use of PLEX in patients with creatinine levels <250 µmol/l. These patients have better renal recovery but no change in overall morbidity and mortality [43].

Glucocorticoids

Recommendation

Induction therapy for AAV includes treatment with high-dose GCs in combination with another immunosuppressive agent (CYC, RTX) (1b/A). Final consensus 100%.

GCs are usually given as daily oral prednisolone, initially at relatively high doses (1 mg/kg up to 60 mg) (1b/B), with the dose rapidly reduced to 15 mg prednisolone at 12 weeks (3/C). Final consensus 100%.

Longer courses of GCs may cause increased risk of infection but may be associated with fewer relapses (1a/A). Final consensus 100%.

Intravenous GC infusions (250–500 mg methylprednisolone) may be given just prior to or with the first two pulses of CYC (1b/C). Final consensus 100%.

Rationale

Induction therapy for AAV includes treatment with high-dose GCs in combination with another immunosuppressive agent (CYC, RTX) [30, 34, 35]. GCs are usually given as daily oral prednisolone. Intravenous GCs are often given with the initial pulses of CYC and RTX. There is very little data assessing the benefits of giving i.v. methylprednisolone. As a group, this committee expressed concern about the side effects related to high-dose GC treatment, particularly evidence suggesting that the infection risk of induction therapy is associated with the use of higher cumulative doses of GC. It should be noted that in the RAVE and RITUXVAS trials comparing RTX with CYC using the same doses of GCs in both arms, there was no difference in adverse event rate, which was not expected with the known differences in toxicity profiles of the two comparator agents. However, longer courses of GCs may cause an increased risk of infection but may be associated with fewer relapses [44, 45].

There is no clear consensus on the rate of steroid reduction, and it is recommended that the aim is to rapidly reduce GCs to 15 mg prednisolone at 12 weeks.

Patients intolerant of or with contraindications to CYC

Recommendation

Patients intolerant of CYC can be effectively treated with RTX (1b/B). Final consensus 100%.

Rationale

RTX can be effectively used, especially when CYC avoidance is desirable, such as with CYC intolerance or allergy, in young people at risk of infertility, avoiding potential effects on spermatogenesis, with previous uroepithelial malignancy and for those patients who are at high risk of infection [34, 35].

Maintenance therapy

Recommendation

Following achievement of successful remission, CYC should be withdrawn and substituted with either AZA or MTX (1b/A). Final consensus 100%.

MMF (3/C) or leflunomide (1b/B) may be used as alternatives for intolerance or lack of efficacy of AZA or MTX. Final consensus 100%.

RTX may also be used as maintenance therapy, and re-treatment can be decided based on fixed interval regimens or evidence of relapse (2b/C). Final consensus 100%.

Rationale

Once remission has been achieved with induction therapy, long-term maintenance treatment is required. AZA is the agent of choice for remission maintenance [29]. In those with normal renal function, MTX is equally effective [46]. MMF [23], leflunomide [47] and gusperimus

(deoxyspergualin) [48] have not been shown to be superior to AZA. Leflunomide has not been compared to AZA for maintenance of remission, however, it was superior to MTX [47]. MMF was inferior to AZA in the IMPROVE study, a European Vasculitis Study Group (EUVAS) open-label RCT [49]. AZA intolerance is relatively common and in this situation alternatives may be considered. MTX is renally excreted, therefore it should be used cautiously in those with impaired renal function and the dose adjusted to chronic kidney disease (CKD) stage.

The role of RTX in remission maintenance remains to be established. Preliminary data from the French MAINRITSAN trial suggest that 500 mg RTX every 6 months is superior to AZA to maintain remission [50]. Most open-label studies have used a dose of 1 g either at fixed intervals or on relapse [36]. There is no clear consensus regarding the timing or dose of RTX re-treatment, but there are four possible options:

- (i) Wait for clinical relapse and re-treat
- (ii) Fixed interval re-treatment
- (iii) Switch to alternative maintenance therapy
- (iv) Biomarker relapse (ANCA, positive or negative CD19/20 return) and re-treatment

The cumulative RTX exposure should be recorded. There is some emerging evidence that the relapse rate is lower with a fixed interval re-treatment strategy [51]. Long-term RTX therapy may be associated with hypogammaglobulinaemia and transient late-onset neutropenia [52]. Progressive multifocal leucoencephalopathy (PML) is a very rare complication. There are no reported cases to date in AAV, but this may reflect the relatively low numbers of patients treated with RTX.

Duration of maintenance therapy

Recommendation

Patients should continue maintenance therapy for at least 24 months following successful disease remission (1b/B). Final consensus 100%.

Patients with GPA or patients who remain PR3-ANCA positive should continue immunosuppression for up to 5 years (3/C). Final consensus 100%.

RTX should be given every 4–6 months for 2 years. For maintenance therapy the recommended RTX regimen uses 1 g (2b/B). Final consensus 90%.

