EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis

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EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis.

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Recommendations for the management of AAV. A collaboration between the European League Against Rheumatism (EULAR) and European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) 2015 Full Guideline.

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Abstract

In this article, the 2009 European League against Rheumatism (EULAR) recommendations for the management of ANCA-associated vasculitis (AAV) have been updated. The 2009 recommendations were on the management of primary and small vessel vasculitis. The 2015 update has been developed by an international task force representing EULAR, the European Renal Association (ERA) and the European Vasculitis Society (EUVAS). The recommendations are based upon evidence from systematic literature reviews, as well as expert opinion where appropriate. The evidence presented was discussed and summarized by the experts in the course of a consensus finding and voting process. Levels of evidence and grades of recommendations were derived and levels of agreement (strengths of recommendations) were determined. The relevance of the recommendations were assessed by an online voting survey amongst the members of the (EUVAS). Fifteen recommendations were developed. Some of the 2009 recommendations were deleted, and others were amended or split and some remain unchanged (specifically those not referring to management of AAV – GPA, MPA, EGPA). The recommendations cover general aspects, such as attainment of remission and the need for shared decision-making between rheumatologists and patients. The more specific items relate to starting immunosuppressive therapy using a strategy in combination with glucocorticoids to induce remission, followed by a period of remission maintenance. For remission induction of life or organ-threatening AAV, cyclophosphamide and rituximab are essentially considered to have similar efficacy. If the first-line strategy fails, such patients should be referred to an expert centre of further management and for potential enrolment in clinical trials. The recommendations also address plasma exchange which is recommended, where licensed, in the setting of rapidly progressive renal failure or severe diffuse pulmonary haemorrhage. These recommendations are intended for use by healthcare professionals, doctors in specialist training, medical students,

pharmaceutical industries and drug regulatory organisations. They are based on evidence and expert opinion and intended to improve outcomes in patients with AAV.

Introduction

Granulomatosis with polyangiitis (Wegener's) (GPA), Microscopic polyangiitis (MPA) and Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) are together termed the ANCA-associated vasculitides (AAV) (1). GPA, MPA, and EGPA have respective annual incidence rates of 2.1 – 14.4, 2.4 – 10.1, and 0.5 – 3.7 per million in Europe, and the prevalence of AAV is estimated at to be 46 – 184 per million (2-8). The 5-year survival rates for GPA, MPA, and EGPA are estimated to be 74-91%, 45-76% and 60-97% respectively (9).

Background and Rationale

In 2009 we published the European League Against Rheumatism (EULAR) recommendations for managing primary systemic vasculitis which included the management of AAV (10). The publication of 1691 papers on primary systemic vasculitis in the past 5 years in internal medicine, rheumatology and nephrology journals, as well as the licensing of rituximab for AAV, make this an opportune time to update the guidelines with an AAV focus.

This paper reassesses standard therapy, including the use of biologic agents, the prognostic value of histopathology and management of long-term complications, integrating these into treatment algorithms.

Methods

The EULAR Standardised Operation Procedures (SOP) for the elaboration, evaluation, dissemination and implementation of recommendations were followed

(11). In line with these recommendations the following wording, category, objective and steering group are defined as:

- Wording: This strength of evidence has allowed for production of recommendations. Importantly this is an update of the previous EULAR guidelines on the management of small and medium vessel vasculitis (10).
- Category: Recommendations for management, monitoring, or treatment in daily practice
- The objective of the project is to produce recommendations for management, monitoring, and treatment in daily practice. The target population will include physicians, particularly rheumatologists and renal physicians treating patients with AAV, doctors in specialist training, specialist nurses, national advisory organisations, and national specialist societies
- Steering group members were experts from Europe and the USA with expertise in the management of patients with AAV. The group was strengthened with the addition of a patient, a nurse and a clinical epidemiologist.

The taskforce

The multidisciplinary taskforce comprised 21 experts including a patient (John Mills), a nurse (Janice Mooney), a pathologist (IMB), an otorhinolaryngologist (ML), a pulmonologist (BC), an immunologist (TH), an ophthalmologist (NY), two general internists (AM, MCC), six renal physicians (MAL, MS, VT, KW, AV and DRJ), and six rheumatologists (RAW, BH, JH, RAL, PAM, and CM) with academic experience and/or clinical expertise in the field of vasculitis. They were from 12 countries (Czech Republic, France, Germany, Ireland, Italy, the Netherlands, Spain, Sweden, Switzerland, Turkey, UK and USA) and represented members of EULAR, the European Renal Association – European

Dialysis and Transplant Association (ERA-EDTA), the European Vasculitis Society (EUVAS) and the Vasculitis Clinical Research Consortium (VCRC). MY was appointed as the Clinical Fellow.

Delphi process

A Delphi exercise was conducted amongst the members of the taskforce in 2014. Individuals were asked to rank the top five choices in order of importance for updating the existing EULAR guidelines. Weighted scores were calculated for each item. The top ten items identified for update consisted of the following:

1. Role of ANCA at diagnosis and follow up
2. Role of biopsy at diagnosis and follow up
3. Staging of disease at diagnosis
4. Choice of remission induction therapy
5. Choice of drug for refractory disease
6. Choice of remission maintenance agent
7. Choice of drug for relapsing disease
8. Dose of glucocorticoid therapy at diagnosis and follow up
9. Role of plasma exchange
10. Length of treatment for remission

Taskforce members were also able to suggest new items that they considered important and appropriate for the purposes of producing recommendations. The new items identified were grouped into the following five themes:

1. Choice of immunosuppressive medication based on clinical characteristics or autoantibody type (including treating granulomatous relapse vs. vasculitic relapse)

2. Role of treatment with biologic agents and their monitoring (the majority of votes were for rituximab)
3. Immunological monitoring (including monitoring immunoglobulin levels during treatment with rituximab and prevention of infection)
4. Managing cardiovascular risk
5. Patient education

Systematic Literature Search Strategy

Three systematic literature searches were performed using MEDLINE, EMBASE and CENTRAL databases. The systematic literature searches were performed in two ways: i) a closed search (search date from 2007 to Feb 2015), focusing on the items to be updated from the last set of recommendations and ii) an open search (no date restrictions) based on items identified by the Delphi method described above.

The committee agreed on the search string to identify the publications. All identified papers were limited to manuscripts indexed for adult patients and those having abstracts. There were no restrictions on language. The EMBASE, CINAHL PLUS and CENTRAL databases were searched using the disease specific keywords. See Appendix 1 for search strings. The final search date was February 2015.

The resulting draft statements were voted upon by the experts and then correlated with a wider vote amongst the European Vasculitis Society (EUVAS) membership.

Quality scoring of manuscripts

The number of evaluated manuscripts is described and presented as a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, see Figure 1 (separate file) (10).

Manuscripts were formally scored using the Critical Appraisal Skills Programme (CASP) checklist (11).

Categorisation of evidence – following EULAR SOP (Table 1). The mode vote for each recommendation amongst the taskforce and EUVAS membership are shown (Table 2) (11).

Table 1: Categorisation of evidence according to EULAR SOP.

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

Table 2: Strength of recommendations according to EULAR SOP.

Strength	Directly based on
A	Category 1 evidence
B	Category 2 evidence or extrapolated recommendations from category

	1 evidence
C	Category 3 evidence or extrapolated recommendation from category 1 or 2 evidence
D	Category 4 evidence or extrapolated recommendation from category 2 or 3 evidence

Expert opinion approach – for recommendation statements which are not derived from clinical trials, consensus was based on clinical recommendations of the taskforce committee; these have a default strength of D.

