ONLINE SUPPLEMENTARY DATA 2

CanVasc Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitides
– Full version –

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ABSTRACT

Objective. The Canadian Vasculitis research network (CanVasc) is composed of physicians from different medical specialties and researchers with expertise in vasculitis. One of its aims was to develop recommendations for the diagnosis and management of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) in Canada.

Methods. Diagnostic and therapeutic questions were developed based on the results of a national needs assessment survey. A systematic review of existing non-Canadian recommendations and guidelines for the diagnosis and management of AAV and studies on AAV published after the 2009 EULAR/EUVAS recommendations (publication date: January 2009) until November 2014 was performed in Medline database, the Cochrane library, and main vasculitis conference proceedings. Quality of supporting evidence for each therapeutic recommendation was graded. The full working group as well as additional reviewers, including patients, reviewed the developed therapeutic recommendations and non-therapeutic statements using a modified 2-step Delphi technique and through discussion to reach consensus.

Results. Nineteen recommendations and 17 statements addressing general AAV diagnosis and management were developed, as well as appendices for practical use, for rheumatologists, nephrologists, respirologists, general internists, and all other health care professionals more occasionally involved in the management of patients with AAV in community and academic practice settings.

Conclusion. These recommendations were developed based on a synthesis of existing international guidelines, other published supporting evidence and expert consensus considering the Canadian healthcare context with the intention of promoting best practices and improving healthcare delivery for patients with AAV.

Key Indexing Terms:
VASCULITIS
ANCA-ASSOCIATED VASCULITIS
DRUG THERAPY
PRACTICE GUIDELINES
CONSENSUS DEVELOPMENT CONFERENCE
QUALITY OF HEALTHCARE

Systemic vasculitides are a heterogeneous group of potentially life-threatening disorders characterized by inflammation of blood vessels with resultant ischemic events, hemorrhagic events, or both. The 2012 revised nomenclature of Chapel Hill distinguishes small, medium, and large vessel vasculitides, according to the calibre of the vessels predominantly affected[1, 2]. Some small vessel vasculitides can be associated with the presence of serum antineutrophil cytoplasm antibodies (ANCA). These vasculitides include: granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss syndrome). Collectively these three small vessel vasculitides are therefore referred to as ANCA-associated vasculitides (AAV).

The rarity and the heterogeneous nature of AAV mean that the management of individual patients can be extremely challenging and may vary markedly across different geographical regions and medical disciplines. The annual incidence rates of GPA and MPA are each around 5–10 per million inhabitants, and that of EGPA around 1–4 per million inhabitants[3-5]. In the past seven years, several guidance documents have been developed in Europe, Australia and Asia in an attempt to outline the optimal evidence-based management of AAV[6-13]. However, these existing guidelines were initially developed prior to 2010 and most have not yet been updated even though significant therapeutic developments have occurred in recent years, particularly with respect to the use of the biologic agent rituximab. In addition, these existing guidelines obviously cannot take into account the specificities of health care system delivery, access to services and drug treatments in Canada.

The Canadian Vasculitis research network (CanVasc) was created in November 2010 and its core committee includes physicians of different specialties, though primarily rheumatologists and nephrologists. One of the major objectives of CanVasc was the development of recommendations for the management of patients with vasculitis. It was first decided to develop and focus on recommendations for AAV. This document reports the recommendations and statements consensually developed by the CanVasc recommendation working group (all members of this group are listed as co-authors).

MATERIALS AND METHODS

Precise objective. The aim was to develop a document to provide guidance and structured recommendations for the management of AAV within Canada, based on a synthesis of existing international guidelines, supporting evidence, and expert consensus of a national Canadian AAV clinical and research network (CanVasc).

Target patient population. The target patient population for these recommendations are patients with, and suspected of having, AAV according to prior and current classification criteria[1, 2, 14, 15] and/or by a healthcare provider.

Target audience and users. We anticipate the target audience of these recommendations to be rheumatologists, respirologists, nephrologists and general internists involved in the management of AAV in community and academic practice settings. We also expect that this document may serve as a point of reference on the management of AAV in Canada for other specialists, medical students, specialists in

training, general practitioners and all other health care professionals occasionally involved in the management of AAV patients. These recommendations may also be of interest to other provincial and federal AAV stakeholders and decision makers.

Health questions covered. These recommendations cover the main domains of the general management strategies for AAV (GPA, MPA and EGPA), including their diagnosis, treatments with glucocorticoids (GC), traditional immunosuppressants and biologic agents, and follow-up. They do not address other non-AAV vasculitides such as polyarteritis nodosa or isolated vasculitic peripheral neuropathy.

Needs assessment questionnaire. As done previously for the development of other Canadian recommendations[16-18], a national Needs Assessment Questionnaire (NAQ) was first disseminated between May and October 2012 to Canadian healthcare professionals from different medical specialties involved in vasculitis patient management. The objectives were to identify the specific areas of need, possible knowledge gaps and outline key questions, uncertainties and challenges in the management of patients with AAV.

The key messages were that 89% of respondents do not have hospital/centre written protocols for the management of AAV, 77% of respondents do not refer patients onto a vasculitis referral centre (at least for 2nd opinion)[19]. The top 5 issues, pertaining to the management of AAV, which respondents felt would be helpful if addressed by AAV recommendations were as follows (in order of priority): i) remission induction, ii) treatment of refractory patients, iii) treatment of relapses, iv) indications and use of biologics, v) remission maintenance therapy.

Review of existing guidelines. The international existing clinical practice guidelines and consensus statements on the management of AAV (exclusively or as part of a general vasculitis guidance document) published in English or French between 2006 and August 2013 were then reviewed. We considered seven such documents: Kidney Health Australia: Caring for Australasians with Renal Impairment Guidelines CARI, 2006), British Society for Rheumatology (BSR, 2007), French Vasculitis Study Group (2007 FVSG), Japanese Circulation Society (JCS, 2008), European League against Rheumatism / European Vasculitis Society (EULAR/EUVAS, 2009), the International Society of Nephrology / Kidney Disease: Improving Global Outcomes (KDIGO, 2012); and the 2011 British recommendations for the use of rituximab in ANCA-associated vasculitis (Guerry et al)[6-13]. We also included two additional guidelines that were published during the development of these recommendations (FVSG recommendations for the use of rituximab for induction and maintenance treatments of adult AAV [2011 FVSG] and the updated British Society of Rheumatologists guidelines for the management of adults with AAV [2014 BSR])[20, 21].

Additional literature search. To access the more recent clinical trial data not referenced in published guidelines, we performed a PubMed Medline search using the terms “vasculitis” *or* “granulomatosis with polyangiitis”, *or* “microscopic polyangiitis” *or* “eosinophilic granulomatosis with polyangiitis” *or* “Wegener’s” *or* “Churg Strauss”, looking for all therapeutic studies (randomized clinical trials, retrospective and cohort studies) of AAV published since the 2009 EULAR/EUVAS recommendations and until May 2014, in English or in French, excluding case reports. We reviewed the reference lists of our search results to ensure no relevant or important studies were missed. We also performed a manual search of relevant

abstracts presented at the American College of Rheumatology (ACR), EULAR/EUVAS and British Society of Rheumatology scientific meetings since 2008 and until May 2014. Finally, we also performed a search of the Cochrane library, without date restriction in August 2013 and again in May 2014, citing "vasculitis" as the principal search term[22, 23].

Development of the recommendations and working group reviews. We first constructed 37 recommendations (*Figure 1*), specifically addressing the areas of need as identified by the NAQ and additional questions identified from CanVasc recommendation working group. We described the rationale behind each recommendation and, where relevant, how and why it has been modified according to prescribing regulations and practice setting within Canada. For each recommendation, we also presented existing recommendations/guidance from other societies. The level of evidence available for each recommendation was categorized and graded according to the criteria previously endorsed by EULAR/EUVAS (*Tables 1A, B)*[6, 24].

Using a modified Delphi method, each member of the CanVasc recommendation working group was asked to vote, review and comment on the grading and wording of each recommendation of this first draft. A teleconference was held on November 22nd, 2013, to review the comments and reach consensus on all debated recommendations, especially those not agreed upon by >80% of the reviewers. It was agreed that recommendations not related to treatment should not be graded as there was no strong evidence or available studies to support them.

The recommendations were then revised and re-written, resulting in a total of 19 recommendations (with grading for evidence) and 17 statements (expert consensus, without grading for evidence). Information from the French Vasculitis Study Group recommendations for the use of rituximab for induction and maintenance treatments of adult AAV and the 2014 update of the British Society of Rheumatologists guidelines for the management of adults with AAV were then added[20, 21]. The revised recommendations and statements were distributed on July 14th, 2014, for review to the working group and a broader spectrum of reviewers, including members of several professional medical societies and specialists (CRA, Canadian Thoracic Society (CTS) and Canadian Society of Nephrology (CSN)), and the Canadian support group for vasculitis patients (Vasculitis Foundation Canada). Their comments were gathered and discussed with CanVasc recommendation working group during a second teleconference (October 9th, 2014) to reach consensus on the final version of the document. This document was then reviewed by the CRA Guidelines Committee and endorsed on March 21st, 2015, for a period of 3 years, before being submitted for publication to both the Journal of Rheumatology and Canadian Journal of Kidney Health and Disease.

Appendices. The appendices include tools for the practicing physicians for diagnosis, assessment, monitoring and prescribing. The content of these appendices was also reviewed and commented on by the working group. As local prescribing and monitoring practices for AAV may vary, this *Appendix* must be considered an aid for AAV healthcare providers in implementing the recommendations.

Meeting organization. These recommendations were developed by internet, through phone conferences and emails, as well as during the regular administrative and business meetings of CanVasc core members.

Funding and conflict of interest. The development of these recommendations was entirely self-funded by CanVasc (to cover the costs of the teleconferences and online surveys). None of the authors received any fees, grants or emoluments for the development of these recommendations. No funding support from pharmaceutical companies was received; no representatives of pharmaceutical companies were involved at any step in the development of these recommendations. Potential conflicts for each working group member including industry funding, consultancies, commercial interests, and direct involvement in any guidelines included in the systematic review are listed in the *Appendix*.

Dissemination strategies and applicability. The present document was prepared following the principles outlined by the AGREE II instrument V1 (www.agreecollaboration.org)[25, 26]. The recommendations, the *Appendix* including tools to aid healthcare providers in the management of AAV patients will be made available through the CanVasc (http://www.canvasc.ca) and CRA websites (http://www.rheum.ca). The recommendations will be updated by means of a literature search and validation by the expert committee by 2018, or earlier if significant changes occur in the field of AAV.

RESULTS

Key to understanding these recommendations and statements

Each therapeutic recommendation and statement is accompanied by supporting text, which reports on the expected health benefits, potential side effects and risks and Canadian system factors that may influence their applicability. Therapeutic recommendations are presented with a level of evidence and strength (*Table 2*). Statements are for non-therapeutic recommendations and working group consensus, for which there is no strong supporting evidence from controlled studies; thereby they are not graded. For each recommendation and statement, we also present corresponding recommendations/guidance previously published on the same topic from other societies, when available.

Recommendations and statements

1. Diagnosis

Statement 1

ANCA testing with ELISA and indirect immunofluorescence methods should be performed for diagnostic purposes in patients in whom there is clinical suspicion of a systemic small- and/or medium-sized vessel vasculitis.

The AAV are systemic vasculitides that predominantly affect small-sized vessels and can manifest in a wide variety of ways depending on the target organ(s) involved and the severity of the disease. There are currently no validated diagnostic criteria for AAV and no precise or specific diagnostic test. The American College of Rheumatology (ACR) criteria[14, 15, 27] and the Chapel Hill Consensus Conference (CHCC)[1, 2] definitions are useful tools in the assessment of a patient with vasculitis, possibly AAV, but it is important

to remember that these are classification criteria and nomenclature definitions, respectively, for use in clinical trials and teaching. The diagnostic and classification criteria for systemic vasculitis (DCVAS) study is ongoing to establish, within a few years, diagnostic criteria for the vasculitides[28].

AAV are often, but not invariably, associated with the presence of circulating ANCA: 60% to 90% of cases of GPA and MPA are ANCA-positive mostly the c-ANCA type (with a cytoplasmic labelling pattern on immunofluorescence) and anti-proteinase 3 (PR3) specificity on ELISA for GPA and p-ANCA (with a perinuclear labelling pattern on immunofluorescence) and anti-myeloperoxidase specificity on ELISA for MPA; only 30% to 40% of cases of EGPA are ANCA-positive mostly p-ANCA with anti-myeloperoxidase specificity.

In the appropriate clinical setting, ANCA testing can be extremely useful in the diagnosis of AAV and should be performed by indirect immunofluorescence (IIF) and samples positive for ANCA by indirect immunofluorescence should be tested for proteinase-3 (PR3) and myeloperoxidase (MPO) by ELISA[2, 29, 30]. The sensitivities and specificities of positive tests for cytoplasm-ANCA (cANCA) targeted against PR3 or perinuclear-ANCA (pANCA) targeted against MPO are high. The combination of IIF and ELISA for ANCA testing at diagnosis can be helpful to identify discordant results. For example, a positive pANCA by IIF with PR3-ANCA on ELISA can occur in cocaine-levamisole induced vasculopathy. A positive ANCA by IIF with ELISA results other than PR3-ANCA or MPO-ANCA in ELISA may also be observed with other conditions, such as inflammatory bowel diseases, cystic fibrosis, or infections[31-34]. In the future, other ANCA screening techniques may be used, in combination or instead of IIF and conventional ELISA, including automated image analysis of immunofluorescence patterns, "third-generation PR3-ANCA and MPO-ANCA ELISA", and multiplex technology[35].

Barriers to implementation. A diagnosis of AAV cannot be excluded on the basis of a negative ANCA test. Some Canadian centres may not have easy access to both IIF and ELISA.

Previous Guidance

2014 BSR[21]

ANCA should be checked at diagnosis, relapse, change of therapy, every 6 months while on treatment and annually while off treatment. The results should be available within 1 working day. ANCA should be detected using IIF with ELISA to confirm PR3 or MPO specificity.

CARI[9, 11]

Serum anti-neutrophil cytoplasmic antibody (ANCA) measurement should not be used alone in the initial diagnosis of ANCA-associated vasculitis (AAV) but should be used in combination with the gold standard of tissue diagnosis.

EULAR/EUVAS[6]

We recommend that anti-neutrophilic cytoplasmic antibody (ANCA) testing (including indirect immunofluorescence and ELISA) should be performed in the appropriate clinical context.

Statement 2

Tissue biopsy should be considered in cases of suspected AAV to confirm diagnosis.

We recommend obtaining a tissue biopsy to confirm the diagnosis and rule out vasculitis mimickers in all patients with suspected AAV, when feasible. Tissue biopsy is particularly important in patients who are

ANCA negative or in whom there is a degree of diagnostic uncertainty. Importantly, tissue biopsy should not delay treatment in obvious cases or life-threatening situations. The proportion of patients with disease and a 'positive' biopsy that demonstrate features of granuloma, vasculitis, or both, has been quoted in the region of 70%[36] but the diagnostic yield varies greatly depending on the organ biopsied (see *Appendix 1*). It is important to recognize that a negative or 'non-diagnostic' biopsy does not exclude a diagnosis of AAV. This is particularly true of ENT biopsies for which sensitivity is below 53%.[37] Biopsy can occasionally guide therapeutic decisions and provide valuable prognostic information. For example, a biopsy can help distinguish active renal vasculitis from renal damage in patients with deteriorating renal function and a prior history of renal involvement. However, kidney biopsy goals should be outlined before the biopsy.

Barriers to implementation. Limitations in the timely access to biopsy and biopsy results.