Rationale

Withdrawal of therapy after short periods of treatment, e.g. 1 year, has been shown to have an unacceptably high risk of relapse. The long-term follow-up of patients after the CYCLOPS and CYCAZAREM trials have shown a high relapse rate even after 18 months of maintenance therapy [31]. Long-term follow-up studies suggest that patients who are PR3-ANCA positive at any stage of their illness remain at high risk of relapse and treatment should be continued for longer in this group. Those who remain PR3-ANCA positive should be treated for up to 5 years. The dose of RTX for maintenance therapy remains

TABLE 7 Factors increasing the risk of relapse

Clinical presentation	Serology	Treatment related
Granulomatosis with polyangiitis	PR3-ANCA	Steroid withdrawal
ENT involvement	ANCA positive after induction	Immunosuppressive withdrawal
Better renal function (creatinine <200 µmol/l)	Increase in ANCA	Lower CYC exposure

uncertain; most open-label studies have used 1 g and the ongoing RITAZAREM trial uses this dose every 4 months for 5 months. However, the MAINRITSAN trial used 1000mg at 6 months then 500mg every 6 months for four doses [49].

Withdrawal of treatment

Recommendation

Patients in continual remission for at least 1 year on maintenance therapy should be considered for tapering of GC treatment (3/D). Final consensus 90%.

Following initial drug (GC) withdrawal, other immunosuppressive therapy may be tapered after 6 months (4/D). Final consensus 100%.

Rationale

Patients with good disease control may not need indefinite therapy. Higher cumulative GC doses are associated with increased toxicity and damage accumulation. It is therefore recommended that GCs be tapered and withdrawn first. Ideally there should be a 6-month interval between withdrawing the GC and tapering the immunosuppressants in a patient with no disease activity. Treatment withdrawal may be associated with relapse.

Relapsing disease

Recommendation

Relapsing disease should be treated with an increase in immunosuppression. A minor relapse may be treated with an increase in prednisolone dosage and optimization of concurrent immunosuppression (3/C). Final consensus 100%.

A major relapse may be treated with RTX (1b/A) or a further course of CYC with an increase in prednisolone (1b/B). Final consensus 100%.

Addition of i.v. methylprednisolone or PLEX may also be considered (2a/C). Final consensus 100%.

Drivers for relapse need to be identified and addressed and may include infection, malignancy and a change in drug therapy (4/D). Final consensus 100%.

Rationale

Relapsing disease is an increase in disease activity as documented by an increase in the BVAS and may be minor or major. Relapse indicates severe or potentially severe and unstable disease. Relapses affecting minor BVAS items, if inadequately treated, can lead to relapses affecting major BVAS items.

Factors influencing the risk of relapse may relate to the clinical presentation, the serology or the initial treatment given and are shown in Table 7.

Drivers of relapse should be carefully sought, especially in patients who are refractory to an increase in immunosuppression. Infection and malignancy are typical drivers of relapse. Poor drug compliance and perseverance may also increase the risk of relapse.

Refractory disease

Recommendation

Refractory disease should ONLY be treated in close collaboration with expert or tertiary centres via a hub-and-spoke model (4/D). Final consensus 80%.

RTX is more effective than CYC in refractory AAV (1b/A). If the patient has not had previous treatment with RTX before, then the first choice is RTX (1b/A). Final consensus 100%.

Drivers for refractory disease should be sought and clinicians should consider revision of the clinical diagnosis (4/D). Final consensus 100%.

Rationale

RTX is more effective than CYC in refractory AAV [34]. The use of anti-TNF medications (infliximab, adalimumab) has not been shown to be helpful and may result in an increased risk of infections or malignancy. Etanercept has not been effective in treating refractory disease [53]. IVIG [16, 54] and alemtuzumab, an anti-CD52 antibody also known as CAMPATH-1H [54], can be used in refractory disease, but further RCTs are awaited. Gusperimus (deoxyspergualin) can be used in refractory disease [48, 55]. Leflunomide can also be used as an alternative for refractory disease [47]. For EGPA, mepolizumab, a humanized monoclonal antibody to IL-5, may be an alternative therapy [56–58].

It is important to identify potential underlying factors influencing refractory or relapsing disease, including infection and malignancy. Revisiting the diagnosis and searching for drivers should always occur in the context of refractory disease [59].

Assessment and monitoring of disease status

Disease assessment tools

Recommendation

A validated tool should be used to assess disease activity and the extent of disease (4/D). Final consensus 90%.

Validated assessment tools, such as the BVAS and Vasculitis Damage Index (VDI), should be used by staff trained in their use. Quality of life (QOL) should be assessed regularly utilizing appropriate and validated tools such as 36-item Short Form (SF-36) (4/D). Final consensus 90%.

