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

Data supplement.

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Methods

The EULAR Standardised Operation Procedures (SOP) for the elaboration, evaluation, dissemination and implementation of recommendations were followed [1]. 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 recommendations on the management of small and medium vessel vasculitis [2].
- 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 recommendations. 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 Figure S1 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.

Search Strings – Figure S1.

MEDLINE Search String

1. exp ANCA associated vasculitis/
2. ANCA vasculiti$.mp.
3. (ANCA adj5 vasculitis).mp.
4. or/1-3
5. clinical trial.pt.
6. randomized.ab.
7. placebo.ab.
8. dt.fs.
9. clinical trial/
10. randomly.ab.
11. trial.ti.
12. groups.ab.
13. or/5-12
14. animals/
15. humans/
16. 14 and 15

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 Data Supplement.

17. 14 not 16
18. 13 not 17
19. 4 and 18

CINAHL Plus Search String

1. exp MH vasculitis/
2. "exp Clinical Trials/" OR (MH "Clinical Trials+") OR (MH "Clinical Trial Registry") OR (MH "Randomized Controlled Trials")
3. (MH "Random Assignment") OR "Random assignment/"
4. (MH "Random Sample+") OR (MH "Simple Random Sample")
5. (MH "Placebo Effect") OR (MH "Placebos")
6. (MH "Quantitative Studies") OR (MH "Multicenter Studies") OR (MH "Pilot Studies")
7. S2 OR S3 OR S4 OR S5 OR S6
8. S1 AND S7

EMBASE Search String

1. exp ANCA vasculitis/
2. exp ANCA associated vasculitis/
3. (ANCA adj5 vasculitis).mp.
4. or/1-3
5. random$.ti,ab.
6. factorial$.ti,ab.
7. (crossover$ or cross over$ or cross-over$).ti,ab.
8. placebo$.ti,ab.
9. (doubl$ adj blind$).ti,ab.
10. (singl$ adj blind$).ti,ab.
11. assign$.ti,ab.
12. allocat$.ti,ab.
13. volunteer$.ti,ab.
14. crossover procedure.sh.
15. double blind procedure.sh.
16. randomized controlled trial.sh.
17. single blind procedure.sh.
18. or/5-17
19. exp animal/ or nonhuman/ or exp animal experiment/
20. exp human/
21. 19 and 20