Previous Guidance

EULAR/EUVAS[6]

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.

2. Classification of disease severity in AAV

Statement 3

Patients with AAV should have the extent and severity of their disease categorized as 'severe' at the time of diagnosis and in case of subsequent relapse if they have life- or major organ-threatening manifestations in order to tailor therapy accordingly.

The AAV are a heterogeneous group of disorders and the clinical course can be extremely varied. Therapy should be tailored according to disease extent and severity and we therefore propose that patients with AAV be classified according to disease severity, as this will impact on therapeutic indications and contra-indications.

For the purpose of these Canadian recommendations, the working committee defines severe AAV by the presence of life- or major organ-threatening manifestations, including severe and progressive kidney involvement, severe alveolar hemorrhage, severe gastrointestinal, cardiac, central nervous system and/or eye involvement(s) or any other manifestations considered severe enough to require induction treatment with cyclophosphamide (CYC) or rituximab. Importantly, the recommendation working committee recognizes that these definitions are wide-ranging and not constrained.

The use of existing tools may help to classify disease severity but should not be restrictive, as there are situations in which it remains difficult to readily classify disease severity. Two tools have been previously used for classifying GPA disease extent and severity in trials: the classification into "limited" or "severe" used by the Wegener's Granulomatosis Etanercept Trial (WGET) research group[36, 38] and that adopted by the European Vasculitis (EUVAS) group with localized, early systemic, generalized, severe and refractory diseases (see *Appendix 2*)[39]. These two classifications have many similarities and there is currently no

data to demonstrate that either classification system is superior to the other, although the binomial WGET classification appears simpler to use to the recommendation working committee.

In the RAVE trial[40], GPA and MPA patients were categorized according to the Birmingham vasculitis activity score for Wegener's granulomatosis (BVAS/WG), with severe disease being defined as the presence of one or more of the major BVAS/WG items or disease severe enough to require treatment with CYC. The original (1996 version) five factor score (FFS) is a prognostic scoring system, which was developed by the FVSG and uses five distinct disease features that have been proven in uni- and multivariate analysis to be valuable prognostic markers in EGPA and PAN[41], and has been further validated in MPA[42]. These five prognostic factors include vasculitis-related cardiomyopathy, central nervous system (CNS) involvement, severe gastrointestinal (GI) tract symptoms, renal insufficiency (creatinine >1.58mg/dL or 140 micromol/L) and proteinuria (>1g/day). A FFS = 1 was associated with a 25.9% 5-year mortality and a FFS ≥ 2 (2 or more factors present) was associated with a 45.9% 5-year mortality rate (see *Appendix 2*). The 2009 revised FFS has yet to be validated and therefore cannot be used similarly to score disease severity in EGPA in order to guide therapy (see *Appendix 2*)[43].

Finally, it is important for treating physicians to regularly assess disease severity, as a patient's disease characteristics may change from their baseline presentation and therapy may have to be adjusted accordingly.

Barriers to implementation. None.

Previous Guidance

BSR[8]

At present there are no data that convincingly demonstrate the superiority of one of the classification systems over the other, and there is no consensus among investigators as to which of these 2 sets of disease states should be preferred. At present we recommend the use of either of the EULAR/EUVAS or WGET/VCRC classification.

2014 BSR[21]

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. Organ involvement and function should be systematically assessed in all patients and those with no evidence of organ damage may be considered for alternative induction therapy with MTX or MMF.

EULAR/EUVAS[6]

We recommend that patients with ANCA-associated vasculitis be categorized according to different levels of severity [localized, early systemic, generalized, severe and refractory] to assist treatment decisions.

3. Role of referral centres for vasculitis

Statement 4

Patients with AAV, particularly those with challenging disease, should be managed at, or in collaboration with, a referral centre for vasculitis.

The AAV are a heterogeneous and rare group of disorders and it can be difficult for general internists, rheumatologists, nephrologists and other sub-specialists to maintain expertise in their management. We recommend therefore that patients with vasculitis be managed in collaboration with a referral centre for

vasculitis, when possible (see *Appendix 9* for list and location of all CanVasc centres). Patients presenting with unusual manifestations of AAV and those with refractory disease may especially benefit from the direct input of a referral centre for vasculitis, where there may be better access to subspecialists, as well as access to clinical studies and trials. There is a continuous need for such studies to be carried out on these diseases. As an integral part of this document, most areas of uncertainty where observational, mechanistic and/or therapeutic randomized controlled trials (RCTs) would significantly inform clinical practice and increase knowledge are underscored.

Barriers to implementation. There is a shortage of healthcare providers trained in the assessment and management of patients with AAV in Canada. The creation of CanVasc and identification of CanVasc centres and collaborators across Canada (see *Appendix 9*) aimed to decrease the lag between identification and referral of patients with AAV.

Previous Guidance

BSR[8]

Cases that require the use of alternative therapies should be supervised by specialists and involve close liaison with specialist centres.

2014 BSR[21]

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.

EULAR/EUVAS[6]

We recommend that patients with primary small and medium vessel vasculitis be managed in collaboration with, or at centres of expertise.

4. Remission induction for newly diagnosed disease

Remission induction in severe (organ/life-threatening) newly-diagnosed disease

Recommendation 1

We recommend remission induction therapy with a combination of high dose glucocorticoids and cyclophosphamide in patients with severe newly diagnosed GPA, MPA or EGPA.

We recommend remission induction with cyclophosphamide administered either orally or intravenously for 3-6 months (see *Appendix 4* for cyclophosphamide prescribing protocols). A meta-analysis of the three RCTs that compared continuous oral versus pulsed intravenous cyclophosphamide concluded that remission was achieved equally with one or the other [22, 44-47] but continuous oral cyclophosphamide is associated with a lower rate of relapse on longer term follow-up[48]. The use of oral cyclophosphamide results in higher cumulative doses of the drug and may be associated with a worse side effect profile.

Treatment with intravenous cyclophosphamide pulses should be accompanied by adequate oral or intravenous hydration, and oral or intravenous antiemetic agents. Patients receiving oral cyclophosphamide should also be advised to ensure adequate oral hydration. Oral and/or intravenous mesna (2-mercaptoethanesulfonate sodium) binds and eliminates acrolein, the metabolite of

cyclophosphamide that can be toxic for the bladder mucosa, and can be considered in patients receiving cyclophosphamide. The risk of bladder toxicity is greater with highest cumulative doses and prolonged use of daily oral cyclophosphamide[49]. However, evidence for the effectiveness of mesna in preventing cystitis remains limited and there is no direct evidence for its effectiveness in preventing bladder cancer in humans[49].

Evidence 1B, Strength of recommendation A

Barriers to implementation. The choice of intravenous or oral cyclophosphamide remains with the treating physician, the patient and is often determined in Canada by the ease of access to each preparation.

Previous Guidance

BSR[8]

Initial treatment of patients with primary systemic vasculitis with generalized/threatened vital organ loss should include cyclophosphamide. CYC may be given orally or intravenously (daily oral 2mg/kg or IV pulses at 2-3 wk intervals at a dose of 15mg/kg).

2014 BSR[21]

All patients with newly diagnosed AAV should be considered as having a potentially severe life- or organthreatening disease and therefore should be assessed for treatment with glucocorticoids (GCs) and pulsed i.v. CYC or RTX.

CYC should be given by i.v. pulses initially at 2-week intervals and then every 3 weeks, following the CYCLOPS trial regimen.

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.

EULAR/EUVAS[6]

We recommend a combination of cyclophosphamide (intravenous or oral) and glucocorticoids for remission induction of generalized primary small and medium vessel vasculitis. EULAR/EUVAS

JCS[10]

Patients with injury of major organs such as the kidneys and lungs due to vasculitis are treated with high dose glucocorticoids and CYC. When treatment is begun promptly after diagnosis, remission can be expected within 3-6 months.

KDIGO[13]

Combination treatment with cyclophosphamide plus prednisolone should be used for induction of disease remission when organ function is threatened. Both intravenous (IV) and oral cyclophosphamide show equal clinical efficacy and toxicity.

We recommend that cyclophosphamide and corticosteroids be used as initial treatment [of pauci-immune focal and segmental necrotizing GN].

Recommendation 2

We recommend using high dose glucocorticoids with rituximab as 1st line remission induction therapy in patients with severe GPA or MPA in whom cyclophosphamide is contraindicated or in whom cyclophosphamide presents an unacceptable risk of infertility.

Two RCTs have shown RTX (375mg/m^2 x 4 weekly infusions) to be non-inferior to cyclophosphamide at inducing remission in adults with organ or life-threatening disease[40, 50]. In RITUXVAS (n= 44) remission at 6 months was achieved in 91% and 82% of patients treated with cyclophosphamide and rituximab respectively (a non-significant difference). In the Rituximab for ANCA-associated Vasculitis (RAVE) study (n= 197), 64% of the rituximab group patients were in remission off glucocorticoids at 6 months compared to 54% of the cyclophosphamide group (a non-significant difference). In both RCTs, there was no

evidence that rituximab is a safer alternative to cyclophosphamide (comparable rate of adverse events in both treatment groups, including infections). For patients in whom cyclophosphamide is not tolerated or there is a valid contraindication to cyclophosphamide, we recommend presenting a case for the funding of rituximab, which is more expensive. We believe that preservation of fertility, when there are no clearly effective methods of doing so, is a valid justification for the use of rituximab in certain individuals, especially patients of child-bearing age. The approved regimen for rituximab in Canada is that used in the RAVE and RITUXVAS trials: 4x weekly infusions of 375mg/m2. An alternate regime of 2 x 1g rituximab infusions administered 14 days apart (as used in the treatment of rheumatoid arthritis) may be of comparable efficacy, based on retrospective studies only[51-53]. We therefore recommend using the former regimen when feasible. See *Appendix 4* for rituximab prescribing protocols.

Evidence 1B, Strength of recommendation A

Barriers to implementation. In August 2012, The Canadian Drug Expert Committee (CDEC) approved rituximab for the induction of remission in adult patients with severely active GPA or MPA who have a history of severe reaction to cyclophosphamide, in whom cyclophosphamide is contraindicated or who have failed an adequate trial of cyclophosphamide. Rituximab is currently approved according to these criteria in Ontario, British Columbia, Alberta, Saskatchewan, Nova Scotia and Newfoundland (see *Appendix 7*). The drug approval process is underway in the other provinces.

Previous Guidance

2014 BSR[21]

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.

RTX is as effective as CYC for remission induction of previously untreated patients and is preferable when CYC avoidance is desirable (infertility, infection).

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

2011 FVSG[20]

For first-line treatment, rituximab may be prescribed for the same indications as cyclophosphamide to induce remission of certain GPA and MPA forms. It should preferentially be prescribed to women of childbearing age, especially when they are over 30 years old.

Because rituximab was not superior to cyclophosphamide in 2 randomized–controlled clinical trials, the therapeutic choice for a first disease flare is left to the discretion of the treating physician. That decision should be based on the patient's medical history, morbidity factors preexisting AAV, the vasculitis symptoms to be treated and the patient's opinion.

The dose of 375mg/m2/week x 4 weeks, established to treat lymphoma, was evaluated in the randomized RAVE trial on AAV. Therefore, we recommend that dose with an evidence level of 1.

Guerry et al., 2011[7]

Rituximab is as effective as CYC for remission induction of previously untreated patients. Rituximab may be preferred, especially when CYC avoidance is desirable.

KDIGO[13]

We recommend that rituximab and corticosteroids be used as an alternative initial treatment [of pauci-immune focal and segmental necrotizing GN] in patients without severe disease or in whom cyclophosphamide is contraindicated.

Recommendation 3

Cyclophosphamide dose should be adjusted in patients >60 years of age and in those with renal impairment.

In clinical trials, cyclophosphamide doses are adjusted in patients over 60 years and in those with renal impairment[47, 54, 55] and this has therefore become standard practice. For oral cyclophosphamide we recommend reducing the dose by 25% for those >60 years of age and by 50% in those >75 years of age, as suggested in the EULAR recommendations[6]. Guidance for dose reductions for pulsed intravenous cyclophosphamide is detailed in *Appendix 4*. Results of a French trial (CORTAGE) also showed that an induction regimen with cyclophosphamide pulses at a fixed dose of 500mg per pulse was effective and safe, when compared to 500mg/m2 per pulse, in patients aged over 65 years of age[56].

Evidence 1B, Strength of recommendation B

Barriers to implementation. None.

Previous Guidance

BSR[8]

Continuous low dose oral cyclophosphamide monitoring: For oral administration, if age >60 years the dose of cyclophosphamide should be reduced by 25%. If the age is >75 years the dose should be reduced by 50% to avoid neutropenia. Renal function should be measured alongside FBC monitoring and adjustments to cyclophosphamide dose should be made accordingly.

Pulsed cyclophosphamide monitoring: The standard dose is 15 mg/kg, reduced for age and renal function. Renal function should be measured on the day of each infusion or previous day and adjustments be made to cyclophosphamide dose.

Statement 5

Complete blood count (CBC) and serum creatinine level must be monitored in patients treated with cyclophosphamide. In patients with abnormal CBC results, temporary withholding of cyclophosphamide and subsequent dose adjustments may be necessary depending on the degree of leucopenia.

We suggest monitoring CBC and renal function at 1-2 weekly intervals initially in patients receiving oral and intravenous cyclophosphamide. The nadir white blood cell count usually occurs 10–14 days post-cyclophosphamide infusion. Cyclophosphamide dosing should be adjusted according to serial creatinine measurements. *Appendix 4* details an example of schedule for cyclophosphamide monitoring, which can be adapted based on characteristics (e.g., age, renal disease and comorbidities) of each patient.

Barriers to implementation. None.

Previous Guidance

BSR[8]

Continuous low dose oral cyclophosphamide monitoring: Check full blood count (FBC), weekly for the first month, 2 weekly for the second and third month and then monthly thereafter. Renal function should be measured alongside FBC monitoring and adjustments to cyclophosphamide dose should be made accordingly.

Pulsed cyclophosphamide monitoring: Check the FBC on the day of the pulse or previous day. Renal function should be measured on the day of each infusion or previous day and adjustments be made to cyclophosphamide dose.

2014 BSR[21]

Patients on CYC should be monitored regularly for leucopenia and the dose should be reduced if there is CYC induced leucopenia/neutropenia

Recommendation 4

We recommend that the remission induction therapy with cyclophosphamide, combined with glucocorticoids, lasts a minimum of 3 to a maximum of 6 months. Once remission is achieved, cyclophosphamide should be stopped and switched to a different maintenance therapy.

Remission is defined by EULAR/EUVAS as the 'complete absence of disease activity attributable to active vasculitis[39]. The main RCTs of remission induction therapy have achieved successful remission within 3-6 months[40, 47, 54, 57] and a maximum of 6 months of cyclophosphamide is now considered the norm. We recommend that patients be switched to maintenance therapy after 3-6 months of remission induction therapy with cyclophosphamide providing remission has been achieved. If remission is delayed beyond this time, then the disease should be considered refractory and alternate therapies sought.

Evidence 1B, Strength of recommendation A

Barriers to implementation. None.

Previous Guidance

BSR[8]

Current clinical practice considers a transfer to maintenance therapy at 3 months or within 3 and 6 months if remission is delayed. The total duration of treatment with cyclophosphamide should not usually exceed 6 months.

2014 BSR[21]

Each individual course of CYC should be a minimum of 3 months and should not exceed 6 months.

Following achievement of successful remission, CYC should be withdrawn and substituted [with either AZA or MTX. MMF or leflunomide may be used as alternatives for intolerance or lack of efficacy of AZA or MTX].