Rationale

Disease activity assessment

Several systems have been developed to assess disease activity and damage. These include the BVAS, Groningen Index and the Vasculitis Activity Index (VAI). The BVAS is the most widely applicable to different types of necrotizing vasculitis and has been systematically validated and used in a number of clinical trials. The BVAS is a comprehensive scoring system that includes nine organ systems. Clinical features that are attributable to active vasculitis and have occurred anew and been present within the previous 4 weeks are recorded. Organ involvement associated with a worse prognosis is given a greater weighting. The updated version of the BVAS (BVAS v3) has been revalidated and evaluated in a large cohort of patients in seven European countries, thus increasing its utility in different populations of patients with systemic vasculitis [60].

Damage assessment

Vasculitis results in organ damage due to either the disease itself or to therapy. Damage is defined as an irreversible process that is the result of scars and is not due to acute inflammation or grumbling disease activity. The VDI is also an organ-based system and is scored after 3 months. The VDI is comprehensive, permits accumulation of damage with time and has been validated. There are concerns that it may not adequately determine the full spectrum of damage experienced by patients with vasculitis of small and medium-size vessels. There is an ongoing international initiative (the OMERACT Vasculitis Working Group) aimed at creating an evidence-based unified approach to disease assessment for the primary systemic vasculitides by revising and improving damage assessment tools [61].

Quality of life assessment

The final component of patient assessment is QOL. The SF-36 has been validated for use in patients with vasculitis and is included in the Vasculitis Integrated Assessment Log (VITAL) for disease assessment [62]. An emerging patient-reported outcome is health-related quality of life (HRQOL). HRQOL is the component of a patient's QOL that is thought to be attributable to their health status rather than their education or socioeconomic status [63]. HRQOL, as measured by the SF-36, is reduced among patients with GPA. SF-36 measures are modestly associated with other disease outcomes and discriminate between disease states of importance in GPA. Fatigue is identified as a principal complaint among patients with AAV causing impaired QOL [64].

The use of these tools in routine practice should facilitate good quality of care and enable outcome audits.

Frequency of disease assessment

Recommendation

Disease assessment should occur monthly during remission induction and every 3 months during initial maintenance treatment and thereafter every 6 months and then annually (2b/B). Final consensus 100%.

Tools assessing damage (VDI) should be used at baseline, 6 and 12 months (2b/B). Final consensus 100%.

Patients with AAV should not be completely discharged from the specialist clinic (4/D). If discharged, there should be rapid access to specialist care. Final consensus 90%.

Rationale

Patients have a long-term risk of relapse of 38% at 5 years and remain at permanent risk of relapse [45]. Risk factors for relapse are shown in Table 7. Long-term drug toxicity (e.g. bladder cancer secondary to CYC) may only become apparent many years after treatment. If patients are discharged there should be a facility in place for rapid referral back into a specialist clinic and a mechanism in place for monitoring long-term outcomes.

ANCA measurements

Recommendation

ANCA should be checked at diagnosis, relapse, change of therapy, every 6 months while on treatment and annually while off treatment (2b/B). The results should be available within 1 working day. Final consensus 100%.

ANCA should be detected using IIF with ELISA to confirm PR3 or MPO specificity (3/C). Final consensus 100%.

Treatment should not be increased solely on the basis of an increase in ANCA (2b/B). Final consensus 100%.

Rationale

Relapse may occur at any time after diagnosis and remission induction. Treatment withdrawal in patients with persistently positive ANCA is associated with relapse. ANCA measurements are not closely associated with disease activity [65]. An increase in ANCA titres should trigger increased clinical vigilance and earlier clinical review, but treatment should not be increased solely on the basis of a change in ANCA. The absence of ANCA in a suspected relapse does not exclude a relapse.

Neither IIF nor ELISA nor the newer multiplex bead assays are standardized and local laboratory values and methods vary [66]. Clinicians should work closely with their local laboratory.

Detection of nasal *Staphylococcus aureus* carriage

Recommendation

Staphylococcus aureus treatment with long-term nasal mupirocin should be considered (3/C). Final consensus 100%. Patients should have bacterial swabs at baseline and every 6–12 months (4/D). Final consensus 100%.

Rationale

Studies have shown that the nasal carriage of *S. aureus* is associated with an increased risk of relapse in patients with GPA, although the causal relation and mechanisms remain speculative [67]. Infection may be a driver for persistent disease or relapse. All patients should have bacterial swabs and be treated with long-term nasal mupirocin if *S. aureus* is detected. Prophylactic treatment with co-trimoxazole could also be considered in cases of persistent endonasal activity of GPA together with *S. aureus* carriage [66].

Detection and prevention of potential adverse effects of immunosuppressive therapy

Drug therapy monitoring

Recommendation

Patients receiving immunosuppressive therapy require routine monitoring of FBC, urea and electrolytes (U&E) and liver function tests (LFTs) following appropriate national guidelines (3/C). Final consensus 100%.

Shared care with primary care for stable patients may enable optimal drug therapy monitoring (4/D). Final consensus 100%.

The disease assessment should take place by specialist staff trained to use the assessment tools (4/D). Final consensus 100%.

Rational

Specific monitoring and screening for individual drugs should follow appropriate national guidelines (e.g. BSR guidelines) [68]. This can be shared with primary care health care professionals.