Developing the recommendations

The results of the systematic literature review were presented and discussed during the taskforce meeting in Zurich in March 2015 and fifteen recommendations were developed. The strength of each recommendation was based on the categories of evidence defined by the EULAR SOP, graded from A (highest) to D (lowest) (11). The recommendations were based on the available evidence and taskforce members agreed on the final wording of each statement. Independent voting of each taskforce member took place at the meeting in Zurich. In addition to the taskforce, the EUVAS group was invited to rate independently the strength of evidence of each recommendation to obtain an indication of the agreement among the final target audience.

Presentation of the recommendations

- Treatment algorithms were formulated and are found in Figure 3 (separate file).

- Advice on recognition and management of eye and otorhinolaryngology complications of AAV has been included in Appendix 2.

- Brief consensus statements were formulated and assessed by an online survey and vote amongst the membership of EUVAS (see Appendix 3).
- An audit tool was developed and is located in Appendix 4.
- Lay summary (Appendix 5).

Statements

The statements in this manuscript are termed ‘‘recommendations’’ as opposed to ‘‘guidelines’’ or ‘‘points to consider’’ because it offers guidance which needs to be tailored to meet individual requirements. They are intended for use by healthcare professionals, doctors in specialist training, medical students, pharmaceutical industries and drug regulatory organisations.

Statement One

We recommend that patients with ANCA-associated vasculitis are managed in close collaboration with, or at, centres of expertise. Level of evidence 3; grade of recommendation C; strength of vote 100%.

The rarity of AAV makes it difficult to maintain expertise in their management (2, 12-14). Assessment of these patients requires expert guidance to differentiate activity from damage or infection and to consider differential diagnoses. Patients may require interventions by specialists with expertise in AAV, such as: immunological monitoring, use of rituximab in patients with refractory disease, specialised radiography, assessment of eye involvement, injection of subglottic stenosis, and renal transplantation (15-22). For patients with refractory disease, the best option may be consideration of referral to centres participating in clinical trials. AAV may relapse years after remission is achieved, even in previously

unaffected organ systems (23-25). Patients may develop complications from the treatment many years after discontinuing treatment (26, 27). Long-term follow-up and rapid access to specialist services are necessary for all patients with AAV. For these reasons patients with AAV should be managed in close collaboration with, or at, centres of expertise (28).

Statement Two

A positive biopsy is strongly supportive of a diagnosis of vasculitis and we recommend biopsies to assist in establishing a new diagnosis and for further evaluation for patients suspected of having relapsing vasculitis. Level of evidence 3; grade of recommendation C; strength of vote 81%.

A positive biopsy for AAV is helpful when considering an initial diagnosis or recurrent disease. Histopathological evidence of vasculitis, such as pauci-immune glomerulonephritis or necrotising vasculitis in any organ remains the gold standard for diagnostic purposes. The likely diagnostic yield varies and is dependent on the organ targeted. In patients with GPA with renal involvement the diagnostic yield from renal biopsy can be as high as 91.5% (29). Otorhinolaryngological examination in patients with GPA often reveals abnormal findings and biopsies of these areas may be positive in up to 68.4% (30, 31). A large study of 60 nasal, 27 paranasal sinus, 17 laryngeal, 5 periorbital, 5 oral, 4 middle ear, 3 mastoid, 2 external ear and 3 salivary gland biopsies revealed that they often yield non-specific chronic inflammation and the more specific findings of granulomas or vasculitis are seen less frequently than in other tissue biopsies (32). Lung biopsies vary in their diagnostic sensitivity, with only 12% of transbronchial biopsies of alveolar tissue positive for GPA and 66.7% for EGPA in one study (30). Open lung biopsies, although more invasive, provide a much higher diagnostic yield (33).

Percutaneous renal biopsy should be performed using ultrasound guidance where possible and has been shown to be associated with a low risk of complications including haemorrhage (34). The risk of bleeding following percutaneous renal biopsy is higher in patients treated with plasma exchange (35). Generic factors associated with an increased risk of bleeding necessitating

transfusion include old age, increased systolic blood pressure and worse renal function (36).

Histological findings of renal biopsy have prognostic value for patients with AAV, with adverse outcomes for those individuals found to have sclerotic change (37-39).

Statement Three

For remission-induction of new-onset organ or life-threatening ANCA-associated vasculitis we recommend treatment with a combination of glucocorticoids and either cyclophosphamide OR rituximab.

- *cyclophosphamide (CYC)*
    - *level of evidence 1A for GPA and MPA; grade of recommendation A; strength of vote 100%.*
    - *level of evidence 3 for EGPA; grade of recommendation C; strength of vote 88%.*
- *rituximab (RTX)*
    - *level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 82%.*
    - *level of evidence 3 for EGPA; grade of recommendation C; strength of vote 59%.*

The AAVs are potentially life-threatening and can involve any organ system. Their protean presentations pose a challenge to clinicians and can lead to delays in diagnosis (40-42). Patients with AAV may initially have involvement of one or two body systems which can then rapidly evolve to affect other organs and become organ or life-threatening (43, 44). This concept of a disease spectrum

should sensitise clinicians to be vigilant about clinical evaluation and follow-up, especially when patients with AAV mention new symptoms.

Definitions of remission in AAV vary between trials. EULAR defines remission as the complete absence of active clinical disease (45), a definition which does not require patients to be off all immunosuppressive treatment. Disease activity should be recorded systematically according to validated and published disease activity scores (45).

In general the current guidelines group GPA and MPA together, as most of the trials have recruited patients in this way. In addition, there are many more trials involving patients with GPA and MPA than with EGPA and this is often reflected in the study design and resulting evidence grade. It is not the intention of the taskforce to maintain the delineation of GPA and MPA vs EGPA. Indeed, the current status quo of classification systems has been called into question by the findings of a recent genome-wide association study, which has provided evidence for possible genetic differences between GPA and MPA which segregate along ANCA specificity lines (46). Cluster analysis of data compiled from several clinical trials suggested five sub-groups for AAV based on the presence of the ANCA sub-type and involvement of the kidney, heart or gut (47). Deriving a new classification system for AAV which may affect treatment decisions is an important part of the ongoing research agenda.

Since the 1970s therapy consisting of a combination of glucocorticoids (1 mg/kg/day – maximum daily dose 80 mg) with cyclophosphamide (2 mg/kg/day – maximum 200 mg/day) has been used for remission induction in AAV (48). Due to concerns about cumulative cyclophosphamide dosage, pulsed intravenous regimens were designed and tested, the largest study being the CYCLOPS trial (49). This trial was designed following a meta-analysis of three studies involving

143 patients (50-52) which concluded that pulsed cyclophosphamide was more likely to achieve remission and was associated with fewer side-effects than oral cyclophosphamide (53).

The CYCLOPS trial recruited 149 participants with GPA or MPA who were given either oral (2 mg/kg/day - maximum oral dose 200 mg) or pulsed cyclophosphamide (15 mg/kg - maximum pulse dose 1.2 g) initially every two weeks for the first three pulses, then every three weeks for the next three to six pulses. Dose reductions were made for those with severe renal disease and for older participants (oral dose reduced by 25% for those aged >60 years and 50% those aged >70 years, pulse dose reduced to 12.5 mg/kg in those aged >60 years and to 10 mg/kg/day in those aged >70 years). No difference was noted between the treatment arms in terms of time to remission or the proportion achieving remission at nine months (49). Long-term follow-up of the CYCLOPS cohort revealed that although the proportion of participants with at least one relapse was higher in those individuals treated with pulsed cyclophosphamide, there were no differences in survival, renal function at the end of the study or adverse events between the two arms (54). However, pulsed regimens are favoured due to the reduced total dose of cyclophosphamide overall and reduced risk of bladder-related complications.