22. 19 not 21
23. 18 not 22
24. 4 and 23

CENTRAL Search String

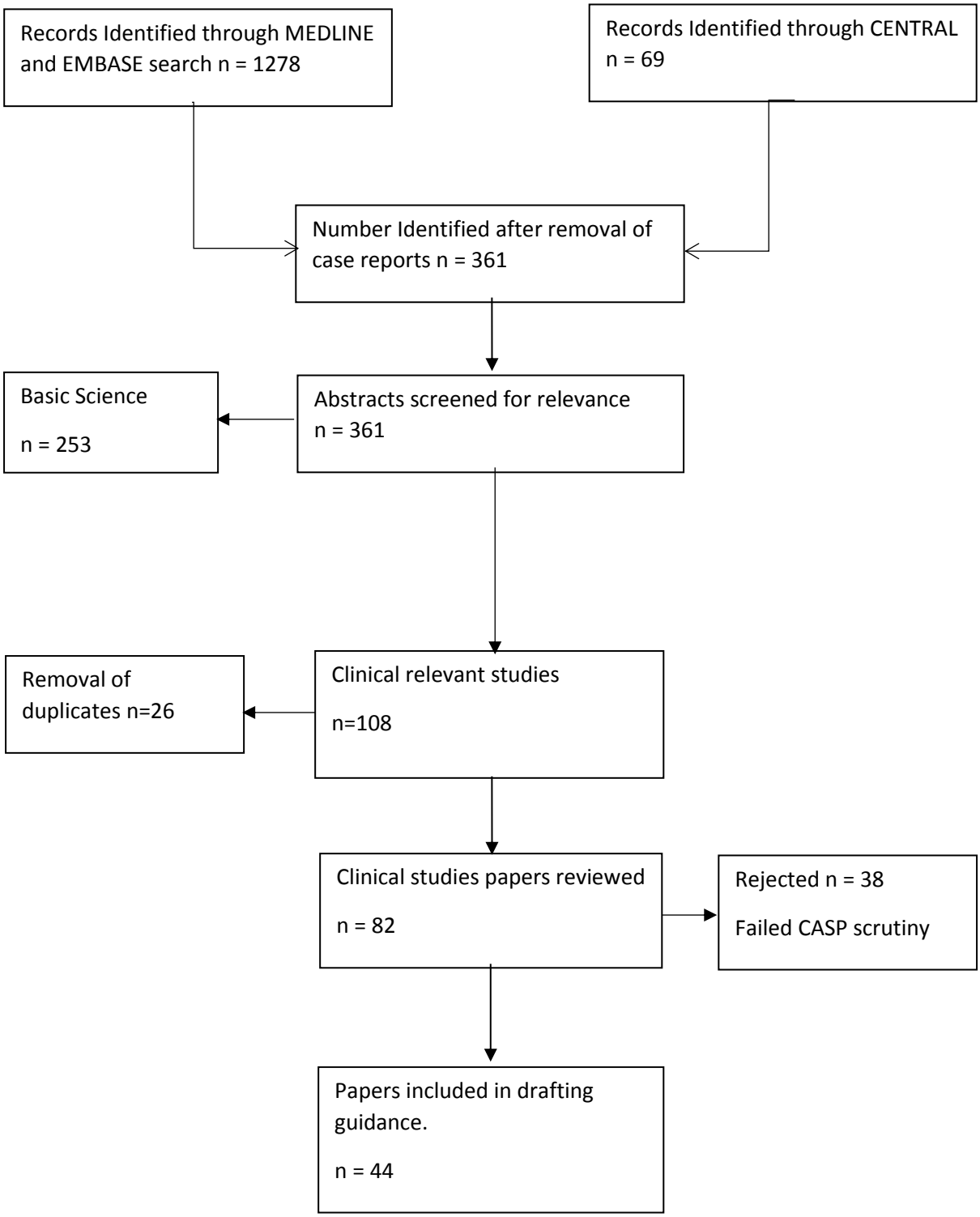
1. #1 ANCA associated vasculitis;ti,ab,kw
2. #2 vasculitis*:ti,ab,kw
3. #3 ANCA near vasculitis;ti,ab,kw
4. #4 (#1 OR #2 OR #3 OR #4)

Items identified for update were search from Jan 2007 to Feb 2015. New items were unrestricted with respect of search date.

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 S2 (10).
- Manuscripts were formally scored using the Critical Appraisal Skills Programme (CASP) checklist (11).
- Categorisation of evidence and strength of recommendation – following EULAR SOP (Tables S1 and S2). The mode vote for each recommendation amongst the taskforce and EUVAS membership are shown. 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.

PRISMA Statement Figure S2.



for update items identified through Delphi process: Date of search 01 Jan 2007 to 01 Feb 2015

Table S1: 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 S2: 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

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) [1]. 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.

Further details of trial data that inform the statements:

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*
    - *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*
    - *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 [3-5]. 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 [6, 7]. 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 [8], however, in order to determine whether or not the absence of clinical symptoms is actually related to the effects of the experimental drug under study and not simply as a result of high-dose GC therapy, “remission” is only defined as occurring when a patient has attained a stable low dose of prednisolone or prednisone of $\leqslant$7.5 mg/day for a defined period. Disease

activity should be recorded systematically according to validated and published disease activity scores [8].

In general the current recommendations, 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 [9]. 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 [10]. 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 [11]. Due to concerns about cumulative cyclophosphamide dosage, pulsed intravenous regimens were designed and tested, the largest study being the CYCLOPS trial [12]. This trial was designed following a meta-analysis of three studies involving 143 patients [13-15] which concluded that pulsed cyclophosphamide was more likely to achieve remission and was associated with fewer side-effects than oral cyclophosphamide [16].

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 [12]. 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 [17]. 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 [18]. 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 [19-21]. If clinically appropriate, patients should be encouraged to drink plenty of fluids or 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 [22]. 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 [22-24].