The disease activity assessment should be performed as recommended above by the specialist team.

CYC-induced toxicity

Recommendation

Mesna (2-mercaptoethane sulphonate sodium) should be considered for protection against urothelial toxicity in all patients receiving CYC, and especially in those receiving oral CYC (2b/C). Final consensus 100%.

Surveillance with regular (3–6 months) urinalysis should be continued indefinitely after a course of CYC (2b/C). Final consensus 100%.

Haematuria (microscopic and macroscopic) or symptoms of recurrent cystitis should be investigated with urine microbiology and cytology. There should be a low threshold for referral for consideration of cystoscopy if haematuria is not considered to be due to active renal vasculitis (2b/B). Final consensus 100%.

Rationale

Bladder toxicity (haemorrhagic cystitis and bladder cancer) is a recognized complication of CYC therapy. An epidemiological study from Sweden suggested a dose-response relationship between cumulative CYC

dose and the risk of bladder cancer [69]. Historical cohort data show that the risk of bladder toxicity is related to the cumulative dose administered and is greatest in patients receiving >100g [70]. In a more recent review looking at the incidence and prevention of bladder toxicity from CYC in rheumatic disease, a substantially elevated risk of bladder cancer associated with CYC treatment was observed [odds ratio (OR) range 3.6–100]. The total cumulative doses of CYC given to patients in whom bladder cancer subsequently developed varied widely, but were >100g in the majority of cases and >30g in the great majority [32]. Over the past two decades, the known substantial toxicity of CYC has produced many efforts to develop CYC-sparing regimens for AAV treatment. Follow-up data from the European Vasculitis Study Group clinical trial looking at the incidence of malignancy in patients treated for AAV reported a standardized infection ratio (SIR) risk of 2.41 (range 0.66–6.17) for bladder cancer and suggested that the use of lower cumulative doses of CYC might have started to show benefits [71]. However, bladder cancer may develop many years after CYC therapy and the long-term risk for patients in these newer protocols is unknown [32].

Mesna protects against the urothelial toxicity of CYC by scavenging the toxic metabolite acrolein. There are no RCTs reporting its use in reducing the urothelial toxicity of CYC in vasculitis.

Mesna may be given orally or intravenously. When CYC is used intravenously, the oral dose of mesna should be 40% of the CYC dosage in milligrams. It should be given 2 h prior to the pulse of CYC and repeated 2 and 6 h after the pulse of CYC. If the mesna is being given intravenously, then the dose should be 20% of the pulsed CYC dosage in milligrams and can be given with the CYC and then at 2 and 6 h (either orally or intravenously). The same dosage of mesna is given each time the patient receives a pulse of i.v. CYC. In patients receiving oral CYC, mesna is given for as long as the patient receives CYC treatment.

RTX therapy

Recommendation

RTX therapy may be associated with long-term B cell depletion and hypogammaglobulinaemia. It is therefore recommended that serum immunoglobulins be measured before each cycle of therapy (3/C). Final consensus 100%.

Rationale

Long-term B cell depletion and hypogammaglobulinaemia may be associated with RTX therapy in AAVs [36]. B cell depletion and hypogammaglobulinaemia are associated with an increased risk of infection in patients with rheumatic diseases [52, 72, 73]. Patients with recurrent infection should have B cell subsets measured to assess the severity of depletion. Gamma globulins should be measured prior to each cycle of therapy: if levels are falling, then therapy may need to change; if associated with recurrent severe infection, then replacement therapy may be needed.

Infection with *Pneumocystis jiroveci*

Recommendation

Trimethoprim/sulphamethoxazole should be considered as prophylaxis against *Pneumocystis jiroveci* (PCJ) in patients receiving intense immunosuppression (CYC) (1a/B) and/or other induction treatment using high-dose GCs (3/C). Final consensus 100%.

Patients receiving CYC and GCs should be considered to receive trimethoprim/sulphamethoxazole 960 mg thrice weekly as prophylaxis against pneumocystis (2b/C). Final consensus 100%.

Rationale

PCJ is a common infectious complication in immunocompromised patients that is associated with significant morbidity and mortality. Although there are no RCT data for AAV patients, observational data from trials and case series support the approach that patients receiving CYC and corticosteroids should receive trimethoprim/sulphamethoxazole 960 mg thrice weekly as prophylaxis against pneumocystis.

The rate of pneumocystis infection in vasculitis patients receiving CYC and GCs has been reported to be as high as 20% in a French multicentre study [74] compared with 6% in the National Institutes of Health (NIH) cohort [75] and 1% in a German cohort [76]. This difference may be explained by the much higher doses of prednisolone used in the French study and the fact that many patients in the German study received trimethoprim/sulphamethoxazole (Septrin) as part of their therapeutic regimen.

A Cochrane review of prophylaxis for PCJ in non-HIV immunocompromised patients supported the use of trimethoprim/sulphamethoxazole for PCJ prophylaxis with a number needed to treat of 15 patients [77].