The grade of evidence for cyclophosphamide use in EGPA is lower than for GPA/MPA as no randomised controlled trials (RCTs) for the treatment of EGPA have been published. One study did compare cyclophosphamide doses: cyclophosphamide (0.6 mg/m^2) was used initially every two weeks for a month then every four weeks (55). The intervention arm was given six pulses in total; whilst the control arm received 12 pulses. Complete remission was achieved in both groups at a similar rate (21/23 in intervention arm, 21/25 in control arm).

Antiemetic therapy should be routinely administered with intravenous cyclophosphamide. Cyclophosphamide metabolites are toxic to the urothelium and can cause haemorrhagic cystitis in the short term and malignancy in the long term (26, 56, 57). Patients should be encouraged to drink plenty of fluids and if thought necessary, given intravenous fluids on the day of the infusion to dilute the metabolites in the urine. Patients receiving pulse cyclophosphamide may also be given oral or intravenous 2-mercaptoethanesulfonate sodium (MESNA) which binds to acrolein, a toxic metabolite of cyclophosphamide, rendering it non-toxic (24). MESNA also retards the degradation of 4-hydroxymetabolites, further reducing the toxic acrolein products in the urine. MESNA may also be beneficial in patients receiving continuous oral cyclophosphamide (23, 24, 58).

Monitoring of patients receiving cyclophosphamide should follow standard protocols (59). In both modalities of administration, dose changes or discontinuation of cyclophosphamide may be necessary in the event of an acute leucopoenia or a gradual fall over time. In the event of a stable leucopoenia, it may be possible to maintain the immunosuppression with stringent blood monitoring. We encourage prophylaxis against infection with *Pneumocystis jirovecii* with trimethoprim/sulphamethoxazole (800/160 mg on alternate days or 400/80 mg daily) in all patients being treated with cyclophosphamide where not contraindicated (60-62). The use of inhaled monthly pentamidine in the event of an adverse reaction or contraindication to trimethoprim/sulphamethoxazole may be useful but is not cost-effective and not routinely indicated (60). Other alternatives include dapsone and atovaquone.

Rituximab in AAV has been tested in two RCTs (RAVE and RITUXVAS) (63, 64). In both studies patients initially received high-dose glucocorticoids with subsequent dose tapering. The rituximab dose in both studies was 375 mg/m^2 of body surface area, once a week for four infusions. Both studies recruited

participants with GPA or MPA; 66% of RAVE and all RITUXVAS participants had renal involvement. In the larger RAVE trial (n = 197) patients in the control arm were initially treated with oral cyclophosphamide (2 mg/kg/day) and later switched to azathioprine (2 mg/kg/day) (64). Rituximab was not inferior to cyclophosphamide at inducing remission and appeared more effective for relapsing disease (64). The RITUXVAS trial recruited 44 participants with newly diagnosed AAV; generally patients were more severely ill than in the RAVE trial (63). It was an open-label study and participants in the rituximab group also received pulsed cyclophosphamide (15 mg/kg) with the first and third rituximab infusions (with a third pulse allowed if the participants had progressive disease within the first six months). Participants in the control arm received pulsed cyclophosphamide (similar to the CYCLOPS regimen: minimum of six pulses, maximum of 10 pulses), followed by azathioprine (2 mg/kg/day). Sustained remissions were high in both groups (76% in the RTX group and 82% in the control group respectively) (63).

The grade of evidence for the use of rituximab in patients with EGPA is lower than for GPA/MPA. A retrospective analysis of 41 patients with EGPA who received differing regimens of rituximab found that 34% achieved complete remission at six months and 49% at 12 months (65). In total, 19/41 patients received a single course of rituximab. Re-treatment was given for 22/41 at six months and 17/22 were re-treated again at 12 months. Two received their first re-treatment at 12 months. The initial treatment schedule was 375 mg/m^2/week for four weeks (n=10) or two doses of 1000 mg given two weeks apart (n=30). One patient received two doses of 800 mg at a two-week interval. Subsequent rituximab courses and doses were 375 mg/m^2/week for four weeks (three patients), two doses of 1000 mg two weeks apart (two patients), 1000 mg single dose (16 patients), and a single dose of 600 mg rituximab (one patient) (65).

The dose of rituximab for remission induction varies between the published studies. This is also reflected in a survey of UK clinical practice. Four centres were surveyed, with data from 65 sequential patients contributing to the analysis (66). Of these, 32 patients were treated with 1000 mg two weeks part, 26 were given 375 mg/m^2 every week for four infusions and seven received a modified regimen (66). Complete remission was achieved in 49/65 patients with no difference between the two main rituximab regimens.

Due to high cost, rituximab use is restricted in some countries and therefore involvement of expert centres is mandated. The efficacy of rituximab induction is comparable to cyclophosphamide induction (63, 64). There may be specific instances where rituximab is preferable to cyclophosphamide, for example in patients who wish to preserve their reproductive potential. Cyclophosphamide is associated with reduced ovarian reserve, ovarian failure and male infertility (67-71). The long-term effects of rituximab on fertility have not been studied but no such concerns have been reported. In patients with severe disease, treatment should not be delayed but discussion of these issues should take place.

The taskforce considered appropriate a target of between 7.5 mg to 10 mg of prednisolone (or equivalent) after three months (12 weeks) of treatment. A review of the prednisolone protocol reduction regimens published for the key trials illustrated that on average a dose of 10mg was achieved after 19 weeks, and a dose of 7.5mg after 21 weeks (Figure 2) (49, 63, 64, 72-77). Therefore although a target prednisolone dose of 7.5mg to 10mg is desirable by 3 months, in practice it may be 5 months before this is achieved.

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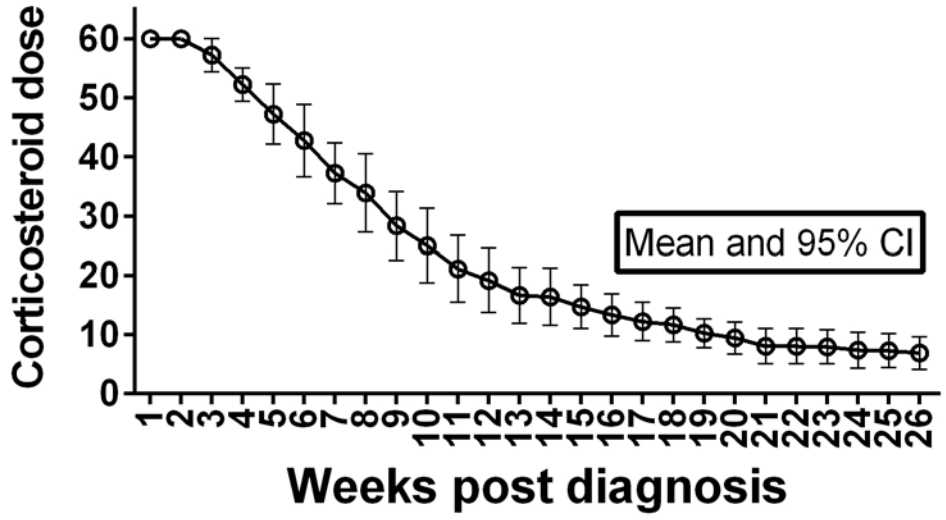

Figure 2. Protocol target prednisolone dosages in the key induction trials of AAV.