JCS[10]

When treatment is begun promptly after diagnosis, remission can be expected within 3 to 6 months.

KDIGO[13]

We suggest discontinuing CYC therapy after 3 months in patients who remain dialysis-dependent and who do not have any extra renal manifestations.

Recommendation 5

We recommend that glucocorticoids should be given in adults at an initial dose of 1 mg/kg/day prednisone-equivalent for remission induction purposes. This may be preceded by pulsed methylprednisolone (0.5 to 1 g/day for 1 to 3 days) in patients with life threatening disease and/or major organ involvement.

Most of the RCTs looking at remission induction and maintenance immunosuppression therapies in adults with AAV have used an initial glucocorticoid dose of 1mg/kg/day (with maximum doses at 60-80mg/day)[32-

[35] and this has become standard practice; although, there have been no RCTs comparing different initial doses of glucocorticoids. We recommend continuing 1mg/kg/day for a maximum of 1 month with a subsequent gradual taper, which should be adjusted according to the patient's clinical course. Examples of glucocorticoid taper regimens are given in *Appendix 4*. In life threatening disease and/or in patients with major organ involvement where rapid onset of action is needed oral glucocorticoids may be preceded by pulsed intravenous methylprednisolone 0.5-1g/day for 3 consecutive days.

Evidence 2A, Strength of recommendation B

Barriers to implementation. None.

Previous Guidance

BSR[8]

Steroids are usually given as daily oral prednisolone as described by the regimen used in CYCAZAREM (starting dose 1mg/kg/day).

2014 BSR[21]

Induction therapy for AAV includes treatment with high dose GCs in combination with another immunosuppressive agent (CYC, RTX). GCs are usually given as daily oral prednisolone, initially at relatively high doses (1 mg/kg up to 60 mg), with the dose rapidly reduced to 15mg prednisolone at 12 weeks.

EULAR/EUVAS[6]

We recommend the use of high-dose glucocorticoids as an important part of remission induction therapy.

Recommendation 6

Prophylaxis against *Pneumocystis jiroveci* infection should be given to patients receiving cyclophosphamide or rituximab. This prophylaxis consists, in the absence of allergy, of trimethoprim/sulfamethoxazole compounds (800/160mg 1 tablet 3 times per week or 400/80mg daily).

While there are no RCTs evaluating the benefit of *Pneumocystis jiroveci* infection prophylaxis in the AAV patients treated with cyclophosphamide, there are numerous reports of this infection in AAV patients treated with glucocorticoids and cyclophosphamide[58, 59] or rituximab[60], and several studies that assessed the effectiveness of *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis among non-HIV immunocompromised patients[61]. There are also several case reports of PJP occurring in patients several months after withdrawal of induction immunosuppression and we therefore suggest PJP prophylaxis be continued for at least 3 months after cessation of cyclophosphamide[60, 62]. The optimal duration of PJP prophylaxis after rituximab-based induction, when no reinfusion is planned, is unknown. There is no consensus for PJP prophylaxis in patients receiving high-dose glucocorticoids alone.

It should be noted that trimethoprim/sulfamethoxazole compounds used at these low doses for PJP prophylaxis are usually safe in combination with methotrexate but not when used at higher therapeutic doses (i.e., 800mg/160mg, twice daily). Patients in whom trimethoprim/sulfamethoxazole compounds are contraindicated (e.g., due to sulfa allergies) should be given alternate prophylaxis with dapsone (100mg daily) or atovaquone (1500mg daily). Dapsone is often the most practical alternative to trimethoprim/sulfamethoxazole compounds in Canada, but prescribers must be aware of its potential

complications, in particular the risk of hemolytic anemia, even in the absence of glucose-6-phosphate dehydrogenase (G6PD) deficiency. Aerosolized pentamidine (300mg given monthly via a nebulizer) may not be as effective as trimethoprim/sulfamethoxazole for PJP prophylaxis [63].

Evidence 3, Strength of recommendation C

Barriers to implementation. Atovaquone use is restricted in Canada owing to its high cost.

Previous Guidance

2014 BSR[21]

Trimethoprim/sulphamethoxazole should be considered as prophylaxis against Pneumocystis jiroveci (PCJ) in patients receiving intense immunosuppression (CYC) and/or other induction treatment using high-dose GCs.

Patients receiving CYC and GCs should be considered to receive trimethoprim/sulphamethoxazole 960mg [i.e., trimethoprim/sulphamethoxazole, 800/160 mg] thrice weekly as prophylaxis against pneumocystis. [The risks of PCJ infection with RTX are unknown but probably relate to the concomitant GC].

EULAR/EUVAS[6]

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. The use of pentamidine in the event of an adverse reaction or contraindication to trimethoprim/sulphamethoxazole is not cost-effective.

2011 FVSG[20]

Prophylactic cotrimoxazole (SMX/TMP 400mg/80mg) is recommended for all patients [in the absence of allergy], with the dose being adjusted to renal function.

JCS[10]

To prevent Pneumocystis pneumonia, SMX/TMP compounds should be administered daily or 2 tablets 2-3 times per week. (Guidelines for PAN treated with cyclophosphamide).

Recommendation 7

There is insufficient evidence to support a recommendation that plasma exchange be used as first line therapy in any AAV patients. Plasma exchange may be a reasonable adjuvant therapy for patients who clinically deteriorate due to active vasculitis despite ongoing remission induction therapy with high-dose glucocorticoids and cyclophosphamide or rituximab.

There is controversy around the efficacy of adjuvant plasma exchange in patients with AAV. Small randomized controlled trials report conflicting evidence of improved renal survival and mortality.[64-66] The largest trial to date, the MEPEX trial, provides insufficient evidence of any sustained benefit, was limited to very ill patients nearing or requiring dialysis (with a serum creatinine 500 mol/L [5.8 mg/dl]) and did not directly address the issue of plasma exchange as an adjuvant since MEPEX compared plasma exchange to pulse steroids.[67] Furthermore, a contemporary meta-analysis demonstrated that even with MEPEX added to all other randomized trial evidence contained insufficient evidence to support a definite treatment effect of plasma exchange in AAV. Uncontrolled, retrospective data suggests a role in severe pulmonary hemorrhage but is unconvincing[66-69]. The PEXIVAS study is an international study with participating centres throughout Europe, the US and Canada, Mexico, Japan, Australia and New Zealand[70], is addressing the safety and

efficacy of plasma exchange as an adjuvant to glucocorticoids and standard remission induction immunosuppression in patients with renal disease or pulmonary hemorrhage. Until the final results of the study are known (likely in 2017), patients with either renal manifestations of AAV resulting in a reduced glomerular filtration rate or those with pulmonary hemorrhage may be referred to centres participating in PEXIVAS. In centres where this is not feasible, the use of plasma exchange can be restricted to patients who have refractory disease activity despite standard remission induction therapy with high dose glucocorticoids combined with cyclophosphamide or rituximab. We do not recommend that plasma exchange be used as an alternative to pulsed methylprednisolone as previously investigated in the MEPEX trial[64]. Plasma exchange may increase the risk of infections and bleeding and physicians should be aware of these possible complications of therapy. If plasma exchange is used, we recommend 7 plasma exchanges (of 60ml/kg or 1 plasma volume exchange) within 14 days using albumin as the replacement fluid except in patients bleeding or with a high risk of bleeding (e.g. after renal biopsy). For such patients, consideration should be made to using either a full or partial exchange with fresh frozen plasma (e.g. with full fresh frozen plasma replacements in patients with pulmonary haemorrhage and until acute bleeding stops, gradually replaced thereafter by albumin only; with 50% fresh frozen plasma and 50% albumin replacements the day and the following day of a renal biopsy) or monitoring and replacement of fibrinogen with cryoprecipitate.

Evidence 4, Strength of recommendation D

Barriers to implementation. Limitations in the access to centres at which plasma exchange treatment is available.

Previous Guidance

BSR[8]

Patients with primary systemic vasculitis presenting with severe renal failure (creatinine >500) should be treated with cyclophosphamide and steroids (as per regimen) with adjuvant plasma exchange (7 x 4l exchanges over 2 weeks). Treatment with plasma exchange should be considered in those with other life-threatening manifestations of disease such as pulmonary haemorrhage.

2014 BSR[21]

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. Treatment with PLEX should also be considered in those with other life-threatening manifestations of disease such as pulmonary haemorrhage.

CARI[9, 11]

Plasma exchange should be preferred to pulse methylprednisolone as an adjunctive therapy in the initial treatment of severe ANCA-associated systemic vasculitis (AASV) causing necrotising glomerulonephritis and acute kidney failure (creatinine >500 µmol/L).

Cochrane Review of Renal Vasculitis[22]

Plasma exchange reduces the risk of end-stage kidney disease in patients presenting with severe acute kidney injury.

EULAR/EUVAS[6]

We recommend plasma exchange for selected patients with rapidly progressive, severe renal disease in order to improve renal survival.

JCS[10]

Plasmapharesis may also be performed for patients with more severe disease.

KDIGO[13]

We recommend the addition of Plasmapharesis for patients requiring dialysis or with rapidly increasing serum creatinine. We suggest the addition of Plasmapharesis for patients with diffuse pulmonary haemorrhage.

Remission induction for limited or non-severe (non organ- and non life-threatening), newly-diagnosed disease

Recommendation 8

In patients with limited and/or non-severe GPA, which is non-life threatening and without any major organ involvement, remission induction regime with methotrexate in combination with glucocorticoids can be used.

In patients with non-severe ("limited") GPA, methotrexate (20–25 mg per week, orally or subcutaneously; adjusted to renal function – see *Appendix 4*) can be used as an alternative to cyclophosphamide, in combination with glucocorticoids, and continued for longer than 12 months if effective. Few studies have found that methotrexate is non-inferior to cyclophosphamide at inducing remission in these patients[71, 72]; although, the time-to-remission may be longer with methotrexate if started initially at a lower starting dose of 15mg per week (NORAM; with a gradual increase of the dose up to 20–25 mg per week at month 3)[73]. The long-term follow up data of the NORAM study suggests also that there is a higher rate of relapse in patients following methotrexate-based induction, if it is stopped after 12 months[74].

The use of mycophenolate mofetil as an alternative to cyclophosphamide in non-severe GPA was investigated in a trial (MYCYC; ClinicalTrials.gov Identifier: NCT00414128). Preliminary results suggest a similar rate of remission but a higher rate of subsequent relapse as well[75]. The data on the use of trimethoprim/sulfamethoxazole, alone or with glucocorticoids, for very limited GPA without any major organ involvement, remains limited and can therefore not support a recommendation that it can be used as an alternative to cyclophosphamide or methotrexate[76].

Evidence 1B, Strength of recommendation A

Barriers to implementation. None.

Previous Guidance

BSR[8]

Recommendation for patients with localized/early systemic disease (without threatened vital organ involvement). Initial treatment of primary systemic vasculitis with localized/early systemic disease (without threatened vital organ disease or damage) may include Methotrexate (15 mg/week escalating to a maximum of 20–25 mg/week by week 12) with oral steroids (regimen as per Table 2).

2014 BSR[21]

MTX (up to 25-30mg 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.

MTX should not be used in patients with moderate or severe renal impairment. MMF may be an alternative to MTX.

CARI[9, 11]

Methotrexate is an alternative to cyclophosphamide-based induction therapy in patients with milder, early disease (serum creatinine <150 mmol/L).

EULAR/EUVAS[6]

We recommend a combination of Methotrexate (oral or parenteral) and glucocorticoids 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)

Recommendation 9

Patients with non-severe EGPA or non-severe MPA without renal involvement can be treated with glucocorticoids alone for remission induction. At present, there is no consensus on the use of any immunosuppressant agents in combination with glucocorticoids in patients with EGPA or MPA that are non-severe (including those with mononeuritis multiplex).

EGPA and MPA patients with non-severe disease (FFS of zero, and no renal disease) have a 5-year mortality rate of 11.9%[41] and as such this subset of patients may not require an additional immunosuppressant agent to induce remission. A study of MPA, EGPA and PAN patients found that glucocorticoids alone induced remission in almost 80% of patients although this remission was sustained in less than 50% of patients[77, 78]. It is acceptable to treat patients with non-severe non-life threatening disease without renal disease or any other major organ involvement, with glucocorticoids alone, introducing additional immunosuppressant therapy for relapsing, deteriorating or glucocorticoid-resistant disease. Close monitoring of patients treated with glucocorticoids alone is mandatory to detect early any such deterioration of their condition and promptly add an immunosuppressant as needed.

The optimum treatment strategy in patients with non-severe disease but peripheral nervous system (PNS) involvement remains controversial. There is insufficient evidence to support a recommendation that the systematic prescription of an immunosuppressant, in combination with glucocorticoids, as first-line therapy is more effective then glucocorticoids alone on the neurologic recovery. Nevertheless, PNS involvement, particularly mononeuritis multiplex, can be severe and/or rapidly progressive, with a risk of significant long-term disability; in such cases a more aggressive treatment with additional immunosuppressant therapy (e.g., with azathioprine, methotrexate or, in the most severe and progressive cases, cyclophosphamide) must be considered[79]. The results of the FVSG CHUSPAN2 trial (expected in late 2015), which looked at the treatment of patients with EGPA, MPA and PAN with a FFS of 0 (including some patients with PNS involvement) with glucocorticoids alone or glucocorticoids with azathioprine, may provide further insight into the treatment of this subgroup of patients.

Evidence 2B, Strength of recommendation C

Barriers to implementation. None.

Previous Guidance

None specifically, except for general comments in the 2007 French Vasculitis Study Group document[12].

5. Remission maintenance therapy

Remission is defined by EULAR/EUVAS as the complete absence of clinical disease activity, including vasculitis and granulomatous manifestations whether receiving immunosuppressive therapy or not[39] (see *Appendix 3*).

Recommendation 10

In patients with severe AAV in remission after a combined cyclophosphamide-glucocorticoid-based induction treatment, maintenance therapy can be based on azathioprine or methotrexate, initially in combination with low-dose glucocorticoids. Leflunomide or mycophenolate may be alternative agents in patients not tolerating or with contra-indications to azathioprine and methotrexate.

Long-term toxicity makes cyclophosphamide an unattractive option for maintenance of remission after successful remission induction in AAV. Following remission induction therapy with cyclophosphamide, the CYCAZAREM trial found that azathioprine (2mg/kg/day) was as effective as continuous cyclophosphamide at maintaining remission and was associated with fewer side effects[54]. Methotrexate (20-25 mg/week) was proven to be of comparable efficacy to azathioprine after remission induction with cyclophosphamide[55, 80]. Methotrexate should be used with caution in patients with renal impairment. The use of leflunomide in maintaining remission is less well studied but results of one prematurely-ended randomized study indicated that, at a dose of 30 mg/day, leflunomide was more effective than methotrexate at preventing relapse despite being associated with a higher rate of adverse events[81]. At present, in parallel with practice in rheumatoid arthritis, a dose of 20 mg/day can be used and is likely associated with a lower frequency of side effects[82]. Mycophenolate mofetil (2-3g/day) has been studied in this setting but has been found in one randomized controlled study to be less effective than azathioprine at maintaining remission and should therefore not be used as a first-line agent for maintenance[57].

Evidence 1B, Strength of recommendation B

Barriers to implementation. None.

Previous Guidance

BSR[8]

In patients with primary systemic vasculitis who have achieved successful remission cyclophosphamide should be withdrawn and substituted with either azathioprine or Methotrexate in combination with oral steroids.

2014 BSR[21]

Following achievement of successful remission, CYC should be withdrawn and substituted with either AZA or MTX. MMF or leflunomide may be used as alternatives for intolerance or lack of efficacy of AZA or MTX.