Although there is an interaction between MTX and trimethoprim/sulphamethoxazole, the studies of MTX used in vasculitis have not shown that this is clinically relevant at these low doses of trimethoprim/sulphamethoxazole, especially if not given on the same day as MTX. Nevertheless, extreme caution should be taken in using trimethoprim/sulphamethoxazole in patients on MTX. In cases of trimethoprim/sulphamethoxazole intolerance, alternative drug options include monthly aerosolized pentamidine (300 mg) or dapsone 100 mg/day.

The risks of pneumocystis are related to the doses of CYC and GC, so the current use of lower cumulative doses of both drugs probably reduces the risk. The risks of PCJ infection with RTX are unknown but probably relate to the concomitant GC.

Fungal infections

Recommendation

Antifungal prophylaxis treatment should be considered in patients receiving intense immunosuppression (high-dose GC and CYC) (3/C). Final consensus 100%.

Rationale

Patients receiving immunosuppressive therapy are at an increased risk of fungal infections. The EUVAS trials

suggested that prophylactic treatment with antifungal agents such as nystatin, oral fluconazole and amphotericin should be considered for patients receiving immunosuppressive therapy.

Although nystatin has been more commonly used, amphotericin suspension can also be considered in all patients under long-term GC medication with a dose of >15 mg prednisolone per day because it is effective, non-absorbable and thus associated with very few side effects. A meta-analysis on the use of antifungal prophylaxis in severely immunosuppressed patients (but not specific to AAV), showed that the non-absorbable nystatin was not more effective in avoiding fungal colonization than placebo and therefore could not be routinely recommended [78]. Additionally, all patients should be encouraged to perform daily self-inspection of the mouth in order to detect mucosal candidiasis early [79].

Cervical intraepithelial neoplasia

Recommendation

Female patients should be considered for cervical intraepithelial neoplasia (CIN) screening and for HPV vaccination (3/C). Final consensus 100%.

Female patients receiving CYC should be considered for an annual cervical smear for the first 3 years and then as per the UK national screening programme (3/C). Final consensus 100%.

Rationale

Cervical carcinoma is a common malignancy associated with infection with HPV (serotypes 16, 19 and 31), which is sexually acquired. Immunosuppressive therapy is associated with the development of secondary malignancies. There are no data on the occurrence of CIN in vasculitis patients. A study in SLE patients reported a significant association between i.v. CYC with prednisolone and the development of CIN in the first 3 years following treatment [80]. Increased rates of CIN have also been observed in patients with lupus receiving AZA.

Infertility

Recommendation

Patients should be counselled about the possibility of infertility following CYC treatment and offered fertility preservation (3/C). Final consensus 100%.

Sperm and oocyte cryopreservation should be considered in male patients wishing to father children and in premenopausal women. These procedures may take time to organize and treatment should not be delayed. They should be considered if the clinical condition of the patient permits (4/D). Final consensus 100%.

Rationale

Both male and female infertility is a recognized complication of CYC therapy. The majority of the evidence comes from other conditions such as SLE. Female infertility is associated with the cumulative dose of CYC and older age at the time of treatment. In a study of 67 women with proliferative LN it was shown that in younger patients who receive relatively low cumulative CYC doses,

infertility and amenorrhoea may be reversible [81]. The dose of CYC should therefore be kept to a minimum, although there are no data to define a specific threshold of the cumulative CYC dose.

Fertility preservation options include oocyte or embryo cryopreservation, hormonal ovarian stimulation or the use of gonadotropin-releasing hormone (GnRH) analogues during CYC therapy to reduce premature ovarian failure [82]. In patients where gonadotropin ovarian stimulation is deemed unsafe, *in vitro* maturation of immature oocytes aspirated during a natural menstrual cycle seems to be safe and feasible [83]. An analysis of 47 female patients <40 years of age with a diagnosis of vasculitis from the German Fertiprotect registry suggested that a combination of the methods has the greatest preservative effect [84].

Male infertility after CYC therapy for autoimmune disease is less well understood since the majority of patients requiring CYC therapy for SLE are female. Ideally, sperm donation should occur prior to initiation of CYC therapy. However, if for clinical reasons CYC is given prior to sperm donation, it is advisable to wait 6 months before sperm donation.

Osteoporosis

Recommendation

Prophylaxis against osteoporosis should be considered in patients receiving corticosteroids. The need for treatment and fracture risk should be assessed following national guidance (1a/A). Final consensus 100%.

Rationale

Osteoporosis is a recognized consequence of high-dose and/or prolonged treatment with corticosteroids. Fracture risk should be assessed using the FRAX tool. It is recommended that all patients receiving standard treatment for AAV should be considered for bisphosphonate therapy with calcium and vitamin D supplementation because of the high doses of steroids used and the prolonged treatment course involved in these patients. Bisphosphonates are contraindicated in those with severe renal disease. Practice should be in line with current national guidelines for the prevention of corticosteroid-induced osteoporosis [85].