Statement Four

For remission-induction of non organ-threatening ANCA-associated vasculitis we recommend treatment with a combination of glucocorticoids and either methotrexate or mycophenolate mofetil.

- *MTX*
    - *Level of evidence 1B; grade of recommendation B; strength of vote 77%.*
- *MMF*
    - *Level of evidence 1B; grade of recommendation C; strength of vote 65%.*

The taskforce was keen to stress that the use of methotrexate or mycophenolate mofetil should not be used for remission induction in the following scenarios:

- Meningeal involvement
- Retro-orbital disease
- Cardiac involvement
- Mesenteric involvement
- Acute-onset mononeuritis multiplex
- Pulmonary haemorrhage of any severity

Methotrexate (20–25 mg/week, oral or parenteral) can be used as an alternative to cyclophosphamide in patients with less severe disease and in those with normal renal function (23, 74, 78-85). There have been trials using either methotrexate or mycophenolate mofetil as the remission induction agent in patients with AAV. The NORAM study, a RCT, was the largest of these and recruited 95 participants with AAV (89 with GPA and 6 with MPA) (74). The exclusion criteria for the NORAM study were those with organ or life-threatening manifestations (severe haemoptysis associated with bilateral infiltrates, cerebral infarction due to vasculitis, rapidly progressive neuropathy, orbital pseudo-tumour, massive gastrointestinal bleeding, heart failure due to pericarditis or myocarditis) or serum creatinine >150 μmol/L, urinary red cell casts, or proteinuria >1.0 g/day. Therefore methotrexate use should be restricted to those individuals with less severe disease manifestations of AAV. Oral methotrexate (15 mg/wk given, escalating to a maximum of 20 to 25 mg/wk by week 12) was compared to oral cyclophosphamide 2 mg/kg/day (maximum 150 mg/day) until remission (minimum three months, maximum six months). Both treatments were tapered from month 10 and were stopped by month 12. Long-term follow-up of NORAM revealed that although there were no differences in major events (serious infection, end-stage renal failure or death) between the two groups, the methotrexate group was less effective at controlling disease and required other immunosuppressive agents for longer periods than the cyclophosphamide group.

(86). Methotrexate should therefore be considered only for non organ-threatening disease. Examples include the following in the ***absence of renal involvement***

- Nasal and paranasal disease without bony involvement (erosion) or cartilage collapse or olfactory dysfunction or deafness
- Skin involvement without ulceration
- Myositis (skeletal muscle only)
- Non-cavitating pulmonary nodules/infiltrate without haemoptysis
- When cyclophosphamide or rituximab are not available or contraindicated or patient choice.

The induction trials involving methotrexate are generally larger and of higher evidence grade than those using mycophenolate mofetil. The previous recommendations from EULAR made reference to two trials using mycophenolate mofetil (MMF) at a dose of 2g/day for remission induction (10). (72, 87). The first study was a retrospective analysis of a case series of patients with AAV treated with MMF: of 22 patients receiving MMF for active disease, 86.4% achieved remission, however 9 (47.4%) relapsed (87). The other study was also an uncontrolled study and recruited 32 patients with AAV (29 with GPA and 3 with MPA) who could not be treated with cyclophosphamide (72). Complete remission (Birmingham Vasculitis Activity Score - BVAS <1 (88)) was achieved in 25 patients (78%) after a median duration of 2.2 months. Nine (36%) patients relapsed within a year (72).

Following these uncontrolled studies, RCTs have been published (89, 90). The first was published in 2008 and compared MMF 2 g/day (1.5 g per day for those <50 kg in weight) to cyclophosphamide 0.75 to 1.0 g/m^2 body surface area (89). There were 35 participants recruited with active AAV with renal involvement (34 MPA, 1 GPA). Important exclusions were severe renal failure, with serum

creatinine ≥500 μmol/L or renal replacement treatment for more than two weeks, or life-threatening organ manifestations (lung hemorrhage, central nervous system involvement). There is therefore little evidence for the use of MMF in such scenarios.

The outcome was measured as complete remission (BVAS <1) at six months. In the intent-to-treatment analysis, 14 of 18 patients (77.8%) treated with MMF and 8 of 17 patients (47.1%) receiving cyclophosphamide (although four participants were lost to follow-up) had complete remission (89). The other RCT was published in 2011 and involved 41 Chinese participants, all of whom had MPA (90). It compared MMF 1 g/day (1.5 g/day in those weighing >70 kg) against cyclophosphamide monthly 1 g per pulses (0.8 g per pulse in those weighing <50 kg). This trial also included those with severe renal failure as defined by a serum creatinine of >500 μmol/L (5/22 participants in the cyclophosphamide group and 4/19 in the MMF group). Important exclusions were: severe lung haemorrhage (haemoptysis >300 ml/24 h or with hypoxemia) or central nervous system involvement and other life-threatening situations or age >70 years, which prevents the generalisability of the findings to other more severe presentations of AAV.

The outcome was measured as complete remission (BVAS <1 and dose of prednisolone <7.5 mg/day) at six months; this was achieved in 63.6% of the cyclophosphamide group and 78.9% of the MMF group (90). To date, the two RCTs using MMF mainly have been conducted primarily in patients with MPA (of the 76 participants 75 had MPA). MPA often affects renal function and in such situations methotrexate would not be indicated. The MYCYC trial compared MMF (2 to 3 g daily) to pulsed cyclophosphamide (15 mg/kg for 6 to 10 pulses); preliminary results have been published in abstract form but full publication is awaited (91). The remission end point (absence of disease activity for four weeks

or longer whilst on prednisolone at six months) was achieved in 66% (MMF) and 69% (cyclophosphamide) of patients (91). No data are yet available on the numbers of participants with GPA or MPA recruited to this trial.

Statement Five

For a major relapse of organ- or life-threatening disease in ANCA-associated vasculitis we recommend treatment as per new disease with a combination of glucocorticoids and either cyclophosphamide OR rituximab.

- *RTX*
    - *level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 94%.*
    - *level of evidence 4 for EGPA; grade of recommendation D; strength of vote 100%*
- *CYC*
    - *level of evidence 1A for GPA and MPA; grade of recommendation A; strength of vote 88%.*
    - *level of evidence 3 for EGPA; grade of recommendation C; strength of vote 88%.*

Most trials published on remission induction in AAV make no distinction between those participants treated for a new or relapsing presentation of their disease. It is for these reasons that the trial evidence for new or relapsing disease is often from the same studies. However, some studies have distinguished between those participants with new and relapsing disease and have stratified by this factor when randomising patients.

The largest RCT to investigate the use of rituximab for remission induction in AAV (RAVE) stratified participants by new or relapsing disease; those with relapsing disease treated with rituximab were more likely to be in disease remission at the 6 and 12 month time points but not the 18 month follow-up visit (64).

The cumulative dose of cyclophosphamide is related to toxicity and is a particular concern with prolonged oral dosing, where cumulative doses are higher (92). For this reason the taskforce has favoured a greater strength of recommendation for rituximab over cyclophosphamide for relapsing disease.