CARI[9, 11]

Once disease remission has been established, azathioprine in combination with lower doses of prednisolone should be used to prevent disease relapse.

EULAR/EUVAS[6]

We recommend remission-maintenance therapy with a combination of low-dose glucocorticoids therapy and, either azathioprine, Leflunomide or Methotrexate.

JCS[10]

Following remission, doses of glucocorticoids are promptly decreased, and Cyclophosphamide is switched to other milder immunosuppressants to maintain remission for 1-2 years.

KDIGO[13]

We recommend azathioprine 1-2mg/kg/day orally as maintenance therapy. We suggest MMF, up to 1g twice daily, be used for maintenance therapy in patients who are allergic to, or intolerant of, azathioprine. We recommend Methotrexate (maximum 25mg/week) for maintenance therapy in patients intolerant of azathioprine and MMF but not if GFR is <60ml/min. We recommend no maintenance therapy in patients who are dialysis-dependent and have no extra renal manifestations of disease.

Recommendation 11

In patients with severe AAV in remission after a combined cyclophosphamide-glucocorticoid-based induction treatment, maintenance therapy with rituximab infusions is an alternative to azathioprine, especially for those patients with PR3-ANCA-positive GPA.

Results of several retrospective studies on the pre-emptive use of rituximab for maintenance following induction with rituximab or cyclophosphamide in combination with glucocorticoids in patients with GPA or MPA have suggested it is safe and effective[53, 83-85]. The results of these studies indicate that it may even be superior to azathioprine or methotrexate to prevent relapses[84, 85]. The results of the FVSG MAINRITSAN trial showed that rituximab 500mg at remission, 2 weeks later, then every 6 months up to month 18 is superior to azathioprine to prevent relapses (relapse rates of 5.3% versus 29.3% at 28 months post-remission, respectively), with a comparable safety profile[86]. Because the patients in this study were predominantly PR3-ANCA-positive GPA patients, the findings could not be generalized to all AAV patients. The role of rituximab in MPA, MPO-ANCA-positive GPA or ANCA-negative patients has to be further studied. The optimal duration, dose and interval between each rituximab infusion have to be further investigated. Whether or not the monitoring of CD19 B cell count, ANCA titer or other biological parameters may guide the need of rituximab re-infusion is also under study (MAINRITSAN 2; ClinicalTrials.gov Identifier: NCT01731561)[53].

Evidence 1B, Strength of recommendation A

Barriers to implementation. Rituximab maintenance funding is not yet approved by Health Canada.

Previous Guidance

2014 BSR[21]

RTX may also be used as maintenance therapy, and re-treatment can be decided based on fixed interval regimens or evidence of relapse.

Patients should continue maintenance therapy for at least 24 months following successful disease remission. Patients with GPA or patients who remain PR3-ANCA positive should continue immunosuppression for up to 5 years. RTX should be given every 4-6 months for 2 years. For maintenance therapy the recommended RTX regimen uses 1 g.

2011 FVSG[20]

In light of our present knowledge based on the results of retrospective studies, rituximab maintenance therapy can apparently be prescribed. Preliminary results [of the MAINRITSAN trial] clearly indicate fewer relapses in the rituximab arm.

Statement 6

To date there is no definitive evidence to guide decisions for maintenance therapy after remission induction with rituximab.

At least theoretically, 4 possible strategies for maintenance therapy after rituximab induction exist: i) patients, at least those with PR3-ANCA-positive GPA, may be re-treated with rituximab at regular intervals regardless of their disease state, similarly to what can be done after cyclophosphamide-based induction therapy[87]; ii) patients may be re-treated with rituximab in response to laboratory parameters i.e. repopulation of peripheral CD19 B-cell counts or rising ANCA titers[53]; iii) patients may be re-treated with rituximab (or another remission-inducing agent) only on the grounds of clinical relapse[88, 89]; and iv) patients may be maintained on conventional maintenance immunosuppressant drugs such as azathioprine, methotrexate, mycophenolate or leflunomide[83, 90]. It is not yet known which of these strategies is optimal. The RITAZAREM (ClinicalTrials.gov Identifier: NCT01697267; results expected in 2018) trial is comparing azathioprine versus rituximab (1g every 4 months for 20 months) for maintenance in patients with relapsing ANCA-associated GPA or MPA who achieve remission with rituximab (4 x 375mg/m^2).

Barriers to implementation. Rituximab maintenance funding is not yet approved by Health Canada.

Previous Guidance

2014 BSR[21]

Following achievement of successful remission, CYC should be withdrawn and substituted with either AZA or MTX. MMF or leflunomide may be used as alternatives for intolerance or lack of efficacy of AZA or MTX.

RTX may also be used as maintenance therapy, and re-treatment can be decided based on fixed interval regimens or evidence of relapse.

Guerry et al., 2011[7]

Pre-emptive re-treatment may be considered in order to reduce relapse rates.

Statement 7

Low dose glucocorticoids should be part of the initial remission maintenance therapy after remission is achieved; there is not enough evidence yet to support further recommendation on the optimal duration of low dose glucocorticoids.

Glucocorticoids should be gradually tapered to a dose of 5-10 mg/day within 3 to 6 months of achieving remission (see *Appendix 4*: examples of glucocorticoid regimens used in RCTs). No randomized controlled trials have yet assessed the optimum duration of glucocorticoids in remission maintenance. One large meta-analysis looked at previous AAV studies that incorporated glucocorticoids into their treatment protocols. Relapse rates were higher in patients who discontinued glucocorticoids within 12 months of achieving remission[91]. Results of another single centre study from Chapel Hill have indicated that long-term prednisone treatment even at low dose does not limit the risk of relapse but can increase the risk of infections[92]. The VCRC TAPIR study (ClinicalTrials.gov Identifier: NCT01940094) aims at evaluating the effects of continuing low-dose prednisone as compared to stopping prednisone treatment

entirely in patients with GPA in remission after a disease flare that occurred within the past 12 months (results expected in mid-2016).

Barriers to implementation. None.

Previous Guidance

2014 BSR[21]

GCs are usually given as daily oral prednisolone, initially at relatively high doses (1 mg/kg up to 60 mg), with the dose rapidly reduced to 15mg prednisolone at 12 weeks. Longer courses of GCs may cause increased risk of infection but may be associated with fewer relapses.

EULAR/EUVAS[6]

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

Recommendation 12

We recommend the use of azathioprine, methotrexate or their alternatives (as per Recommendation 10 and 11) for remission maintenance therapy to be continued for a minimum of 18 months after successful remission induction. There is not enough evidence yet to support further recommendation on the optimal duration of their use for maintenance.

To date, the optimum duration of maintenance immunosuppressant therapy is not known. There are retrospective studies suggesting that relapse rates are lower in patients continuing on maintenance therapy beyond 36 months[93]. The REMAIN study is a EUVAS RCT which has randomized patients, after successful remission induction therapy, to receive 24 months of low-dose glucocorticoid and azathioprine or 48 months low-dose glucocorticoid and azathioprine (results expected in 2015). In the future, there may be data to support tailoring the duration of maintenance therapy according to clinical and biological predictors of relapse, such as the presence of PR3 versus MPO ANCA, but at present work is ongoing in this field and no firm conclusions have been reached that can impact practice[94-96]. Until these results are available we recommend that maintenance therapy be continued for at least 18 months after successful remission induction, then subsequently discontinued or not at the physician's discretion and according to individual patient's characteristics, treatment tolerance and understanding of their subsequent risk of relapse.

Evidence 3, Strength of recommendation C

Barriers to implementation. None.

Previous Guidance

BSR[8]

Patients with primary systemic vasculitis should continue maintenance therapy for at least 24 months following successful disease remission. Patients with WG or who remain ANCA positive should continue immunosuppression for up to 5 years.

2014 BSR[21]

Patients should continue maintenance therapy for at least 24 months following successful disease remission. Patients with GPA or patients who remain PR3-ANCA positive should continue immunosuppression for up to 5 years. RTX should be given every 4-6 months for 2 years. For maintenance therapy the recommended RTX regimen uses 1 g.

EULAR/EUVAS[6]

Remission maintenance therapy should be continued for at least 18 months.

2011 FVSG[20]

The optimal duration of AAV treatment has not yet been established. The total treatment duration [when using rituximab for maintenance] is 18 months to 2 years, by analogy with the results of clinical trials evaluating immunosuppressant(s)

KDIGO[13]

We suggest continuing maintenance therapy for at least 18 months in patients who remain in complete remission.

Recommendation 13

The use of trimethoprim/sulfamethoxazole (800/160mg twice daily) as remission maintenance therapy can be considered in GPA as an adjuvant to immunosuppressant or after the cessation of maintenance immunosuppressive treatment.

The use of full dose trimethoprim/sulfamethoxazole (800/160mg, twice daily) as remission maintenance monotherapy has been associated with a higher overall relapse rate than that observed with conventional remission maintenance agents[97, 98]. Full dose trimethoprim/sulfamethoxazole has demonstrated efficacy at preventing upper airway/ENT disease relapse[76, 99], but has no proven benefit at reducing any other form of disease relapse. It should only be used as an adjunct agent or after completion of the maintenance immunosuppressive therapy. It should not be used as remission maintenance monotherapy. Due to important drug interactions, it should not be used at this high dose in conjunction with methotrexate but is safe as an adjunct with azathioprine and leflunomide.

Evidence 3, Strength of recommendation C

Barriers to implementation. None.

Previous Guidance

BSR[8]

There is also evidence for the use of trimethoprim/sulfamethoxazole in maintaining disease remission.

CARI[9, 11]

Prolonged oral co-trimoxazole may decrease the incidence of upper airway disease relapse in patients with Wegener's granulomatosis (WG) but has not been shown to reduce relapse rates in other organs

EULAR/EUVAS[6]

The addition of trimethoprim/sulfamethoxazole to standard remission maintenance can reduce the risk of relapse in WG.

KDIGO[13]

We suggest trimethoprim/sulfamethoxazole as an adjunct to maintenance therapy in patients with upper respiratory tract disease.

Recommendation 14

Topical therapies may be considered, in combination with the systemic therapy and in collaboration with ENT subspecialists, to alleviate the symptoms of upper airway and ENT disease.

The consequences of upper airway and ENT disease often continue to manifest (as damage) despite achieving successful disease remission. It should be noted that such persistent upper airway symptoms such as nasal crusting or congestion, and symptoms due to stenosis of nasal passage or upper airway are thus not always attributable to active granulomatous disease and therefore do not necessarily require additional immunosuppressant therapy. Therapies aimed at managing these symptoms are often essential for patient well-being. Nasal and sinus rinses with saline may be helpful. Topical antibiotic creams and ointments, such as mupirocin or fusidic acid, can also be considered but are usually of limited benefit. There are no clinical trial data to support their use for patients with symptomatic nasal crusting and ulcers, including those with chronic nasal carriage of *Staphylococcus aureus*. These local therapies have not been shown to lower the risk of relapse or progression from a limited ENT to a more systemic form of the disease in GPA patients.

Evidence 3, Strength of recommendation C

Barriers to implementation. There is a shortage of ENT subspecialists trained in the assessment and management of patients with AAV in Canada.

Previous Guidance

BSR[8]

Cyclical nasal application of mupirocin should be considered in patients with WG.

2014 BSR[21]

Staphylococcus aureus treatment with long-term nasal mupirocin should be considered. Patients should have bacterial swabs at baseline and every 6-12 months.

EULAR/EUVAS[6]

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.

6. Relapsing disease

Relapsing disease is defined by EULAR/EUVAS as the re-occurrence or new onset of disease activity attributable to active vasculitis-related inflammation (see *Appendix 3*)[39]. It is useful to define the severity of disease at the time of relapse in order to guide treatment decisions. It must be recognized, however, that no classification criteria or scoring systems (including the FFS or Birmingham Vasculitis Activity Score, BVAS) have been validated in the context of relapsing disease as opposed to newly diagnosed disease. In the context of clinical trials, EULAR/EUVAS suggest that relapses should be recorded as either minor or major. A major relapse is defined as the re-occurrence or new onset of potentially organ- or life-threatening disease activity that cannot be treated with an increase of glucocorticoids alone and requires further escalation of treatment. All other relapses should be classified as minor. This classification strategy has not been validated but may prove to be a useful tool in the setting of relapsing disease. In RAVE, severe GPA or MPA flares or relapses were defined as with a BVAS/WG score of 3 or more (≥3 minor items or 1 major item)[40].

Recommendation 15

We recommend remission induction of a major organ- or life-threatening relapse with either cyclophosphamide or rituximab in conjunction with high dose glucocorticoids. In patients who already received cyclophosphamide for initial remission induction or a previous disease flare, we recommend using rituximab for remission re-induction.

The RAVE study showed that rituximab was more effective at month 6 than cyclophosphamide for remission induction in relapsing disease (67% vs. 42% of relapsing patients achieved remission with rituximab vs. cyclophosphamide, respectively)[40]. At 18 months, without any maintenance therapy after rituximab-based induction, this difference with the conventional staged cyclophosphamide-azathioprine treatment persisted, though it was no longer a significant difference[88]. We therefore recommend using rituximab for remission re-induction in patients previously treated with cyclophosphamide (irrespective of the cumulative dose previously received), those in whom cyclophosphamide is contraindicated, in whom cyclophosphamide was previously ineffective or not tolerated, and for patients wishing to preserve fertility (see *Appendix 4* for rituximab prescribing). For the patients in whom rituximab is contra-indicated or who fail to respond to rituximab, given at appropriate doses, retreatment with cyclophosphamide can still be considered (in the absence of a clear contra-indication, such as severe allergy). Such patients presenting with complex refractory disease may especially benefit from the direct input of a referral centre for vasculitis (see Statement 4).

Evidence 1B, Strength of recommendation A

Barriers to implementation. Current funding approval in Canadian provinces (see *Appendix 7)* for the use of rituximab for remission induction is for patients with newly diagnosed or relapsing disease only in the context of a contraindication to cyclophosphamide, including the previous administration of >25g of cumulative dose of cyclophosphamide.

Previous Guidance

BSR[8]

Major relapse is treated with cyclophosphamide as in remission induction and an increase in prednisolone to 30 mg/day, intravenous methyl prednisolone or plasma exchange may also be considered.

2014 BSR[21]

A major relapse may be treated with RTX or a further course of CYC with an increase in prednisolone.

EULAR/EUVAS[6]

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.

2011 FVSG[20]

Considering treatment for GPA or MPA relapse, rituximab should preferentially be chosen for patients who have received at least one full cyclophosphamide cycle (either 6–9 infusions or a cumulative dose >10g), as recommended in the French National Guidelines endorsed by the Haute Autorité de santé(HAS)

KDIGO[13]

We recommend treating patients with severe relapse of ANCA vasculitis (life- or organ-threatening) according to the same guidelines as for the initial therapy.

Recommendation 16

There is insufficient evidence to support a recommendation that plasma exchange be used as first line therapy in all patients with relapsing AAV with severe renal (GFR <50ml/min) or pulmonary hemorrhage. Plasma exchange may be a reasonable adjuvant therapy for patients who clinically deteriorate due to active relapsing vasculitis despite ongoing remission induction therapy with high-dose glucocorticoids and cyclophosphamide or rituximab.

See Recommendation 7 for more details on plasma exchange.

Evidence 4, Strength of recommendation D

Barriers to implementation. Limitations in the access to centres at which plasma exchange treatment is available.

Previous Guidance

BSR[8]

Major relapse is treated with cyclophosphamide with an increase in prednisolone; intravenous methylprednisolone or plasma exchange may also be considered.

2014 BSR[21]

Addition of i.v. methylprednisolone or PLEX may also be considered [for major relapse].