Mycobacterium infection

Recommendation

Patients receiving immunosuppression should be screened for tuberculosis (TB) as per the recommendations of the British Thoracic Society (BTS) guidelines. All patients should be assessed for risk of TB by taking a full history, physical examination and performing a chest X-ray. It is recommended that the guidelines provided by the BTS and NICE for the assessment of risk and for managing mycobacterium tuberculosis infection and disease, as in patients due to start anti-TNF treatment, should be followed (2b/C). Final consensus 100%.

Rationale

Patients receiving intensive immunosuppressive therapy are potentially at an increased risk of reactivation of

latent TB or, less commonly, new infection. For immunocompromised patients, the NICE and BTS recommendations are to offer an IFN- γ test alone or an IFN- γ test with a concurrent Mantoux test. If either test is positive, then a clinical assessment should be performed to exclude active TB and consider treating latent TB [86].

Vaccinations

Recommendation

Patients receiving immunosuppression should be screened and vaccinated against pneumococcal infection, influenza and hepatitis B as recommended by the EULAR guidelines on vaccination of the immunocompromised patient (1a/B). Herpes zoster vaccination should be avoided, as this is a live vaccine. Vaccination protocols for each organism and drug should follow appropriate national guidance. Final consensus 90%.

Rationale

It is recommended that patients starting immunosuppressive therapy should have their vaccination status assessed [87]. Patients not known to be vaccinated against pneumococcal infection should be immunized preferably before starting therapy, but therapy initiation should not be delayed. Patients should have pneumococcal titres measured and undergo revaccination if required [88].

Immunosuppressed patients should receive an annual influenza vaccination. Vaccination against influenza does not increase the relapse rate in patients with AAV [89]. Live vaccines should be postponed until at least 3 months after stopping immunosuppressive therapy.

Patients receiving RTX therapy should have their vaccinations completed at least 2 weeks before RTX is given, and preferably 4–6 weeks; if done at <2 weeks, there is a risk of reduced protection from the vaccine. If vaccination is not completed before initiation of RTX therapy, it should be postponed for 4 months [37].

Varicella titres should be measured in all patients prior to commencing CYC therapy, however, CYC treatment should not be delayed for the results. Consider giving varicella-specific immunoglobulin if contact risk is significant.

Further advice on the use of live vaccines in immunocompromised patients can be found in the EULAR guidelines on vaccination [87] and the Department of Health national guidance [90].

Live vaccines should not be given to immunocompromised patients, as the response to vaccines may be reduced and there is a risk of generalized infection.

Antibody titres tend to decline more rapidly in immunocompromised patients and more frequent boosters may be required.

Cardiovascular risk

Recommendation

Cardiovascular risk should be assessed and appropriate prophylaxis provided in accordance with national guidance (3/C). Final consensus 100%.

It is recommended that patients with AAV should be screened and treated where appropriate for hypertension,

hypercholesterolaemia and diabetes. Patients should also be strongly advised against smoking and given healthy lifestyle advice (3/C). Final consensus 100%.

Rationale

There is good evidence that there is an increased cardiovascular risk in patients with AAV. Within 5 years of diagnosis of GPA or MPA, 14% of patients will have a cardiovascular event. In patients with vasculitis, PR3-ANCA is associated with a reduced cardiovascular risk compared with MPO-ANCA or negative ANCA status. A validated tool to quantify the risk of a cardiovascular event based on age, diastolic hypertension, and PR3-ANCA status in patients without prior cardiovascular disease is now available [91]. However, the potential benefit of intervention has not been investigated. Therefore the recommendation is to actively seek and address conventional cardiovascular risk factors.

Thromboembolic risk

Recommendation

Thromboembolic risk should be assessed and appropriate prophylaxis provided in accordance with national guidance (3/C). Final consensus 100%.

Rationale

Patients with AAV have an increased risk of developing venous thromboembolism (VTE), especially when AAV is active. This finding could not be explained by classic risk factors, but is probably related to endothelial changes and hypercoagulability induced by AAV and its therapy [92].

There is an increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in the first 3–6 months after diagnosis and 5–15% of patients have VTE. There is an association of VTE with active vasculitis and also with the presence of autoantibodies.

It is recommended that patients with AAV should be considered for prophylactic anticoagulation during periods of prolonged immobility. Attempts to avoid risk factors for thromboembolic disease should be undertaken and a high index of suspicion should be used in these patients. There are currently no assays available for antiplasminogen antibodies.

Patient involvement and education

Recommendation

Patients should receive ongoing tailored education and information about AAV (4/D). Final consensus 100%.

Patients should be encouraged to engage in self-monitoring to improve compliance with treatment and long-term outcomes (4/D). Final consensus 100%.

Rationale

Patient education is of paramount importance and it should be safeguarded and supported. It is the clinician's responsibility to ensure patients are encouraged to be actively involved in their treatment and are given all the relevant information they need in order to make informed decisions about their health care [93,94].