Further analysis of the RAVE trial data has revealed some important insights with respect to minor relapses. There were 44 participants with a non-severe relapse (BVAS for Wegener's Granulomatosis (BVAS/WG) (93) <4 and absence of a major item). These patients were more likely to be PR3-ANCA positive (82%), diagnosed with GPA (91%) and have a history of relapsing disease at baseline (64%) (94). An increase in the prednisolone dosage led to remission in 35 (80%) cases, but 31 had a second relapse (14 severe) (94). The mean time to second relapse was 9.4 months. A similar percentage of patients achieved and maintained remission when treated with high-dose prednisolone (≥20 mg/day) as opposed to low-dose prednisolone (<20 mg/day). Seventy-seven percent of patients with relapsing disease who were treated with high-dose prednisolone achieved remission, and 23% of those patients maintained those remissions for the remainder of follow-up. In comparison, 82% of the patients with relapsing disease who were treated with low-dose prednisolone achieved remission, and 36% maintained those remissions (94). In conclusion, treatment of non-severe relapses in AAV with a temporary increase in the glucocorticoid dose restores disease remission in most patients but recurrent relapses within a relatively short time period remain common. Given these data, alternative approaches to the

treatment of non-severe relapses must be considered, especially if relapses are frequent. We therefore recommend treatment with intensification or modification of the immunosuppressive remission maintenance regimen.

Statement Six

Plasma exchange should be considered for patients with ANCA-associated vasculitis and a serum creatinine level of greater than 500 µmol/L (5.7 mg/dL) due to rapidly progressive glomerulonephritis in the setting of new or relapsing disease. Level of evidence 1B; grade of recommendation B; strength of vote 77%.

Plasma exchange can also be considered for the treatment of severe diffuse alveolar haemorrhage. Level of evidence 3; grade of recommendation C; strength of vote 88%.

Plasma exchange (PLEX) use is usually reserved for patients with either severe renal impairment or those with diffuse alveolar haemorrhage (95-97). The largest trial published to date is MEPEX which recruited those individuals with either a serum creatinine >500µmol/L (5.7 mg/dL) or those requiring dialysis (77). Long-term follow-up and analysis of this trial has also been published (98). In this trial 137 participants with AAV were recruited and received cyclophosphamide and glucocorticoids in addition to either PLEX or pulsed IV methylprednisolone (up to 3g). The primary end point was end-stage renal disease (ESRD) or death at three months. Of those treated with IV methylprednisolone, 33 (49%) were alive and dialysis-independent at three months, compared with 48 (69%) in the PLEX group (95% confidence interval for the difference 18 to 35%; P = 0.02) (77). However, a long-term follow-up study revealed no statistically significant benefit for the PLEX group when comparing a composite outcome of ESRD or death

(99). Prior to the publication of this long-term follow-up data, a meta-analysis had concluded that plasma exchange may decrease the composite end point of ESRD or death in patients with renal vasculitis (100). However most trials of PLEX did not restrict use to individuals with a serum creatinine >500 µmol/L (5.7 mg/dL). One RCT with long-term follow-up that has tested whether PLEX may benefit individuals with a serum creatinine of <500 µmol/L (5.7 mg/dL) (101). This trial recruited 32 participants with GPA and compared the effects of PLEX versus no PLEX and of oral cyclophosphamide (100 or 150 mg daily for 3 to 12 months) versus cyclosporine A (5 mg/kg) with a Latin square design (101). Elevated serum creatinine at enrolment was noted in 22 of the 32 participants who were equally allocated amongst the four groups. After 1 month, none of the PLEX participants required haemodialysis (HD) or had worsening renal function compared with six with declining renal function and five on HD in the reference group ($p < 0.05$) (101). Despite the improvements in renal function, there were no differences in all-cause mortality between the PLEX and reference groups after five years of follow-up (101). PEXIVAS is a global trial that is currently recruiting with a target of 700 participants with moderate renal impairment (eGFR <50 ml/min) and aims to provide definitive answers regarding the use of PLEX in AAV, especially regarding the cut-off of serum creatinine of 500 µmol/L (5.66 mg/dL). The PEXIVAS trial uses the following protocol for PLEX (102):

- Seven plasma exchanges of 60 mL/kg, either with centrifugation or filter separation according to local practice and availability.
- Anticoagulation by heparinisation or citrate according to local practice.
- Replacement fluid with human serum albumin (3-5% depending on local availability). Albumin may be combined with crystalloid (e.g. saline).
- Patients with active bleeding to receive supplemental plasma to replace clotting factors according to local practice.

All participants in the PEXIVAS trial will also receive IV methylprednisolone (1000 mg pulses for 1 to 3 days) with standard induction therapy either pulsed cyclophosphamide or rituximab. The trial investigators suggest waiting 48 hours after RTX is given prior to undertaking a session of PLEX.

There is also potential benefit for PLEX in patients with AAV who are also anti-GBM antibody positive, particularly those in whom there is linear staining of IgG on the glomerular basement membrane, and PLEX should be performed early in such patients to improve outcome (97, 103).

Statement Seven

For remission-maintenance of ANCA-associated vasculitis we recommend treatment with a combination of low-dose glucocorticoids and either azathioprine, rituximab, methotrexate, or mycophenolate mofetil.

GPA/MPA

- *AZA*
    - *Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 94%.*
- *RTX*
    - *Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 59%.*
- *MTX*
    - *Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 53%*
- *MMF*

- *Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 53%*

EGPA

- *AZA*
  - *Level of evidence 3 for EGPA; grade of recommendation C; strength of vote 77%.*

Long-term therapy with cyclophosphamide has been used to maintain remission in patients with AAV (23). However the toxicity of long-term cyclophosphamide makes it an unattractive option (26, 56, 57). Azathioprine (2 mg/kg/day) is safer than oral cyclophosphamide but as effective at 18 months in preventing relapse (76, 104). Methotrexate (20–25 mg/kg/week) has been effectively used for maintenance therapy after induction of remission with cyclophosphamide (if the serum creatinine is >130 µmol/L or 1.5 mg/dL) (105, 106). Leflunomide (20–30 mg/day) may be more effective than methotrexate in remission maintenance but is associated with more adverse effects (107). Therefore Leflunomide is considered for second-line treatment in cases of intolerance to AZA, MTX, MMF or RTX. Early cessation of therapy is associated with an increased risk of relapse (74).

Long-term follow-up of the CYCAZAREM study which recruited 155 participants with AAV (95 GPA, 60 MPA) was published in 2014 (108). Participants received remission induction therapy with oral cyclophosphamide (2 mg/kg per day) with prednisolone (initially 1 mg/kg reducing to 0.25 mg/kg per day by 12 weeks) and 93% were in remission by six months (76). Those patients in whom remission had been achieved by three months, or between three and six months, were randomly assigned to treatment with azathioprine as a substitute for cyclophosphamide (azathioprine group) or to continued cyclophosphamide

therapy (cyclophosphamide group). Twelve months after study entry, the patients in the cyclophosphamide group were switched to the same azathioprine regimen as the azathioprine group was receiving and continued to receive this regimen until the end of the study, 18 months after entry. The initial paper concluded there was no difference in relapse rate at 18 months between the two groups. Long-term follow-up revealed no statistical significance differences for outcome between the two groups (108).