Recommendation 17

We recommend that relapses that are non-severe, i.e. non-life and non-organ threatening, be treated with an increase in glucocorticoid dose in addition to optimizing the patient's concurrent immunosuppressant agent.

The treatment of non-life and non-organ threatening disease relapses should include increasing the glucocorticoid dose and optimizing the patient's concurrent immunosuppressant agent. There is no evidence to suggest superiority of methotrexate over azathioprine, and data on leflunomide, mycophenolate mofetil, abatacept or rituximab is very limited in this setting and mostly related to GPA[100, 101]. Furthermore, it is not known if patients with disease relapse after cessation of maintenance therapy should be treated with a more prolonged course of maintenance immunosuppressant therapy following their relapse. We therefore cannot make further or specific recommendations regarding the choice or change of immunosuppressant agent and the duration of therapy following a non-major disease relapse.

Evidence 3, Strength of recommendation C

Barriers to implementation. None.

Previous Guidance

BSR[8]

Minor relapse is treated with an increase in prednisolone dosage and optimization of concurrent immunosuppression.

2014 BSR[21]

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.

KDIGO[13]

We suggest treating other relapses of ANCA vasculitis by reinstituting immunosuppressive therapy or increasing its intensity with agents other than cyclophosphamide, including instituting or increasing dose of glucocorticoids, with or without azathioprine or MMF.

7. Refractory disease

The term refractory disease applies to patients who fail to attain remission following 'standard' induction therapy, which is tailored according to the severity and extent of disease. The precise timing of when disease should be labeled as refractory is less clear. EULAR/EUVAS propose that refractory disease is defined as either i) unchanged or increased disease activity after 4 weeks of appropriate-dose cyclophosphamide with glucocorticoids; ii) lack of response defined as ≤ 50% reduction in the disease activity score and/or lack of improvement in at least 1 major item after 4-6 weeks of treatment; or, iii) chronic persistent disease, defined as the presence of at least 1 major or 3 minor items on the Birmingham Disease Activity Score (BVAS) list despite 8 weeks of treatment[39]. These EULAR/EUVAS definitions of refractory disease are complex and difficult to apply in every day clinical practice. We therefore propose a simplified version: refractory disease being disease that is unchanged or worsened despite 6 weeks of appropriate remission induction therapy or the presence of persistent disease activity after 3 months of appropriate remission induction therapy.

Consideration should be given to the referral of patients with refractory disease to a centre for vasculitis. In all cases of apparent refractory disease it is imperative to re-evaluate the patient to ensure the following:

i) the diagnosis is correct,
ii) alternate infectious/neoplastic diagnoses have been excluded,
iii) the treatment, including choice of drug(s), dosage and duration, was appropriate.

Having considered the above and confirmed a patient has refractory disease, the following recommendations should be taken into account for the ongoing management of this challenging patient group.

Recommendation 18

We recommend the use of rituximab, in combination with glucocorticoids, in patients with severe GPA or MPA who fail to respond to cyclophosphamide as remission induction therapy.

RITUXVAS[50] and RAVE[40] trials demonstrated that rituximab is non-inferior to cyclophosphamide at inducing remission in patients with severe or life threatening manifestations of AAV. Several retrospective series have reported the efficacy of rituximab in patients with refractory disease[51, 53]. We recommend that patients who have an inadequate response to either 6 infusions of appropriate dose of IV cyclophosphamide (see *Appendix 4*) or 3 months of oral cyclophosphamide, be treated with rituximab (see *Appendix 4* for Rituximab prescribing advice).

Evidence 3, Strength of recommendation C

Barriers to implementation. Rituximab is approved in Canada for these patients, but access may be limited by the delay to obtain a timely approval for the drug coverage, which can vary according to the province.

Previous Guidance

***BSR*[8]**

The use of infliximab, intravenous immunoglobulin, antithymocyte globulin, CAMPATH-1H (alemtuzumab, anti-CD52), deoxyspergualin and rituximab in refractory disease is still under investigation.

Rituximab may be considered for the treatment of refractory vasculitis or the treatment of vasculitis when conventional agents are contra-indicated.

***2014 BSR*[21]**

RTX is more effective than CYC in refractory AAV. If the patient has not had previous treatment with RTX before, then the first choice is RTX.

***EULAR/EUVAS*[6]**

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

***2011 FVSG*[20]**

The Committee also recommends prescribing rituximab for failure or incomplete response to IV cyclophosphamide, prescribed as recommended by the HAS National Guidelines, and patients intolerant of cyclophosphamide or who developed complication(s) resulting from prior cyclophosphamide exposure (e.g., hemorrhagic cystitis).

Despite conflicting data, some GPA forms seem to respond incompletely to rituximab: orbital tumors, ENT manifestations, tracheal and bronchial stenoses, and pachymeningitis. Treating them with cyclophosphamide or methotrexate seems preferable, at least for first-line therapy.

***Guerry et al., 2011*[7]**

Rituximab is an effective treatment of refractory and/or relapsing forms of ANCA-associated vasculitis and can be recommended when conventional therapy has failed.

***KDIGO*[13]**

In ANCA GN resistant to induction therapy with cyclophosphamide and corticosteroids, we recommend the addition of rituximab (1C), and suggest i.v. immunoglobulin (2C) or plasmapheresis (2D) as alternatives

Statement 8

Patients with refractory disease should be managed in a referral centre for vasculitis in collaboration with subspecialists with experience in managing such patients.

Due to the rarity of these diseases, it can be difficult for all physicians to achieve and maintain skills in managing patients with refractory disease. We therefore suggest these patients be referred to a referral centre for vasculitis. These patients usually also require the input of different subspecialists who work regularly in close collaboration with referral centres for vasculitis. Granulomatous head and neck manifestations of GPA, such as subglottic stenosis and retro-orbital pseudo tumors, are examples of disease manifestations that are frequently resistant to systemic treatments and may require other specific treatments to improve symptoms and quality of life[102-106].

Barriers to implementation. There is a shortage of healthcare providers trained in the assessment and management of patients with AAV in Canada. The creation of CanVasc and identification of CanVasc centres and collaborators across Canada (see *Appendix 9*) aimed to decrease the lag between identification and referral of patients with AAV.

Previous Guidance

2014 BSR[21]

Refractory disease should ONLY be treated in close collaboration with expert or tertiary centres via a hub-and-spoke model.

Statement 9

Patients with EGPA and persistent asthmatic symptoms, despite remission of their vasculitic manifestations, should be managed in collaboration with a physician subspecializing in asthma management.

Patients with a diagnosis of EGPA may have resurgence of their asthma symptoms while on maintenance immunosuppressant therapies or after discontinuing such therapies[107]. If the vasculitic manifestations of the disease are in remission, we do not recommend that worsening asthmatic symptoms be regarded as refractory disease. Although the escalation or reintroduction of immunosuppressant therapy is not necessarily warranted, it (including azathioprine, methotrexate, leflunomide or mycophenolate mofetil) may be considered as a glucocorticoid-sparing option. There is very little evidence looking at the optimal management of these patients. Follow-up with an asthma specialist to ensure adherence with asthma management guidelines should be systematically considered. Referral of patients to a referral centre for vasculitis for further assessment should also be considered, as therapeutic trials may exist for these patients.

Barriers to implementation. There is a shortage of physician subspecializing in asthma management and trained in the assessment and management of patients with AAV in Canada. The creation of CanVasc and identification of CanVasc centres and collaborators across Canada (see *Appendix 9*) aimed to decrease the lag between identification and referral of patients with AAV.

Previous Guidance: *No specific guidelines.*

8. Additional and Experimental Therapies

Statement 10

In patients in whom the aforementioned therapies are ineffective, contraindicated or poorly tolerated, consideration can be given to alternate, additional and/or experimental therapies in collaboration with a referral centre for vasculitis.

Intravenous immunoglobulin (IVIG): A few series and open-label studies suggested that IVIG can help achieve remission, in combination with glucocorticoids, in patients with refractory disease (in addition to

immunosuppressants) and/or in those with contra-indication to immunosuppressants[108, 109]. There has been only one RCT studying the use of IVIG therapy in AAV. Patients with active AAV despite immunosuppressant therapy were randomized to receive IVIG or placebo in addition to "standard" therapy: 82% versus 35% of patients demonstrated a 50% reduction in disease activity in the IVIG vs. placebo groups, respectively[110]. This difference was observed up to three months following therapy, but no differences were noted beyond this time. The benefit of IVIG does not appear to be sustained after the cessation of the infusions. On the basis of the limited evidence, IVIG (see *Appendix 4* for IVIG prescribing advice) is not a substitute for more conventional immunosuppressant therapies. IVIG could however be a useful therapy in certain patient subgroups: as an adjunct in those with refractory disease, in pregnant patients in whom alternate immunosuppressants are contraindicated and/or in patients with active vasculitis and a current severe infection or high recurrence rate of severe infections. *Evidence 3, Strength of recommendation C*

Anti-tumor necrosis factor-α (anti-TNFα) agents. The Wegener's Granulomatosis Etanercept Trial (WGET) studied 180 GPA patients who received standard induction therapy with either cyclophosphamide followed by maintenance with methotrexate or azathioprine (severe disease) or methotrexate for both induction and maintenance (limited disease), in combination with glucocorticoids, and either etanercept or placebo during induction and maintenance therapies[38]. At 27 months, only 50% of patients achieved a sustained remission and there was no difference in sustained remission rates between the etanercept and placebo groups. Furthermore, there was a significantly higher rate of occurrence of solid tumors in both group compared to the general population and in the etanercept compared to placebo group during the study period. However, the latter difference between study groups was no longer significantly different during post-study closure follow-up[111]. Data on other anti-TNFα agents are limited, with only retrospective and open-labelled studies, which showed possible efficacy in selected patients. One small controlled study of infliximab versus rituximab for refractory GPA showed that rituximab was superior at inducing and maintaining remission during long-term follow-up[112-115]. We therefore recommend that etanercept not be used in regular practice for the treatment of AAV. The use of other anti-TNFα agents, such as infliximab, should be limited to very specific cases of refractory disease, when other alternative therapeutic options have failed or cannot be used, and they should not be given in combination with cyclophosphamide. *Evidence 1B, Strength of recommendation A*

Mepolizumab. A few series showed promising results for IV mepolizumab, a monoclonal antibody directed against interleukin-5 (IL-5), for patients with EGPA, mainly those patients glucocorticoid-dependent and/or refractory to other immunosuppressant[116, 117]. The MIRRA trial (ClinicalTrials.gov Identifier: NCT02020889) aims at studying subcutaneous mepolizumab for EGPA patients who cannot taper prednisone below 7.5 mg/day without the reappearance of disease manifestation(s). *Evidence 3, Strength of recommendation D*

Anti-CD52 therapy. Alemtuzumab or CAMPATH-1H is a humanized monoclonal antibody to CD52 with anti-lymphocyte activity and has been shown in a case series to induce remission in AAV, although

relapses and adverse events are common; its use in GPA is considered experimental[118] and there is no approval for this drug for vasculitis in Canada. *Evidence 3, Strength of recommendation D*

Barriers to implementation. There is a shortage of healthcare providers trained in the assessment and management of patients with AAV in Canada. The creation of CanVasc and identification of CanVasc centres and collaborators across Canada (see *Appendix 9*) aimed to decrease the lag between identification and referral of patients with AAV. Access to the aforementioned therapies is not possible in every province and none of them is approved by Health Canada for AAV (restricted access with provincial formularies and/or need to apply for provincial exceptional access program approval).

Previous Guidance

BSR[8]

IVIg may be considered as an alternative therapy in patients with refractory disease or in patients for whom conventional therapy is contra-indicated

Cochrane Review of IVIG[23]

There is insufficient evidence to determine if IVIG has an advantage over corticosteroids and immunosuppressants for the treatment of Wegener's granulomatosis.

EULAR/EUVAS[6]

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

KDIGO[13]

In ANCA GN resistant to induction therapy with cyclophosphamide and corticosteroids, we recommend the addition of rituximab (1C), and suggest i.v. immunoglobulin (2C) or plasmapheresis (2D) as alternatives.

9. Follow up of Patients with AAV

Statement 11

Patients with AAV should be followed regularly for many years with full clinical assessment and routine laboratory work to assess disease course and track for disease activity and disease- or treatment-related damage.

Patients receiving remission induction and maintenance therapy require regular clinical assessment to monitor their disease course, response to treatment and the potential adverse effects of treatments. The frequency at which this is done depends on the individual patient, the nature and history of their disease and the therapies required. We suggest that patients receiving remission induction therapy be seen on a monthly basis and those on maintenance therapy be seen on a 3-monthly basis for the first two years. The frequency of subsequent follow-up visits could be tailored to the individual patient, in continued and close collaboration with the patient's family physician and other subspecialists possibly involved. Given that relapses of AAV can occur at any stage, we recommend that all patients be reviewed long-term, at least annually, to monitor for signs of relapse, to assess for potential long term toxicities of

immunosuppressant therapies and in some cases to manage the repercussions of vasculitis-induced damage. At each visit, irrespective of the disease state, we recommend patients undergo a full clinical assessment and routine laboratory work (see *Appendix 1* for suggested blood tests at follow-up).

There is currently no evidence to suggest that rising ANCA titers alone warrant therapeutic changes, and therefore the need for serial ANCA testing is debatable[119-121]. The value of monitoring CD19 B cell count in patients treated with rituximab also remains to be determined, as currently available data do not support that it is sensitive or specific enough to help predict relapses.

Barriers to implementation. There is a shortage of healthcare providers trained in the assessment and management of patients with AAV in Canada. The creation of CanVasc and identification of CanVasc centres and collaborators across Canada (see *Appendix 9*) aimed to decrease the lag between identification and referral of patients with AAV.

Previous Guidance

BSR[8]

Recommendation: An initial assessment prior to starting treatment should be done. Assessment should then be performed approximately monthly for the first 3 months and then every 3–6 months for the next year according to clinical need. Thereafter as clinically indicated (C). In the randomized trial of maintenance therapy in primary systemic vasculitis by Jayne and colleagues, assessment of remission was made at 3 months, with the aim of changing immunosuppression from cyclophosphamide to azathioprine if remission had been induced (A).

The primary systemic vasculitides are relapsing conditions, relapse can occur at anytime even many years after diagnosis and remission induction. Follow-up after 12 months should be as dictated by the clinical condition of the patient, but should not be less frequent than every 6 months (C).

2014 BSR[21]

Disease assessment should occur monthly during remission induction and every 3 months during initial maintenance treatment and thereafter every 6 months and then annually.

Patients with AAV should not be completely discharged from the specialist clinic.

KDIGO[13]

We suggest not changing immunosuppression based on changes in ANCA titer alone.

Statement 12

All patients previously treated with cyclophosphamide should have a urinalysis every 3-6 months as a lifelong means of screening for cyclophosphamide-induced bladder toxicity. If micro- or macroscopic hematuria is present, in the absence of an alternate explanation, the patient should be referred for consideration of a cystoscopy.

It is widely recognized that the use of cyclophosphamide is associated with bladder toxicity, namely hemorrhagic cystitis and bladder cancer[49, 122, 123]. The risks have lessened somewhat over recent years, perhaps due to the more frequent co-prescription of mesna (at least for hemorrhagic cystitis) and the lower cumulative doses of cyclophosphamide used in patients with AAV. Nevertheless, we suggest that all patients previously treated with cyclophosphamide, especially those who received high total cumulative doses of cyclophosphamide have urine dipstick testing at least every 3-6 months as part of their regular follow-up (cumulative doses given to patients in whom bladder cancer developed varied

widely, above 30 gm in almost all cases and above 100 gm in the majority of them). If hematuria is present, the quantification of hematuria and urine cytopathology may be helpful. In the absence of an alternate explanation such as infection, active renal disease or renal damage of AAV, screening cystoscopy may be indicated and the patient should be referred for cystoscopy.