Educational material and purposeful educational consultations with members of the health care team should be encouraged. Appropriate education material and resources (patient information leaflets, patient groups) should be accessible to patients and caregivers.

Patients should be encouraged and supported to engage in self-monitoring. Patient organizations, such as Vasculitis UK (<http://www.vasculitis.org.uk>), may play an important role in supporting and educating people with vasculitis about their illness and raise the general awareness of the issues they face.

Primary care health care professionals that are involved and assist in the monitoring of these patients should have adequate support and training to facilitate this role.

Overview of care and collaboration

Clinicians within clinical networks

Recommendation

Patients with AAV should be managed by a nominated lead clinician within clinical networks linked with centres of expertise and other specialities within the local organization (4/D). Final consensus 100%.

Rationale

Networks should be utilized to support and facilitate the care of AAV patients. Not all AAV patients have to be seen at tertiary centres all the time, but their overall care should be managed by clinicians working in collaboration with centres of expertise and with the involvement of other specialities, as AAV is a severe and multisystem disease.

In England the development of specialized commissioning will aid the development of multicentre collaborative networks (<http://www.england.nhs.uk/resources/spec-comm-resources>). A hub-and-spoke model may facilitate an effective way to safely manage patients with AAV with the input of centres of expertise.

Access to specialist services

Recommendation

People with a suspected diagnosis of systemic vasculitis should be rapidly assessed by a specialist physician with an expertise in vasculitis (4/D). Final consensus 100%.

Self-referral mechanisms for patients to enable rapid access to specialists when flares occur should be in place (4/D). Final consensus 100%.

Rationale

Prompt recognition of vasculitis either as a new presentation or a clinical relapse is key in optimizing management and preventing organ damage. Prompt access to specialist care, even when the patient has been in drug-free remission for a prolonged period and not regularly seen in the specialist clinic, needs to be facilitated.

Clinical research

Recommendation

Patients should be encouraged to take part in studies and registries (4/D). Final consensus 100%.

Rationale

The AAVs are rare disease and clinical research with patient participation will enhance our understanding of the pathogenesis, aid in the development of new therapies and improve our understanding of the patient experience. Registries like UKIVAS should be supported to improve patient care and facilitate commission pathways (<https://research.ndorms.ox.ac.uk/public/ukvas/>).

Complementary and alternative therapies

Recommendation

Complementary and alternative medicine (CAM) therapies are widely used, although there is no specific evidence to support their use in AAV. Patients should have access to information about CAM treatments that might be helpful for symptomatic relief (4/D). Final consensus 100%.

Rationale

There are no studies looking specifically at the role of complementary and alternative medicine for patients with vasculitis. A study looking at the perceived efficacy of various methods of complementary and alternative medicine for patients with rheumatological diseases showed that satisfaction with complementary and alternative medicines was lowest among CAM users with RA, vasculitis and connective tissue diseases compared with other disease groups [95]. Information and summaries of published reports regarding the use of CAM for rheumatological disease are available in patient information leaflets published by Arthritis Research UK (<http://www.arthritisresearchuk.org/arthritis-information/complementary-and-alternative-medicines/complementary-therapies.aspx>).

Applicability and utility

Statement of potential organizational barriers to introduction

Pulsed i.v. CYC and RTX require day unit facilities in which there is appropriate expertise to assess and provide treatment. AAV is rare and it is recommended that patients have access to physicians and nursing staff experienced in the vasculitides. This may require the development of networks both within and across hospitals and specialties. Guidance on the development of networks, access to tertiary centres and novel therapies will be developed via the NHS England specialized commissioning process (<http://www.england.nhs.uk/resources/spec-comm-resources>).

Potential cost implications for introduction of the guideline

A formal health economics assessment is outside the scope of these guidelines. We have considered the available cost-effectiveness literature and it is very limited.

There is no published health economic assessment of the costs associated with treatment of AAV.

The use of RTX may be associated with increased drug costs, but some of this may be offset by decreased frequency of infusions compared with the use of pulsed i.v. CYC. Patients receiving i.v. CYC will have 6–12 infusions over a course of induction therapy (6 months), whereas RTX patients will have 2–4 infusions depending on the regimen.

In England, RTX is commissioned centrally by NHS England, if used in accordance with the criteria outlined in the commissioning policy (patients with primary treatment failure, relapsing disease or with adverse reactions or contraindications to CYC) [19].