The WEGENT trial compared methotrexate to azathioprine and recruited 126 participants with AAV (GPA 96 and MPA 30) (109). Participants received pulsed cyclophosphamide and prednisolone for remission induction. The first three cyclophosphamide pulses were given two weeks apart, following which the interval was increased to every three weeks for the next three pulses. Prednisolone target dose at six months was 12.5mg/day with withdrawal after 24 months (109). Methotrexate (0.3 mg/kg increasing in 2.5 mg increments weekly to maximum 25 mg per week) or azathioprine (2 mg/kg/day) were started after the sixth pulse of cyclophosphamide and both were withdrawn over a period of three months after 24 months (109). 24 months after randomisation, relapse-free survival rates were 71.8% (95% CI, 59.7% to 83.8%) in the azathioprine group and 74.5% (95% CI, 62.7% to 86.4%) in the MTX group. The hazard ratio for the risk of relapse among MTX vs AZA was 0.92 (95% CI, 0.52 to 1.65; P = 0.78).

The MAINRITSAN trial compared rituximab to azathioprine for remission maintenance (110). This trial recruited 115 participants with AAV (87 GPA, 23 MPA and five with renal limited vasculitis) all of whom were treated with pulsed cyclophosphamide (initially 0.6 g/m^2 every 2 weeks for three pulses then 0.7 g/m^2 every three weeks for a further three to six pulses) and prednisolone for remission induction. During the month after the last cyclophosphamide pulse, patients in the rituximab group received intravenous rituximab (at a fixed 500 mg

dose) on days 0 and 14 after randomisation, and then at months 6, 12, and 18 after the first infusion. Patients in the azathioprine group took azathioprine at a dosage of 2 mg/kg/day for 12 months, and then 1.5 mg/kg/day for 6 months and 1 mg/kg/day for 4 months. In addition, prednisolone treatment was further tapered and kept at a low dose (approximately 5 mg/day) for at least 18 months after randomisation. Prednisolone dose tapering and the decision to stop prednisolone treatment after 18 months were left to each site investigator's discretion (110). Rituximab was superior to azathioprine at preventing relapse. At month 28, major relapses had occurred: 17 in the azathioprine group (eight occurred within 12 months of treatment, two when dosage of AZA was between 1.5 and 1 mg/kg/day and the rest once AZA stopped), 3 in the rituximab group (at months 8, 22 and 24). Renal relapses occurred in 8/17 major relapses in the AZA group and 0/3 in the RTX group (110).

Azathioprine (AZA) is preferred over mycophenolate mofetil (MMF) for remission maintenance, primarily because of the results from the IMPROVE trial (111). This study recruited 156 participants with AAV (GPA 100, MPA 56), who were treated initially with cyclophosphamide induction and randomised to receive either azathioprine (2 mg/kg per day, n=80) or MMF (2 g daily, n=76). In both groups the remission maintenance agent was reduced at two time points (after 12 and 18 months) and withdrawn after 42 months. Prednisolone was given as part of remission reduction with the regimen taper resulting in withdrawal after 24 months (111). The primary end point was relapse-free survival from the time remission was first achieved. Relapses were noted in 42 participants treated with MMF (55.3%; 18 major and 24 minor) and in 30 participants in the AZA group (37.5%; 10 major and 20 minor, $p < 0.01$).

The addition of trimethoprim/sulphamethoxazole (800/160 mg twice daily) to standard remission maintenance can reduce the risk of relapse in GPA (112).

Although trimethoprim/sulphamethoxazole has been used as the sole remission maintenance agent in half the patients of one RCT, trimethoprim/sulphamethoxazole monotherapy may not be effective for maintenance of remission (112, 113). 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* (114).

Statement Eight

We recommend that remission-maintenance therapy for ANCA-associated vasculitis be continued for at least 24 months following induction of sustained remission. Level of evidence 4; grade of recommendation D; strength of vote 75% for MPO persistent disease, 62% for MPO negative disease, 100% for PR3 persistent disease and 92% for PR3 negative disease.

No published RCTs have directly compared duration of maintenance therapy regimens. Early cessation of therapy is associated with an increased risk of relapse (74). Most of the data regarding relapse risk are derived from a combination of observational cohort data and long-term follow-up from clinical trials. There are however important differences in the make-up of the participants from these sources, with many more patients with GPA likely to be present in observational cohort studies (115). A meta-analysis of 13 studies (eight RCTs and five observational studies with 983 participants) examining the effect of duration of glucocorticoids on relapse rate concluded that continuing glucocorticoids is associated with fewer relapses (116). The pooled total estimate for the proportion of patients suffering with a relapse recruited to RCTs was 36% (95% confidence interval 25% to 47%) but only 14% for those studies which continued glucocorticoids. In patients with AAV with renal involvement, worse

prognosis is associated with those who have MPO-ANCA, even after adjustment for baseline factors such as age, sex and serum creatinine (117). Furthermore, patients with MPO-ANCA have more severe tubulointerstitial inflammation and both CD3(+) T cell tubulitis and tubular atrophy are independently associated with eGFR at 12 months (118). In addition, kidney biopsies displaying sclerosis are associated with worse outcomes in AAV (119). However, patients with PR3-ANCA and those with cardiovascular or lung involvement are more likely to relapse (43, 120). The resultant grade for the strength of recommendation of the taskforce reflects the lack of data for this area. It should be noted that there was a trend to increase the duration of therapy in patients who are PR3-ANCA positive and this was reflected with median of the vote for 36 months of maintenance therapy in this particular scenario.

Statement Nine

For patients with ANCA-associated vasculitis refractory to remission-induction therapy we recommend switching from cyclophosphamide to rituximab or from rituximab to cyclophosphamide. These patients should be managed in close conjunction with, or referred to, an expert centre for further evaluation and potential enrolment in clinical trials. Level of evidence 3; grade of recommendation C; strength of vote 71%.

Refractory disease is defined by EULAR as (45):

- Unchanged or increased disease activity in acute AAV after 4 weeks of treatment with standard therapy in acute AAV, or
- Lack of response, defined as <50% reduction in the disease activity score (e.g. BVAS or BVAS/WG), after 6 weeks of treatment, or

- Chronic, persistent disease defined as presence of at least one major or three minor items on the disease activity score after >12 weeks of treatment.

It is important to consider why a particular patient may have refractory disease and what it is that is driving the conclusion that they have refractory disease. Items to consider are:

- Re-evaluate the primary diagnosis are they truly refractory – do they have AAV?
- Has the treatment regimen been optimised i.e. have target dosages for therapy been reached?
- Is this active disease or could it be damage?
- Is the present disease due to AAV or could it be due to an infection or other co-morbidity or possible malignancy?

Rituximab has proven useful in patients with refractory disease, particularly those who have been previously treated with cyclophosphamide. Patients with refractory renal disease have the greatest chance of improvement, while those with retro-orbital disease pose a particular challenge (44, 65, 121, 122). Based on the results of an additional analysis of the WEGENT trial, the taskforce suggested a switch from pulsed to oral cyclophosphamide as a potential strategy under the guidance of an expert centre when rituximab is unavailable (123).