Barriers to implementation. None.

Previous Guidance

BSR[8]

Surveillance with 3-6 monthly urinalysis should be continued indefinitely after a course of cyclophosphamide. Haematuria or symptoms of recurrent cystitis should be investigated with urine culture and there should be a low threshold for referral for consideration of cystoscopy, if not considered due to active renal disease.

2014 BSR[21]

Surveillance with regular (3-6 months) urinalysis should be continued indefinitely after a course of CYC.

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

Statement 13

As part of their lifelong annual follow-up, cardiovascular risk factors (including smoking status, diabetes, hypercholesterolemia, hypertension and obesity) and risk for osteoporosis should be systematically assessed, with treatment as needed according to the current respective guidelines for each of these conditions.

There is good evidence that chronic inflammatory disorders such as rheumatoid arthritis or systemic lupus are associated with an increased risk of long-term cardiovascular events[124, 125]. Recent publications in GPA and MPA describe a rate of cardiovascular events around 10% over a median 4.3 year follow-up period[48, 126]. The long-term use of glucocorticoids increases the risk of osteoporosis. The presence of renal impairment in AAV patient adds a level of complexity in the therapeutic decisions for the prevention of osteoporosis.

As part of their long-term annual follow-up, patients with AAV should thus also be assessed, in collaboration with their primary care provider and/or subspecialist co-managing them, for osteoporosis and cardiovascular risk factors, including smoking status, diabetes, hypercholesterolemia, hypertension and obesity, and be appropriately counseled and treated, irrespective of the state of their vasculitis. There is not enough evidence at present to recommend a standardized list of investigations to perform in all patients or an optimal frequency, other than annual cardiovascular (risk) assessment. The prevention of osteoporosis should rely on the last, updated and available Canadian guidelines (available at http://www.osteoporosis.ca)[127-129].

Barriers to implementation. Collaborations with patient's family physician and other health care providers specialized in the prevention and management of cardiovascular risk factors or osteoporosis must be encouraged to optimize this mandatory long-term follow-up.

Previous Guidance

***BSR*[8]**

It is recommended that patients with AAV should be screened and treated where appropriate for hypertension, hypercholesterolemia and diabetes. Patients should be strongly advised against smoking.

***2014 BSR*[21]**

Cardiovascular risk should be assessed and appropriate prophylaxis provided in accordance with national guidance. 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.

Prophylaxis against osteoporosis should be considered in patients receiving corticosteroids. The need for treatment and fracture risk should be assessed following national guidance.

***EULAR/EUVAS*[6]**

Local guidelines for the prevention of glucocorticoid-induced osteoporosis should be followed in all patients.

10. Special patient groups

Statement 14

Women with AAV should not consider pregnancy earlier than 6 months after sustained remission of their disease has been achieved. Women with AAV planning pregnancy and those pregnant should be managed in close collaboration with an obstetrician with expertise in this field and/or in high-risk pregnancies.

In the past, the high morbidity associated with AAV and the toxic nature of the available treatments meant that pregnancy was unusual in this patient group. Thus there is limited data available on pregnancy, its management and outcomes in women with AAV. Retrospective reports suggest that while significant worsening of the patient's vasculitis is unusual during pregnancy, there are reports of pregnancy complications related to previous vasculitis-induced damage, such as cardiac decompensation or problems related to chronic impairment of renal function. There may also be a higher rate of first-trimester miscarriage, pre-term labor and the need for caesarean section deliveries in these patients[130-132]. Therefore, we suggest that these patients be seen before conception and monitored closely throughout pregnancy in close collaboration with the obstetric team. Published case series suggest that worsening vasculitis is less likely to occur in patients in sustained remission at the time of conception. Patients should therefore probably wait for at least 6 months after achieving sustained remission before attempting to conceive[130, 131, 133, 134], and those stable on maintenance immunosuppression should be on pregnancy safe options (i.e., azathioprine but not methotrexate, mycophenolate mofetil, leflunomide or any other teratogenic drugs). In view of the known teratogenicity of some of the drugs used in the management of AAV, including cyclophosphamide, methotrexate, leflunomide and mycophenolate mofetil, it is imperative to advise patients to take appropriate contraceptive measures when treated with those immunosuppressants.

Barriers to implementation. There is a shortage of physicians subspecializing in high-risk pregnancies and trained in the assessment and management of patients with AAV in Canada. The creation of CanVasc and identification of CanVasc centres and collaborators across Canada (see *Appendix 9*) aimed to decrease the lag between identification and referral of patients with AAV.

Previous Guidance: *None*

Statement 15

There are no pediatric specific management guidelines for pediatric AAV, and most knowledge in pediatric AAV is adapted from adult research. Management of children with AAV should be provided by pediatric physicians at an academic healthcare Centre, in collaboration with referral centres for vasculitis and/or centres with special interest in pediatric vasculitis.

Because of the rarity of pediatric AAV, there have been no studies from which to develop pediatric specific guidelines and most knowledge has been adapted from adult literature and experience. For the same reason few pediatricians have experience in diagnosing and managing children with AAV. Notwithstanding, children should be managed at a pediatric academic healthcare centre by pediatric physicians who have an understanding of the potential effects of disease and treatments on growth and development. If necessary there should be close collaboration with centres having a special interest in pediatric Vasculitis. All patients should be invited to participate in national or international registries of childhood vasculitis with a view to improving pediatric specific knowledge and care.

Barriers to implementation. There is a shortage of pediatric physicians subspecializing and/or trained in the assessment and management of patients with AAV in Canada. The creation of CanVasc and identification of CanVasc centres and collaborators across Canada (see *Appendix 9*) aimed to decrease the lag between identification and referral of patients with AAV. Several pediatric referral centres for vasculitis are participating in the CanVasc research network.

Previous Guidance: *None*

Statement 16

AAV in children should be classified at the time of diagnosis based on the childhood EULAR/PRINTO/PReS criteria in order to tailor therapy accordingly.

GPA is the most common of these rare childhood AAV followed by MPA, and EGPA is extremely rare. A pediatric adaptation of American College of Rheumatology criteria taking into account common pediatric manifestations and the presence of ANCA has enabled a specific classification for pediatric GPA, validated using a cohort of pediatric patients - Pediatric Rheumatology International Trial Organization and the Pediatric Rheumatology European Society (EULAR/PRINTO/PReS) criteria[135-137]. Systematic use of pediatric classification and adopting adult systems for “disease severity classification” will provide a framework for tailoring therapy (see Statement 3) and will provide the cornerstone for subsequent development of pediatric specific management guidelines.

Barriers to implementation. None.

Previous Guidance: *None*

Statement 17

Children with newly diagnosed AAV should be treated according to adult recommendations for induction remission then maintenance, with dose of medications adjusted for this specific population.

Induction treatment for children with severe GPA or MPA should rely on a combination of high dose glucocorticoids plus either cyclophosphamide or rituximab. The dose of cyclophosphamide must be adjusted in children with renal impairment and therapy should be monitored according to adult recommendations. Consideration should be given to rituximab as first-line remission induction therapy in children with severe GPA or MPA in whom cyclophosphamide is contraindicated or in whom cyclophosphamide presents an unacceptable risk of infertility. An international open-label study is ongoing to assess the role of rituximab in children with severe GPA or MPA (ClinicalTrials.gov Identifier: NCT01750697; results expected in mid-2017)

Plasma exchange should be considered in children with rapidly progressive, severe renal disease or severe pulmonary hemorrhage despite induction therapy with glucocorticoids and cyclophosphamide or rituximab. In children with limited non-severe disease, induction therapy regimen with methotrexate in combination with glucocorticoids may be considered.

As in adults, prophylaxis against *Pneumocystis jiroveci* infection should be given to children receiving cyclophosphamide or rituximab.

Remission induction therapy with cyclophosphamide should be switched to maintenance treatment within 3-6 months. Maintenance treatment after glucocorticoid-and-cyclophosphamide-based induction is based on adult recommendations of a combination of low-dose glucocorticoid plus azathioprine or methotrexate for a minimum of 24 months. There is no evidence to guide decisions regarding the duration of glucocorticoid therapy.

Barriers to implementation. In Canada, rituximab is approved for induction therapy in adults with severe ANCA-positive GPA or MPA, but is not yet approved for children.

Previous Guidance: *None*

Recommendation 18

In children, severe relapsing AAV or severe AAV refractory to the combination of cyclophosphamide and glucocorticoids (with major organ involvement or life-threatening manifestations) should be treated with rituximab, in combination with glucocorticoids.

Because AAV are relapsing conditions and a previous relapse is a risk factor for another and subsequent one[95], limiting the exposure to cyclophosphamide in children is crucial. Children may experience multiple flares during their lifetime and repeated or sustained exposure to cyclophosphamide can induce infertility, bladder cancer or lymphoma[138, 139]. The use of rituximab in combination with glucocorticoids, as first-line

treatment for disease relapses, should therefore be considered in children, especially if they have already received cyclophosphamide, independent of their cumulative dose. However, it must be remembered that data on long-term safety of rituximab in children in AAV are lacking.

Evidence 4, Strength of recommendation D

Barriers to implementation. In Canada, rituximab is approved for induction therapy in adults with severe ANCA-positive GPA or MPA, but is not yet approved for children.

Previous Guidance: *None*

DISCUSSION

Seventeen statements and 19 recommendations were developed by the CanVasc working group. These were based on a synthesis and reappraisal of international guidelines on AAV, supporting evidence from observational studies and randomized controlled trials, and consensus from health care professionals from different medical specialties, taking into account the present Canadian healthcare specificities. We anticipate that this document and practical appendices will serve as useful knowledge to support decision-making for any physician involved in the care of patients with AAV, including adults and children. Best clinical judgment must however always prevail when confronted with each specific patient scenario.

The guidelines were developed following an adaptation of the process previously used for the CRA endorsed recommendations for the management of rheumatoid arthritis and with guidance from the CRA therapeutic committee[16-18]. Along with the needs assessment questionnaire, the existence of earlier published international guidelines helped the working group to delineate the set of recommendations and statements addressed in this document. Supporting evidence from observational studies and randomized controlled trials linked to each recommendation were reviewed and graded. However, as for many guidelines and recommendations, it appears that strong evidence lacks for many of the addressed points. We opted to list those non-therapeutic points as statements, without grading them to simply reflect that these represent working group consensus.

Limitations include the fact that a systematic review of original literature prior to 2010 was not performed. It had already been completed by other groups, including the European EUVAS/EULAR group, when devising their recommendations[6, 140]. We therefore indirectly incorporated the earlier literature by reviewing other existing guidelines in our process. Second, although more up-to-date than those previously published recommendations or guidelines on AAV, basic, clinical and therapeutic research in the field of AAV is progressing at a fast pace nowadays. Therefore, new information from ongoing research may already have become available by the time the present document is published. Regular updates will thus be mandatory. It is our hope that this document will support decision-making by health care professionals, promote and harmonize best practices throughout Canada and ultimately improve patient outcomes.

Warning

These recommendations and statements were based on the highest quality of evidence available at the time the working group undertook this review, and are intended to promote best practices and improve healthcare delivery for persons with AAV. However, they should not be interpreted as rigid or legal standards, nor are they meant to replace the clinical judgment of specialists and other healthcare providers trained in AAV, who must always act according to the individual needs of the patient and the unique clinical circumstance.

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Table 1. Level of evidence and grading of therapeutic recommendations, according to criteria endorsed by EULAR/EUVAS.[6, 24]

Table 1A**:** Method of categorizing level of evidence available for each topic.

Category of Evidence	**Evidence Available**
1A	From meta-analysis of randomized controlled trials.
1B	From at least 1 randomized controlled trial.
2A	From at least 1 controlled study without randomization.
2B	From at least 1 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.

Table 1B**:** Strength of recommendation.

Strength of Recommendation	**Directly based on (level of evidence)**
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.

From Dougados, *et al*. Ann Rheum Dis;63:1172-6; with permission.

Table 2. Summary table of the CanVasc recommendations and statements

Recommendation or statement	Text of the recommendation or statement	Evidence level / strength*
Diagnosis		
Statement 1	ANCA testing with ELISA and indirect immunofluorescence methods should be performed for diagnostic purposes in patients in whom there is clinical suspicion of a systemic small- and/or medium-sized vessel vasculitis.	
Statement 2	Tissue biopsy should be considered in cases of suspected AAV to confirm diagnosis.	
Classification of disease severity in AAV		
Statement 3	Patients with AAV should have the extent and severity of their disease categorized as 'severe' at the time of diagnosis and in case of subsequent relapse if they have life- or major organ-threatening manifestations in order to tailor therapy accordingly.	
The role of referral centres for vasculitis		
Statement 4	Patients with AAV, particularly those with challenging disease, should be managed at, or in collaboration with, a referral centre for vasculitis.	
Remission induction for newly-diagnosed disease		
	Remission induction in severe (organ/life-threatening disease) newly-diagnosed disease	
Recommendation 1	We recommend remission induction therapy with a combination of high dose glucocorticoids and cyclophosphamide in patients with severe newly diagnosed GPA, MPA or EGPA.	*1B / A*
Recommendation 2	We recommend using high dose glucocorticoids with rituximab as 1st line remission induction therapy in patients with severe GPA or MPA in whom cyclophosphamide is contraindicated or in whom cyclophosphamide presents an unacceptable risk of infertility.	*1B / A*
Recommendation 3	Cyclophosphamide dose should be adjusted in patients >60 years of age and in those with renal impairment.	*1B / B*
Statement 5	Complete blood count (CBC) and serum creatinine level must be monitored in patients treated with cyclophosphamide. In patients with abnormal CBC results, temporary withholding of cyclophosphamide and subsequent dose adjustments may be necessary depending on the degree of leucopenia.	
Recommendation 4	We recommend that the remission induction therapy with cyclophosphamide, combined with glucocorticoids, lasts a minimum of 3 to a maximum of 6 months. Once remission is achieved, cyclophosphamide should be stopped and switched to a different maintenance therapy.	*1B / A*
Recommendation 5	We recommend that glucocorticoids should be given in adults at an initial dose of 1 mg/kg/day prednisone-equivalent for remission induction purposes. This may be preceded by pulsed methylprednisolone (0.5 to 1 g/day for 1 to 3 days) in patients with life threatening disease and/or major organ involvement.	*2A/ B*
Recommendation 6	Prophylaxis against *Pneumocystis jiroveci* infection should be given to patients receiving cyclophosphamide or rituximab. This prophylaxis consists, in the absence of allergy, of trimethoprim/sulfamethoxazole compounds (800/160mg 1 tablet 3 times per week or 400/80mg daily).	*3 / C*
Recommendation 7	There is insufficient evidence to support a recommendation that plasma exchange be used as first line therapy in any AAV patients. Plasma exchange may be a reasonable adjuvant therapy for patients who clinically deteriorate due to active vasculitis despite ongoing remission induction therapy with high-dose glucocorticoids and cyclophosphamide or rituximab.	*4 / D*
	Remission induction for limited or non-severe (non organ- and non life-threatening), newly-diagnosed disease	
Recommendation 8	In patients with limited and/or non-severe GPA, which is non-life threatening and without any major organ involvement, remission induction regime with methotrexate in combination with glucocorticoids can be used.	*1B / A*
Recommendation 9	Patients with non-severe EGPA or non-severe MPA without renal involvement can be treated with glucocorticoids alone for remission induction. At present, there is no consensus on the use of any immunosuppressant agents in combination with glucocorticoids in patients with EGPA or MPA that are non-severe (including those with mononeuritis multiplex).	*2B / C*
Remission maintenance therapy		
Recommendation 10	In patients with severe AAV in remission after a combined cyclophosphamide-glucocorticoid-based induction treatment, maintenance therapy can be based on azathioprine or methotrexate, initially in combination with low-dose glucocorticoids. Leflunomide or mycophenolate may be alternative agents in patients not tolerating or with contra-indications to azathioprine and methotrexate.	*1B / B*
Recommendation 11	In patients with severe AAV in remission after a combined cyclophosphamide-glucocorticoid-based induction treatment, maintenance therapy with rituximab infusions is an alternative to azathioprine,	*1B / A*