Key quality standards

- (i) People with a suspected diagnosis of systemic vasculitis should be rapidly assessed by a specialist physician with an expertise in vasculitis.
- (ii) People diagnosed with vasculitis should be offered personalized information, disease education, vocational/occupational advice and support. They will be given opportunities for discussion throughout their care to help them understand their condition and be involved in self-management. People should be given information and contact details of appropriate patient support groups (e.g. Vasculitis UK).
- (iii) People with vasculitis require access to a multidisciplinary team consisting of professionals, either based locally or part of a regional network, with appropriate knowledge and skills and should have a single point of contact responsible for managing their care (e.g. consultant rheumatologist or nephrologist).
- (iv) The management of people with vasculitis should include knowledge of the impact of the disease on their ability to work, and treatment and support should be offered throughout their disease to optimize their chances of maintaining employment.
- (v) People with vasculitis should have access to the full range of effective therapies available, including biologic drugs, following an appropriate treatment pathway. Periodic treatment reviews should ensure that all individuals receive treatment that is optimally effective and tolerated.
- (vi) People with vasculitis should be provided with written advice on early detection and management of disease flares. They will need prompt access to the multidisciplinary team.
- (vii) People with vasculitis should receive long-term expert care and support, including an annual holistic review of the social and biological effects of their disease with an action plan to address issues identified. This should include social roles and work, disease activity, pain, mood, functional ability, a review of diagnoses and co-morbidities (including cardiovascular disease and osteoporosis).
- (viii) People with vasculitis should be offered the opportunity to participate in local and national research

and projects to improve the quality of their care and help others in the future. This should include collection of data on response to and side effects of treatment.

Mechanism for audit of the guideline

Systemic vasculitis, and more specifically AAV, is rare and therefore audit may need to be conducted on a collaborative basis. The following are some topics that may be audited:

Service delivery

- (i) Time from receiving referral with a clinical suspicion of AAV:
 - Inpatient within 1 working day. Standard 100%.
 - Outpatient within 1 working week. Standard 100%.
- (ii) Nominated lead clinician for each patient. Standard 100%.
- (iii) Access to a multidisciplinary team and a recognized specialist network centre. Standard 100%.
- (iv) Availability of ANCA test results within 1 working day. Standard 100%.
- (v) Adherence to CYC best practices. Standard 100%.
- (vi) Availability of facilities for RTX administration. Standard 100%.

Patient specific

- (i) Documented management plan for each patient, including an assessment of disease activity. Standard 100%.
- (ii) Documentation of infertility risk in appropriate patients. Standard 100%.
- (iii) Documented advice regarding immunization. Standard 100%.
- (iv) CYC dosing appropriately adjusted with regard to age and renal function. Standard 100%.
- (v) Proportion of patients achieving remission, as defined in the guideline, by 6 months. Standard 80%.

Vasculitis annual review

Patients with AAV require long-term follow-up that should follow a structured format. The mechanism for this may be determined locally. Components of an annual review could include the domains outlined in [Table 8](#).

Research agenda

- (i) Validation of definitions of remission and disease control states
- (ii) Evaluation of the concept of induction remission and maintenance of remission
- (iii) Definition of the disease severity that equals a major item in BVAS
- (iv) Optimization of RTX regimens (induction and maintenance)
- (v) Steroid-free regimens for induction of remission
- (vi) Role of i.v. GCs
- (vii) Timing of GC initiation and tapering

TABLE 8 Possible components of a vasculitis annual review

Disease activity
BVAS
VDI
ANCA status
Organ assessment
Blood pressure
Urinalysis
Renal function
FBC
Co-morbidities
Infections
Vaccination status
Cardiovascular risk
Smoking status
Cholesterol
Glucose
Functional status
Patient-reported outcome measure
Work status

VDI: Vasculitis damage index; FBC: full blood count.

- (viii) Order of treatment withdrawal (GCs and immunosuppressants)
- (ix) Evidence for management of lung disease
- (x) Thiopurine methyltransferase (TPMT) testing/monitoring for AZA
- (xi) Management of EGPA
- (xii) Management of refractory disease

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Appendix

Literature review strategy

A modified Delphi exercise was carried out to identify the scope of the recommendations. This identified 20 points for the literature search. A search string was then agreed upon to identify publications in PubMed for each topic; e.g. AAV (MeSH terms) AND induction of remission (MeSH).

To identify papers that may not have been indexed as ANCA-associated vasculitis, an additional search was performed using specific conditions, e.g. Wegener granulomatosis (MeSH) AND induction of remission (MeSH) and repeated for all related terms (e.g. GPA) and all conditions (e.g. MPA). For terms/conditions that were not a

MeSH in PubMed (e.g. eosinophilic polyangiitis, etc.), the terms were inserted as free text in all fields.

To address all areas highlighted by the Delphi exercise, a further search was performed for each topic, e.g. vaccinations, cardiovascular risk [e.g. anti-neutrophil cytoplasmic antibody associated vasculitis (MeSH terms) AND vaccinations (MeSH terms)].

The search was limited to the time frame 1 January 2005–1 October 2012 and to the English language and human adult subjects. A manual search of abstracts presented at the annual meetings of the EULAR and BSR from 2009 to 2012 was performed. The Cochrane database was searched separately.

Each paper was reviewed and included if one or more of the topics identified in the modified Delphi exercise were studied. Case reports and publications with insufficient outcome data and duplicate entries were discarded. Identified papers were categorized and the evidence graded according to international criteria (Table 3 and 4). The evidence was then reviewed by the committee and assimilated to form the above statements and a research agenda.