Additional analysis of the 52% of patients enrolled into the RAVE trial who had renal involvement (biopsy proven pauci-immune glomerulonephritis, red blood cell casts in the urine, and / or a rise in serum creatinine concentration attributed to vasculitis) revealed no difference in remission rates at 6, 12 or 18 month between the two groups (124). However, when the 47 (24%) of the participants

who failed to achieve the primary end point were treated with blinded crossover or according to best medical judgment by the trial physician, this led to disease control in the majority (125). Of the participants with uncontrolled disease or who experienced a severe relapse, 91% had proteinase 3 (PR3)-ANCA. Re-analysis of 37 of these 47 participants (excluding the 10 (5%) with uncontrolled disease) revealed treatment with rituximab was better than cyclophosphamide for those participants who were PR3-ANCA positive had fewer flares (8 of 59 [14%] versus 20 of 62 [32%]; P = 0.02) (125).

For patients who fail to achieve remission and have persistent low activity, adjunctive therapy with intravenous immunoglobulin may help patients achieve remission (126-128). Prior to therapy, serum immunoglobulin levels must be measured because patients with selective IgA deficiency may develop an anaphylactic reaction on receiving intravenous immunoglobulin (IVIG) or a pre-existing hyperglobulinemia may become aggravated leading to a hyperviscosity state.

Statement Ten

We recommend that structured clinical assessment rather than anti-neutrophil cytoplasmic antibody (ANCA) testing should inform decisions on changes in treatment for ANCA-associated vasculitis. Level of evidence 4; grade of recommendation D; strength of vote 100%.

The role of ANCA testing as a means of predicting future relapse is controversial and evolving (129, 130). ANCA testing should be performed at accredited labs which take part in quality assurance testing programmes (131, 132). A negative ANCA does not rule out AAV in the appropriate clinical context of active disease (133, 134).

The role of serial ANCA testing to guide therapy is controversial (135-137). Some studies have shown that patients in whom the ANCA titres persist, rise fourfold or become positive have a higher incidence of relapse, while other studies have not shown this association (104, 135, 137). It remains controversial as to whether a rise in ANCA, or switch from a negative to a positive ANCA, indicates an increase in risk of relapse. This should not in itself lead to a change in therapy but more frequent clinical assessment may be considered.

Multi-organ involvement is common in AAV. It is therefore important that a structured clinical assessment is conducted of all patients with a suspicion of ANCA-associated vasculitis. This examination may be facilitated by the use of clinical tools which form a checklist of common items affecting various systems. Structured/standardised assessment of disease activity and damage should be used e.g. BVAS and the Vasculitis Damage Index (VDI) (88, 138-140). BVAS(v.3) was modified in 2008 (141). Other tools for measuring disease extent and activity include a Physician Global Assessment (PGA – which is included in BVAS/WG), the Disease Extent Index (DEI) and the Five Factor Score (FFS) (142, 143). A study comparing these tools was published in 2009 and showed the available tools for measuring disease extent and activity in AAV are highly correlated and reliable (144). Training and certification in using these tools is recommended for clinicians caring for patients with AAV.

A structured examination of the patient should be carried out at each clinic visit to detect new organ involvement, which may develop at any time in the disease course (145). Urinalysis should be performed on each patient at each visit to screen for infection, renal relapse or response, as well as bladder complications (26, 56, 57). Inflammatory markers and renal function should be measured periodically (every 1–3 months) to monitor disease status. A full blood count and liver function should be performed at similar intervals to screen for drug toxicity

(59, 76). An acute fall in white cell count or a progressive leukopenia may require reduction or discontinuation of immunosuppressive drugs. Similarly, declining renal function may necessitate dose adjustment or alteration of immunosuppressive agents. Patients should have periodic assessment of their blood glucose while on glucocorticoid therapy (10).

Statement Eleven

We recommend the investigation of persistent unexplained haematuria in patients with prior exposure to cyclophosphamide. Level of evidence 2B; grade of recommendation C; strength of vote 100%.

The use of cyclophosphamide is strongly associated with the risk of bladder cancer (26, 56, 57). The use of MESNA as an uroprotective agent lowers the risk of haemorrhagic cystitis but there is no clear evidence that it protects against bladder cancer (92). Transitional cell cancer can occur within months of commencement of cyclophosphamide or many years after its discontinuation (26). Tobacco smokers are particularly susceptible and may develop the cancer at lower doses and earlier than non-smokers (26). All patients should have periodic urinalysis for the duration of their follow-up. In the presence of haematuria confirmed on urine microscopy, an urgent urology opinion must be sought.

Statement Twelve

Hypoimmunoglobulinaemia has been noted after treatment with rituximab. We recommend testing of serum immunoglobulin levels prior to each course of rituximab and in patients with recurrent infection. Level of evidence 3; grade of recommendation C; strength of vote 65%.

Hypoimmunoglobulinaemia (note the term is not *hypogammaglobulinaemia* as modern lab techniques do not use globulin electrophoresis extraction) is associated with repeated use of rituximab. In a retrospective analysis of 55 participants with AAV (GPA 44, EGPA 7, MPA 4), immunoglobulin levels and B cell subsets were measured serially after each course of induction treatment (22). Cyclophosphamide (CYC) treatment resulted in a decrease in immunoglobulin (Ig) levels (median; interquartile range IQR) from IgG 12.8 g/L (8.15-15.45) to 9.17 g/L (8.04-9.90) ($p=0.002$), IgM 1.05 g/L (0.70-1.41) to 0.83 g/L (0.60-1.17) ($p=0.046$) and IgA 2.58 g/L (1.71-3.48) to 1.58 g/L (1-31-2.39) ($p=0.056$) at a median follow-up time of 4 months. IgG remained significantly below the initial value at 14.5 months and 30 months analyses. Subsequent rituximab (RTX) treatment in patients who had previously received CYC resulted in a further decline in Ig levels from pre RTX IgG 9.84 g/L (8.71-11.60) to 7.11 g/L (5.75-8.77; $p=0.007$), from pre RTX IgM 0.84 g/L (0.63-1.18) to 0.35 g/L (0.23-0.48; $p<0.001$) and from pre RTX IgA 2.03 g/L (1.37-2.50) to IgA 1.62 g/L (IQR 0.84-2.43; $p=0.365$) 14 months after RTX. Treatment with RTX induced a complete depletion of B cells in all patients. After a median observation time of 20 months median B lymphocyte counts remained severely suppressed (4 B-cells/µl, 1.25-9.5, $p<0.001$). Seven patients (21%) that had been treated with CYC followed by RTX were started on immunoglobulin replacement because of severe bronchopulmonary infections and serum IgG concentrations below 5 g/L. In patients with AAV, treatment with CYC also leads to a decline in immunoglobulin concentrations. Subsequent treatment with RTX may aggravate the decline in serum immunoglobulin concentrations and may result in a profoundly delayed B cell repopulation but it is unknown as to what extent further RTX infusions worsen the immunodeficiency. Surveying patients with AAV post CYC and RTX treatment for serum immunoglobulin concentrations and persisting hypoimmunoglobulinaemia is warranted (22). In patients who develop this

complication, involvement of a clinical immunologist is recommended. Not all patients who develop hypoimmunoglobulinaemia have infectious complications. A retrospective study of one centre of 63 patients with AAV (GPA 62, MPA 7) treated with rituximab revealed that 41% developed hypoimmunoglobulinaemia at some point in the disease course, but only two patients required IVIG for recurrent infection (146).

Patients with AAV should be immunised against infectious disease according to local policy. It should be noted that influenza vaccination does not appear to be associated with relapse in patients with AAV (147, 148). In addition patients with GPA show an adequate immune response to influenza vaccination (149). Vaccination against herpes zoster, pneumococcus and influenza should be considered in patients with AAV. However one should take into account the patient's need for treatment of their AAV and of likely treatment choice for both induction and maintenance therapy. Live attenuated vaccines should be avoided whenever possible. We refer readers to the EULAR recommendation for vaccination in adult patients with autoimmune inflammatory rheumatic diseases (150).