	especially for those patients with PR3-ANCA-positive GPA.	
Statement 6	To date there is no definitive evidence to guide decisions for maintenance therapy after remission induction with rituximab.	
Recommendation 12	We recommend the use of azathioprine, methotrexate or their alternatives (as per Recommendation 10 and 11) for remission maintenance therapy to be continued for a minimum of 18 months after successful remission induction. There is not enough evidence yet to support further recommendation on the optimal duration of their use for maintenance.	*3 / C*
Statement 7	Low dose glucocorticoids should be part of the initial remission maintenance therapy after remission is achieved; there is not enough evidence yet to support further recommendation on the optimal duration of low dose glucocorticoids.	
Recommendation 13	The use of trimethoprim/sulfamethoxazole (800/160mg twice daily) as remission maintenance therapy can be considered in GPA as an adjuvant to immunosuppressant or after the cessation of maintenance immunosuppressive treatment.	*3 / C*
Recommendation 14	Topical therapies may be considered, in combination with the systemic therapy and in collaboration with ENT subspecialists, to alleviate the symptoms of upper airway and ENT disease.	*3 / C*
Relapsing disease		
Recommendation 15	We recommend remission induction of a major organ- or life-threatening relapse with either cyclophosphamide or rituximab in conjunction with high dose glucocorticoids. In patients who already received cyclophosphamide for initial remission induction or a previous disease flare, we recommend using rituximab for remission re-induction.	*1B / B*
Recommendation 16	There is insufficient evidence to support a recommendation that plasma exchange be used as first line therapy in all patients with relapsing AAV with severe renal (GFR <50ml/min) or pulmonary hemorrhage. Plasma exchange may be a reasonable adjuvant therapy for patients who clinically deteriorate due to active relapsing vasculitis despite ongoing remission induction therapy with high-dose glucocorticoids and cyclophosphamide or rituximab.	*4 / D*
Recommendation 17	We recommend that relapses that are non-severe, i.e. non-life and non-organ threatening, be treated with an increase in glucocorticoid dose in addition to optimizing the patient's concurrent immunosuppressant agent.	*3 / C*
Refractory disease		
Recommendation 18	We recommend the use of rituximab, in combination with glucocorticoids, in patients with severe GPA or MPA who fail to respond to cyclophosphamide as remission induction therapy.	*3 / C*
Statement 8	Patients with refractory disease should be managed in a referral centre for vasculitis in collaboration with subspecialists with experience in managing such patients.	
Statement 9	Patients with EGPA and persistent asthmatic symptoms, despite remission of their vasculitic manifestations, should be managed in collaboration with a physician subspecializing in asthma management.	
Additional and experimental therapies		
Statement 10	In patients in whom the aforementioned therapies are ineffective, contraindicated or poorly tolerated, consideration can be given to alternate, additional and/or experimental therapies in collaboration with a referral centre for vasculitis.	
Follow up of patients with AAV		
Statement 11	Patients with AAV should be followed regularly for many years with full clinical assessment and routine laboratory work to assess disease course and track for disease activity and disease- or treatment-related damage.	
Statement 12	All patients previously treated with cyclophosphamide should have a urinalysis every 3-6 months as a lifelong means of screening for cyclophosphamide-induced bladder toxicity. If micro- or macroscopic hematuria is present, in the absence of an alternate explanation, the patient should be referred for consideration of a cystoscopy.	
Statement 13	As part of their lifelong annual follow-up, cardiovascular risk factors (including smoking status, diabetes, hypercholesterolemia, hypertension and obesity) and risk for osteoporosis should be systematically assessed, with treatment as needed according to the current respective guidelines for each of these conditions.	
Special patient groups		
Statement 14	Women with AAV should not consider pregnancy earlier than 6 months after sustained remission of their disease has been achieved. Women with AAV planning pregnancy and those pregnant should be managed in close collaboration with an obstetrician with expertise in this field and/or in high-risk pregnancies.	

Statement 15	There are no pediatric specific management guidelines for pediatric AAV, and most knowledge in pediatric AAV is adapted from adult research. Management of children with AAV should be provided by pediatric physicians at an academic healthcare Centre, in collaboration with referral centres for vasculitis and/or centres with special interest in pediatric vasculitis.	
Statement 16	AAV in children should be classified at the time of diagnosis based on the childhood EULAR/PRINTO/PReS criteria in order to tailor therapy accordingly.	
Statement 17	Children with newly diagnosed AAV should be treated according to adult recommendations for induction remission then maintenance, with dose of medications adjusted for this specific population.	
Recommendation 19	In children, severe relapsing AAV or severe AAV refractory to the combination of cyclophosphamide and glucocorticoids (with major organ involvement or life-threatening manifestations) should be treated with rituximab, in combination with glucocorticoids.	*4 / D*

** Statements are not related to specific treatments and were not be graded as there was no strong evidence or available studies to support them.*

REFERENCES

1. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994;37:187-92.
2. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65:1-11.
3. Mohammad AJ, Jacobsson LT, Mahr AD, Sturfelt G, Segelmark M. Prevalence of Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg-Strauss syndrome within a defined population in southern Sweden. Rheumatology (Oxford) 2007;46:1329-37.
4. Mohammad AJ, Jacobsson LT, Westman KW, Sturfelt G, Segelmark M. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa. Rheumatology (Oxford) 2009;48:1560-5.
5. Anderson K, Klassen J, Stewart SA, Taylor-Gjevre RM. Does geographic location affect incidence of ANCA-associated renal vasculitis in northern Saskatchewan, Canada? Rheumatology (Oxford) 2013;52:1840-4.
6. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 2009;68:310-7.
7. Guerry MJ, Brogan P, Bruce IN, D'Cruz DP, Harper L, Luqmani R, et al. Recommendations for the use of rituximab in anti-neutrophil cytoplasm antibody-associated vasculitis. Rheumatology (Oxford) 2011;51:634-43.
8. Lapraik C, Watts R, Bacon P, Carruthers D, Chakravarty K, D'Cruz D, et al. BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis. Rheumatology (Oxford) 2007;46:1615-6.
9. Luxton G, Langham R. The CARI guidelines. ANCA serology in the diagnosis and management of ANCA-associated renal vasculitis. Nephrology (Carlton) 2008;13 Suppl 2:S17-23.
10. JCS. Guideline for management of vasculitis syndrome (JCS 2008). Japanese Circulation Society. Circ J 2008;75:474-503.
11. Menahem S, Hiremagalur B, Mudge D, Toussaint N, Walters G. The CARI guidelines. Induction and maintenance therapy in ANCA-associated systemic vasculitis. Nephrology (Carlton) 2008;13 Suppl 2:S24-36.
12. Pagnoux C, FVSG. Vascularites nécrosantes systémiques - Protocole national de diagnostic et de soins. wwwhas-santefr 2009.
13. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. . Kidney inter 2012:139-274.
14. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990;33:1094-100.
15. Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101-7.
16. Bykerk VP, Schieir O, Akhavan P, Hazlewood GS, Cheng CK, Bombardier C. Emerging issues in pharmacological management of rheumatoid arthritis: results of a national needs assessment survey identifying practice variations for the development of Canadian Rheumatology Association clinical practice recommendations. J Rheumatol 2012;39:1555-8.
17. Bombardier C, Hazlewood GS, Akhavan P, Schieir O, Dooley A, Haraoui B, et al. Canadian Rheumatology Association recommendations for the pharmacological management of rheumatoid

arthritis with traditional and biologic disease-modifying antirheumatic drugs: part II safety. J Rheumatol 2012;39:1583-602.
18. Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, Dooley A, Haraoui B, et al. Canadian Rheumatology Association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. J Rheumatol 2012;39:1559-82.
19. Famorca L, Twilt M, Barra L, Bakowsky V, Benseler SM, Cabral D, et al. Development of Canadian Recommendations for the Management of ANCA-Associated Vasculitides: Results of the National Needs Assessment Questionnaire. Open J Rheumatol 2015;[In press].
20. Charles P, Bienvenu B, Bonnotte B, Gobert P, Godmer P, Hachulla E, et al. Rituximab: Recommendations of the French Vasculitis Study Group (FVSG) for induction and maintenance treatments of adult, antineutrophil cytoplasm antibody-associated necrotizing vasculitides. Presse Med 2013;42:1317-30.
21. Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, Jayne D, et al. BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology (Oxford) 2014;53:2306-9.
22. Walters G, Willis NS, Craig JC. Interventions for renal vasculitis in adults. Cochrane Database Syst Rev 2008:CD003232.
23. Fortin PM, Tejani AM, Bassett K, Musini VM. Intravenous immunoglobulin as adjuvant therapy for Wegener's granulomatosis. Cochrane Database Syst Rev 2009:CD007057.
24. Dougados M, Betteridge N, Burmester GR, Euller-Ziegler L, Guillemin F, Hirvonen J, et al. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. Ann Rheum Dis 2004;63:1172-6.
25. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66:719-25.
26. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
27. Hunder GG, Arend WP, Bloch DA, Calabrese LH, Fauci AS, Fries JF, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Introduction. Arthritis Rheum 1990;33:1065-7.
28. Craven A, Robson J, Ponte C, Grayson PC, Suppiah R, Judge A, et al. ACR/EULAR-endorsed study to develop Diagnostic and Classification Criteria for Vasculitis (DCVAS). Clin Exp Nephrol 2013;17:619-21.
29. Choi HK, Liu S, Merkel PA, Colditz GA, Niles JL. Diagnostic performance of antineutrophil cytoplasmic antibody tests for idiopathic vasculitides: metaanalysis with a focus on antimyeloperoxidase antibodies. J Rheumatol 2001;28:1584-90.
30. Hagen EC, Daha MR, Hermans J, Andrassy K, Csernok E, Gaskin G, et al. Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR Project for ANCA Assay Standardization. Kidney Int 1998;53:743-53.
31. Wiesner O, Russell KA, Lee AS, Jenne DE, Trimarchi M, Gregorini G, et al. Antineutrophil cytoplasmic antibodies reacting with human neutrophil elastase as a diagnostic marker for cocaine-induced midline destructive lesions but not autoimmune vasculitis. Arthritis Rheum 2004;50:2954-65.
32. Milman N, Smith CD. Cutaneous vasculopathy associated with cocaine use. Arthritis Care Res (Hoboken) 2011;63:1195-202.
33. Mahr A, Batteux F, Tubiana S, Goulvestre C, Wolff M, Papo T, et al. Brief report: prevalence of antineutrophil cytoplasmic antibodies in infective endocarditis. Arthritis Rheumatol 2014;66:1672-7.
34. Csernok E, Lamprecht P, Gross WL. Clinical and immunological features of drug-induced and infection-induced proteinase 3-antineutrophil cytoplasmic antibodies and myeloperoxidase-antineutrophil cytoplasmic antibodies and vasculitis. Curr Opin Rheumatol 2010;22:43-8.

35. Csernok E, Moosig F. Current and emerging techniques for ANCA detection in vasculitis. Nat Rev Rheumatol 2014;10:494-501.
36. Stone JH. Limited versus severe Wegener's granulomatosis: baseline data on patients in the Wegener's granulomatosis etanercept trial. Arthritis Rheum 2003;48:2299-309.
37. Borner U, Landis BN, Banz Y, Villiger P, Ballinari P, Caversaccio M, et al. Diagnostic value of biopsies in identifying cytoplasmic antineutrophil cytoplasmic antibody-negative localized Wegener's granulomatosis presenting primarily with sinonasal disease. Am J Rhinol Allergy 2012;26:475-80.
38. WGET. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005;352:351-61.
39. Hellmich B, Flossmann O, Gross WL, Bacon P, Cohen-Tervaert JW, Guillevin L, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis 2007;66:605-17.
40. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221-32.
41. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholary O, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. Medicine (Baltimore) 1996;75:17-28.
42. Gayraud M, Guillevin L, Le Toumelin P, Cohen P, Lhote F, Casassus P, et al. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. Arthritis Rheum 2001;44:666-75.
43. Guillevin L, Pagnoux C, Seror R, Mahr A, Mouthon L, Le Toumelin P. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. Medicine (Baltimore) 2011;90:19-27.
44. Adu D, Pall A, Luqmani RA, Richards NT, Howie AJ, Emery P, et al. Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis. Qjm 1997;90:401-9.
45. Guillevin L, Cordier JF, Lhote F, Cohen P, Jarrousse B, Royer I, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. Arthritis Rheum 1997;40:2187-98.
46. de Groot K, Adu D, Savage CO. The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review. Nephrol Dial Transplant 2001;16:2018-27.
47. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 2009;150:670-80.
48. Harper L, Morgan MD, Walsh M, Hoglund P, Westman K, Flossmann O, et al. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. Ann Rheum Dis 2012;71:955-60.
49. Monach PA, Arnold LM, Merkel PA. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: a data-driven review. Arthritis Rheum 2010;62:9-21.
50. Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211-20.
51. Jones RB, Ferraro AJ, Chaudhry AN, Brogan P, Salama AD, Smith KG, et al. A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2009;60:2156-68.

52. Charles P, Neel A, Tieulie N, Hot A, Pugnet G, Decaux O, et al. Rituximab for induction and maintenance treatment of ANCA-associated vasculitides: a multicentre retrospective study on 80 patients. Rheumatology (Oxford) 2014;53:532-9.
53. Cartin-Ceba R, Golbin JM, Keogh KA, Peikert T, Sanchez-Menendez M, Ytterberg SR, et al. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center. Arthritis Rheum 2012;64:3770-8.
54. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349:36-44.
55. Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med 2008;359:2790-803.
56. Pagnoux C, Quemeneur T, Ninet J, Perrodeau E, Diot E, Kyndt X, et al. Systemic Necrotizing Vasculitides in patients over 65 years old: results of the multicenter randomized CORTAGE trial [abstract]. Presse Med 2013;42:679-80.
57. Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. JAMA 2010;304:2381-8.
58. Jarrousse B, Guillevin L, Bindi P, Hachulla E, Leclerc P, Gilson B, et al. Increased risk of Pneumocystis carinii pneumonia in patients with Wegener's granulomatosis. Clin Exp Rheumatol 1993;11:615-21.
59. Godeau B, Mainardi JL, Roudot-Thoraval F, Hachulla E, Guillevin L, Huong Du LT, et al. Factors associated with Pneumocystis carinii pneumonia in Wegener's granulomatosis. Ann Rheum Dis 1995;54:991-4.
60. Hugle B, Solomon M, Harvey E, James A, Wadhwa A, Amin R, et al. Pneumocystis jiroveci pneumonia following rituximab treatment in Wegener's granulomatosis. Arthritis Care Res (Hoboken) 2010;62:1661-4.
61. Stern A, Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. Cochrane Database Syst Rev 2014;10:CD005590.
62. Suryaprasad A, Stone JH. When is it safe to stop *Pneumocystis jiroveci* pneumonia prophylaxis? Insights from three cases complicating autoimmune diseases. Arthritis Rheum 2008;59:1034-9.
63. Kimura M, Tanaka S, Ishikawa A, Endo H, Hirohata S, Kondo H. Comparison of trimethoprim-sulfamethoxazole and aerosolized pentamidine for primary prophylaxis of Pneumocystis jiroveci pneumonia in immunocompromised patients with connective tissue disease. Rheumatol Int 2008;28:673-6.
64. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007;18:2180-8.
65. Walsh M, Catapano F, Szpirt W, Thorlund K, Bruchfeld A, Guillevin L, et al. Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: a meta-analysis. Am J Kidney Dis 2011;57:566-74.
66. Cybulsky AV, Walsh M, Knoll G, Hladunewich M, Bargman J, Reich H, et al. Canadian Society of Nephrology Commentary on the 2012 KDIGO clinical practice guideline for glomerulonephritis: management of glomerulonephritis in adults. Am J Kidney Dis 2014;63:363-77.
67. Walsh M, Casian A, Flossmann O, Westman K, Hoglund P, Pusey C, et al. Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. Kidney Int 2013;84:397-402.

68. Klemmer PJ, Chalermskulrat W, Reif MS, Hogan SL, Henke DC, Falk RJ. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. Am J Kidney Dis 2003;42:1149-53.
69. Casian A, Jayne D. Management of alveolar hemorrhage in lung vasculitides. Semin Respir Crit Care Med 2011;32:335-45.
70. Walsh M, Merkel PA, Peh CA, Szpirt W, Guillevin L, Pusey CD, et al. Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial. Trials 2013;14:73.
71. Stone JH, Tun W, Hellman DB. Treatment of non-life threatening Wegener's granulomatosis with methotrexate and daily prednisone as the initial therapy of choice. J Rheumatol 1999;26:1134-9.
72. Hoffman GS, Leavitt RY, Kerr GS, Fauci AS. The treatment of Wegener's granulomatosis with glucocorticoids and methotrexate. Arthritis Rheum 1992;35:1322-9.
73. de Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461-9.
74. Faurschou M, Westman K, Rasmussen N, de Groot K, Flossmann O, Hoglund P, et al. Brief Report: long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012;64:3472-7.
75. Furuta S, Jayne D. Emerging therapies in antineutrophil cytoplasm antibody-associated vasculitis. Curr Opin Rheumatol 2014;26:1-6.
76. Stegeman CA, Tervaert JW, Kallenberg CG. Co-trimoxazole and Wegener's granulomatosis: more than a coincidence? Nephrol Dial Transplant 1997;12:652-5.
77. Ribi C, Cohen P, Pagnoux C, Mahr A, Arene JP, Lauque D, et al. Treatment of Churg-Strauss syndrome without poor-prognosis factors: a multicenter, prospective, randomized, open-label study of seventy-two patients. Arthritis Rheum 2008;58:586-94.
78. Ribi C, Cohen P, Pagnoux C, Mahr A, Arene JP, Puechal X, et al. Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: A prospective randomized study of one hundred twenty-four patients. Arthritis Rheum 2010;62:1186-97.
79. Samson M, Puechal X, Devilliers H, Ribi C, Cohen P, Bienvenu B, et al. Mononeuritis multiplex predicts the need for immunosuppressive or immunomodulatory drugs for EGPA, PAN and MPA patients without poor-prognosis factors. Autoimmun Rev 2014;13:945-53.
80. Langford CA, Talar-Williams C, Barron KS, Sneller MC. Use of a cyclophosphamide-induction methotrexate-maintenance regimen for the treatment of Wegener's granulomatosis: extended follow-up and rate of relapse. Am J Med 2003;114:463-9.
81. Metzler C, Miehle N, Manger K, Iking-Konert C, de Groot K, Hellmich B, et al. Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis. Rheumatology (Oxford) 2007;46:1087-91.
82. Keen HI, Conaghan PG, Tett SE. Safety evaluation of leflunomide in rheumatoid arthritis. Expert Opin Drug Saf 2013;12:581-8.
83. Smith RM, Jones RB, Guerry MJ, Laurino S, Catapano F, Chaudhry A, et al. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012;64:3760-9.
84. Roubaud-Baudron C, Pagnoux C, Meaux-Ruault N, Grasland A, Zoulim A, J LG, et al. Rituximab maintenance therapy for granulomatosis with polyangiitis and microscopic polyangiitis. J Rheumatol 2012;39:125-30.

85. Besada E, Koldingsnes W, Nossent JC. Long-term efficacy and safety of pre-emptive maintenance therapy with rituximab in granulomatosis with polyangiitis: results from a single centre. Rheumatology (Oxford) 2013;52:2041-7.
86. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis [Abstract]. Arthritis Rheum 2012;64:S706.
87. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis. N Engl J Med 2014;371:1771-80.
88. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med 2013;369:417-27.
89. Miloslavsky EM, Specks U, Merkel PA, Seo P, Spiera R, Langford CA, et al. Clinical outcomes of remission induction therapy for severe antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2013;65:2441-9.
90. Azar L, Springer J, Langford CA, Hoffman GS. Rituximab with or without a conventional maintenance agent in the treatment of relapsing granulomatosis with polyangiitis (Wegener's): a retrospective single-center study. Arthritis Rheumatol 2014;66:2862-70.
91. Walsh M, Merkel PA, Mahr A, Jayne D. Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: A meta-analysis. Arthritis Care Res (Hoboken) 2010;62:1166-73.
92. McGregor JG, Hogan SL, Hu Y, Jennette CE, Falk RJ, Nachman PH. Glucocorticoids and relapse and infection rates in anti-neutrophil cytoplasmic antibody disease. Clin J Am Soc Nephrol 2012;7:240-7.
93. Springer J, Nutter B, Langford CA, Hoffman GS, Villa-Forte A. Granulomatosis with polyangiitis (Wegener's): impact of maintenance therapy duration. Medicine (Baltimore) 2014;93:82-90.
94. Walsh M, Flossmann O, Berden A, Westman K, Hoglund P, Stegeman C, et al. Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012;64:542-8.
95. Pagnoux C, Hogan SL, Chin H, Jennette JC, Falk RJ, Guillevin L, et al. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: comparison of two independent cohorts. Arthritis Rheum 2008;58:2908-18.
96. Pierrot-Deseilligny Despujol C, Pouchot J, Pagnoux C, Coste J, Guillevin L. Predictors at diagnosis of a first Wegener's granulomatosis relapse after obtaining complete remission. Rheumatology (Oxford) 2010;49:2181-90.
97. Reinhold-Keller E, De Groot K, Rudert H, Nolle B, Heller M, Gross WL. Response to trimethoprim/sulfamethoxazole in Wegener's granulomatosis depends on the phase of disease. Qjm 1996;89:15-23.
98. Zycinska K, Wardyn KA, Zielonka TM, Krupa R, Lukas W. Co-trimoxazole and prevention of relapses of PR3-ANCA positive vasculitis with pulmonary involvement. Eur J Med Res 2009;14 Suppl 4:265-7.
99. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. N Engl J Med 1996;335:16-20.
100. Langford CA, Monach PA, Specks U, Seo P, Cuthbertson D, McAlear CA, et al. An open-label trial of abatacept (CTLA4-Ig) in non-severe relapsing granulomatosis with polyangiitis (Wegener's). Ann Rheum Dis 2014;73:1376-9.
101. Langford CA, Talar-Williams C, Sneller MC. Mycophenolate mofetil for remission maintenance in the treatment of Wegener's granulomatosis. Arthritis Rheum 2004;51:278-83.
102. Wolter NE, Ooi EH, Witterick IJ. Intralesional corticosteroid injection and dilatation provides effective management of subglottic stenosis in Wegener's granulomatosis. Laryngoscope 2010;120:2452-5.

103. Gluth MB, Shinners PA, Kasperbauer JL. Subglottic stenosis associated with Wegener's granulomatosis. Laryngoscope 2003;113:1304-7.
104. Lebovics RS, Hoffman GS, Leavitt RY, Kerr GS, Travis WD, Kammerer W, et al. The management of subglottic stenosis in patients with Wegener's granulomatosis. Laryngoscope 1992;102:1341-5.
105. Langford CA, Sneller MC, Hallahan CW, Hoffman GS, Kammerer WA, Talar-Williams C, et al. Clinical features and therapeutic management of subglottic stenosis in patients with Wegener's granulomatosis. Arthritis Rheum 1996;39:1754-60.
106. Pagnoux C, Wolter NE. Vasculitis of the upper airways. Swiss Med Wkly 2012;142:w13541.
107. Comarmond C, Pagnoux C, Khellaf M, Cordier JF, Hamidou M, Viallard JF, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum 2013;65:270-81.
108. Martinez V, Cohen P, Pagnoux C, Vinzio S, Mahr A, Mouthon L, et al. Intravenous immunoglobulins for relapses of systemic vasculitides associated with antineutrophil cytoplasmic autoantibodies: results of a multicenter, prospective, open-label study of twenty-two patients. Arthritis Rheum 2008;58:308-17.
109. Jayne DR, Davies MJ, Fox CJ, Black CM, Lockwood CM. Treatment of systemic vasculitis with pooled intravenous immunoglobulin. Lancet 1991;337:1137-9.
110. Jayne DR, Chapel H, Adu D, Misbah S, O'Donoghue D, Scott D, et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. Qjm 2000;93:433-9.
111. Silva F, Seo P, Schroeder DR, Stone JH, Merkel PA, Hoffman GS, et al. Solid malignancies among etanercept-treated patients with granulomatosis with polyangiitis (Wegener's): long-term followup of a multicenter longitudinal cohort. Arthritis Rheum 2011;63:2495-503.
112. de Menthon M, Cohen P, Pagnoux C, Buchler M, Sibilia J, Detree F, et al. Infliximab or rituximab for refractory Wegener's granulomatosis: long-term follow up. A prospective randomised multicentre study on 17 patients. Clin Exp Rheumatol 2011;29:S63-71.
113. Booth A, Harper L, Hammad T, Bacon P, Griffith M, Levy J, et al. Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis. J Am Soc Nephrol 2004;15:717-21.
114. Booth AD, Jefferson HJ, Ayliffe W, Andrews PA, Jayne DR. Safety and efficacy of TNFalpha blockade in relapsing vasculitis. Ann Rheum Dis 2002;61:559.
115. Josselin L, Mahr A, Cohen P, Pagnoux C, Guaydier-Souquieres G, Hayem G, et al. Infliximab efficacy and safety against refractory systemic necrotising vasculitides: long-term follow-up of 15 patients. Ann Rheum Dis 2008;67:1343-6.
116. Kim S, Marigowda G, Oren E, Israel E, Wechsler ME. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. J Allergy Clin Immunol 2010;125:1336-43.
117. Herrmann K, Gross WL, Moosig F. Extended follow-up after stopping mepolizumab in relapsing/refractory Churg-Strauss syndrome. Clin Exp Rheumatol 2012;30:S62-5.
118. Walsh M, Chaudhry A, Jayne D. Long-term follow-up of relapsing/refractory anti-neutrophil cytoplasm antibody associated vasculitis treated with the lymphocyte depleting antibody alemtuzumab (CAMPATH-1H). Ann Rheum Dis 2008;67:1322-7.
119. Boomsma MM, Stegeman CA, van der Leij MJ, Oost W, Hermans J, Kallenberg CG, et al. Prediction of relapses in Wegener's granulomatosis by measurement of antineutrophil cytoplasmic antibody levels: a prospective study. Arthritis Rheum 2000;43:2025-33.
120. Finkielman JD, Lee AS, Hummel AM, Viss MA, Jacob GL, Homburger HA, et al. ANCA are detectable in nearly all patients with active severe Wegener's granulomatosis. Am J Med 2007;120:643 e9-14.

121. Tomasson G, Grayson PC, Mahr AD, Lavalley M, Merkel PA. Value of ANCA measurements during remission to predict a relapse of ANCA-associated vasculitis - a meta-analysis. Rheumatology (Oxford) 2012;51:100-9.
122. Faurschou M, Sorensen IJ, Mellemkjaer L, Loft AG, Thomsen BS, Tvede N, et al. Malignancies in Wegener's granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. J Rheumatol 2008;35:100-5.
123. Le Guenno G, Mahr A, Pagnoux C, Dhote R, Guillevin L. Incidence and predictors of urotoxic adverse events in cyclophosphamide-treated patients with systemic necrotizing vasculitides. Arthritis Rheum 2011;63:1435-45.
124. Crowson CS, Nicola PJ, Kremers HM, O'Fallon WM, Therneau TM, Jacobsen SJ, et al. How much of the increased incidence of heart failure in rheumatoid arthritis is attributable to traditional cardiovascular risk factors and ischemic heart disease? Arthritis Rheum 2005;52:3039-44.
125. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum 2005;52:722-32.
126. Suppiah R, Judge A, Batra R, Flossmann O, Harper L, Hoglund P, et al. A model to predict cardiovascular events in patients with newly diagnosed Wegener's granulomatosis and microscopic polyangiitis. Arthritis Care Res (Hoboken) 2011;63:588-96.
127. Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. Cmaj 2010;182:1864-73.
128. Leib ES, Saag KG, Adachi JD, Geusens PP, Binkley N, McCloskey EV, et al. Official Positions for FRAX((R)) clinical regarding glucocorticoids: the impact of the use of glucocorticoids on the estimate by FRAX((R)) of the 10 year risk of fracture from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX((R)). J Clin Densitom 2011;14:212-9.
129. McCloskey EV, Binkley N. FRAX((R)) Clinical Task Force of the 2010 Joint International Society for Clinical Densitometry & International Osteoporosis Foundation Position Development Conference. J Clin Densitom 2011;14:181-3.
130. Pagnoux C, Le Guern V, Goffinet F, Diot E, Limal N, Pannier E, et al. Pregnancies in systemic necrotizing vasculitides: report on 12 women and their 20 pregnancies. Rheumatology (Oxford) 2011;50:953-61.
131. Clowse ME, Richeson RL, Pieper C, Merkel PA. Pregnancy outcomes among patients with vasculitis. Arthritis Care Res (Hoboken) 2013;65:1370-4.
132. Tuin J, Sanders JS, de Joode AA, Stegeman CA. Pregnancy in women diagnosed with antineutrophil cytoplasmic antibody-associated vasculitis: outcome for the mother and the child. Arthritis Care Res (Hoboken) 2012;64:539-45.
133. Seo P. Pregnancy and vasculitis. Rheum Dis Clin North Am 2007;33:299-317.
134. Langford CA, Kerr GS. Pregnancy in vasculitis. Curr Opin Rheumatol 2002;14:36-41.
135. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, et al. EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis 2008;69:798-806.
136. Cabral DA, Uribe AG, Benseler S, O'Neil KM, Hashkes PJ, Higgins G, et al. Classification, presentation, and initial treatment of Wegener's granulomatosis in childhood. Arthritis Rheum 2009;60:3413-24.
137. Morishita K, Li SC, Muscal E, Spalding S, Guzman J, Uribe A, et al. Assessing the performance of the Birmingham Vasculitis Activity Score at diagnosis for children with antineutrophil cytoplasmic

antibody-associated vasculitis in A Registry for Childhood Vasculitis (ARChiVe). J Rheumatol 2012;39:1088-94.
138. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488-98.
139. Langford CA, Klippel JH, Balow JE, James SP, Sneller MC. Use of cytotoxic agents and cyclosporine in the treatment of autoimmune disease. Part 2: Inflammatory bowel disease, systemic vasculitis, and therapeutic toxicity. Ann Intern Med 1998;129:49-58.
140. Mukhtyar C, Flossmann O, Hellmich B, Bacon P, Cid M, Cohen-Tervaert JW, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. Ann Rheum Dis 2008;67:1004-10.