Statement Thirteen

We recommend periodic assessment of cardiovascular risk for patients with ANCA-associated vasculitis. Level of evidence 2B; grade of recommendation B; strength of vote 53%.

Patients with AAV are at risk of complications, both from their disease and its treatment (145). In AAV, renal, otolaryngological and treatment-related complications (cardiovascular disease, diabetes, osteoporosis and malignancy) and damage increase over time. Around one-third of patients have ≥5 items of damage at a mean of 7 years post diagnosis. At long-term follow-up, the most

commonly reported items of treatment-related complications or damage were hypertension (41.5%; 95% CI 35.6 to 47.4%), osteoporosis (14.1%; 9.9% to 18.2%), malignancy (12.6%; 8.6% to 16.6%), and diabetes (10.4%; 6.7% to 14.0%). Given that hypertension and diabetes are well known cardiovascular risk factors it is perhaps unsurprising that patients with AAV are at an increased risk for cardiovascular disease. However, the risk of cardiovascular disease appears to be greater than can be explained through traditional cardiovascular risk factors alone. In a comparison of 535 participants with five year follow-up from four EUVAS trials (MEPEX, CYCLOPS, CYCAZAREM and NORAM) revealed that within five years of diagnosis, 14% of patients with GPA or MPA will have a cardiovascular event (151). This study also showed that independent determinants of adverse cardiovascular outcome were: older age (odds ratio [OR] 1.45, 95% confidence interval [95% CI] 1.11–1.90), diastolic hypertension (OR 1.97, 95% CI 0.98–3.95), and PR3-ANCA (OR 0.39, 95% CI 0.20–0.74) (151).

Patients with AAV are at risk of long-term kidney damage. Guidelines exist on the management of CKD such as KDIGO (*http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf*).

Statement Fourteen

We recommend that patients with ANCA-associated vasculitis should be given a clear verbal explanation of the nature of their disease, the treatment options, the side effects of treatment, and the short- and long-term prognosis. Level of evidence 3; grade of recommendation C; strength of vote 88%.

It is a generally accepted principle in medical practice that patients who are well informed and educated about their illness and understand it, have better outcomes. An evaluation of patient education has taken place using an inpatient education programme in a tertiary referral centre, although this was not a RCT (152). Patients should be encouraged to share responsibility for dealing with their illness (152).

AAV can be a bewildering and confusing illness for patients who can be very fearful when receiving a diagnosis of such an uncommon disease. Like all rare disease there is little common experience and understanding of vasculitis, so there are no readily available sources of information. Patients with rare diseases often feel isolated and alone (153).

The internet can now provide access to reliable and up-to-date information and advice and to online discussion groups which provide the reassurance of peer support and the ability to share knowledge and experience. The internet can also provide incorrect, unproven and even dangerous information. It is often the least articulate and least confident who are most vulnerable and need support.

AAV is characteristically a relapsing disease. Each relapse may result in further morbidity so early prediction or recognition of relapse is essential. A patient who is educated about and understands the disease is frequently better able to recognise the early signs and symptoms of relapse.

Statement Fifteen

We recommend that following the remission-induction phase of treatment, patients with ANCA-associated vasculitis be assessed for the extent and ongoing impact of co-morbidities associated with their diagnosis. Patients

should then be advised where they might find the necessary therapies or support for these conditions. Level of evidence 4; grade of recommendation D; strength of vote 100%.

AAV is a systemic disease with the potential to affect almost any organ (154). Patients may be left with permanent damage to kidneys, lungs and respiratory tract, heart, peripheral and central nervous system, total or partial loss of sight or hearing (155, 156). Patients may lose digits or limbs or be left with facial disfigurement or severe skin scarring (25). Severe fatigue, muscle weakness and chronic pain are frequent direct consequences of AAV (157, 158). Side-effects of treatment can be serious, even life-threatening (159).

The consequences of AAV may have a serious impact on education, employment prospects and job retention (160). Personal and social relationships may be seriously disrupted, sometimes resulting in the total breakdown of family bonds. These factors may contribute to depression as a secondary consequence of AAV (161, 162).

AAV is a controllable but currently incurable life-long illness. Treating clinicians need to be aware that AAV often has long-term lifestyle consequences. A “holistic” approach to treatment and ongoing care should be adopted.

Discussion

Implementation of these recommendations

The recommendations have been based on an extensive literature search. In the absence of evidence, the statements have been based on the opinion and practice of experts from twelve countries (Czech Republic, France, Germany, Ireland, Italy, Netherlands, Spain, Sweden, Switzerland, Turkey, UK and USA).

The application of internationally-accepted grading criteria prevents us from supporting some of the statements with stronger grades. The project has also led the committee to propose a research agenda for AAV (See box 1). These guidelines have been multi-disciplinary with input from rheumatologists, internists, renal physicians and also from a clinical immunologist, an otorhinolaryngologist, a chest physician, an ophthalmologist, a vasculitis nurse, and a vasculitis patient. In addition to these recommendations, this has also allowed us to produce advice for AAV involving the eye and the nose (Appendix 2) and a lay summary for patients and relatives (Appendix 6)

The previous guidelines were published in 2009 and importantly had a wider remit, covering small and medium vessel vasculitis and not just AAV (10). Readers are encouraged to refer to them for treatment decisions on: mixed essential cryoglobulinemic vasculitis (non-viral), the use of antiviral therapy for the treatment of hepatitis C associated cryoglobulinaemic vasculitis and antiviral therapy, plasma exchange and glucocorticoids for hepatitis B-associated PAN. Ultimately the treatment aim of viral-associated cryoglobulinaemic vasculitis should be to treat the underlying viral disease according to current best management strategies.

The current recommendations provide a framework of practice that should apply to the majority of patients with AAV and have updated the previous recommendations. Although once again 15 statements have been formulated, some have been changed and some have been combined, for example there is no longer a separation of glucocorticoids as they are used in conjunction with other immunosuppressive agents.

Each statement should be an opportunity for auditing clinical practice (an audit tool has been produced - see Appendix 4). In addition these current

recommendations have also produced algorithms which provide clear and concise information for the management of AAV (see Figure 3) (separate file).

These recommendations have also been voted on by the EUVAS membership the results of which are available as a supplementary online file (see Appendix 3). The results of the EUVAS vote are largely in agreement with the strength of recommendation vote by the taskforce. There are differences particularly when there are a number of options available and the resultant vote may represent the diversity of the EUVAS membership. Importantly taskforce members who are also members of EUVAS did not vote in the EUVAS survey. Recommendations for clinical management need periodic updating and because of the many advances and on-going research in this field, this group recommends an update of these recommendations should be conducted in 3 years.

Competing interests:

David Jayne has received research grants and consulting fees from Roche/Genentech.

Recommendations for the management of AAV. A collaboration between the European League Against Rheumatism (EULAR) and European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) 2015 Full Guideline.

Research Agenda – Box 1.

- Diagnostic and classification criteria for AAV
- Identification of biomarkers for AAV
- Adjunctive plasma exchange – indications for use including serum creatinine cut-off
- Adequately powered clinical trials of novel biological agents for the treatment of refractory AAV
- Adequately powered RCTs in EGPA
- Long-term outcome studies in AAV

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