Monitoring of patients receiving cyclophosphamide should follow standard protocols [25]. In both modalities of administration, dose changes or discontinuation of cyclophosphamide may be necessary in the event of an acute leucopenia or a gradual fall over time. The reduction of cyclophosphamide in the event of leucopenia could be made as in the CYCLOPS protocol (25% reduction in the dose of the pulse if WBC $<4 \times 10^9$/L – the pulse was postponed till the WBC had risen to $>4 \times 10^9$/L). However, other local protocols could also be followed. 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 [26-28]. 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 [26]. Other alternatives include dapsone and atovaquone.

Rituximab in AAV has been tested in two RCTs (RAVE and RITUXVAS) [29, 30]. 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) [30]. Rituximab was given at induction (375 mg/m^2 once a week for four weeks) only with only placebo given as remission maintenance. Rituximab was not inferior to cyclophosphamide at inducing remission at the primary end point of achieving remission at six months and having stopped prednisolone therapy. In addition rituximab appeared more effective for relapsing disease [30]. The RITUXVAS trial recruited 44 participants with newly diagnosed AAV; generally patients were more severely ill than in the RAVE trial [29]. 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 rituximab group and 82% in the control group respectively) [29]. Remission in the RITUXVAS trial was defined as: as an absence of clinical disease activity, as indicated by a Birmingham Vasculitis Activity Score (BVAS) of 0 that was maintained for 2 months, sustained remission was defined as BVAS of 0 for at least 6 months. Remission was achieved

in 30/33 in the rituximab group and 10/11 in the control group. Sustained remission was achieved in 25/33 participants in the rituximab group and 9/11 participants in the control group. The primary end point in the RAVE trial was a BVAS/WG of 0 and successful completion of the prednisone taper at 6 months. Sixty-three of the 99 patients in the rituximab group (64%) reached the primary end point, as compared with 52 of 98 in the control group (53%).

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 [31]. 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) [31].

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 [32]. 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 [32]. 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 [29, 30]. 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 [33-37].

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) [12, 29, 30, 38-43]. 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.

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.

- *Methotrexate*
    - *Level of evidence 1B; grade of recommendation B; strength of vote 77%.*
- *Mycophenolate mofetil*
    - *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, 40, 44-51]. 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) [40]. 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. [52]. 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 (mycophenolate mofetil) at a dose of 2g/day for remission induction [2]. [38, 53]. The first study was a retrospective analysis of a case series of patients with AAV treated with mycophenolate mofetil: of 22 patients receiving mycophenolate mofetil for active disease, 86.4% achieved remission, however 9 (47.4%) relapsed [53]. 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 [38]. Complete remission (Birmingham Vasculitis Activity Score - BVAS <1 [54]) was achieved in 25 patients (78%) after a median duration of 2.2 months. Nine (36%) patients relapsed within a year [38].

Following these uncontrolled studies, RCTs have been published [55, 56]. The first was published in 2008 and compared mycophenolate mofetil 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 [55]. 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 haemorrhage, central nervous system involvement). There is therefore little evidence for the use of mycophenolate mofetil 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 mycophenolate mofetil and 8 of 17 patients (47.1%) receiving cyclophosphamide (although four participants were lost to follow-up) had complete remission [55]. The other RCT was published in 2011 and involved 41 Chinese participants, all of whom had MPA [56]. It compared mycophenolate mofetil 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 mycophenolate mofetil 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 mycophenolate mofetil group [56]. To date, the two RCTs using mycophenolate mofetil 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 mycophenolate mofetil (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 [57]. The remission end point (absence of disease activity for four weeks or longer whilst on prednisolone at six months) was achieved in 66% (mycophenolate mofetil) and 69% (cyclophosphamide) of patients [57]. 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.

- *Rituximab*
    - *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%*
- *Cyclophosphamide*
    - *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 [30].

The cumulative dose of cyclophosphamide is related to toxicity and is a particular concern with prolonged oral dosing, where cumulative doses are higher [58]. For this reason the taskforce has favoured a greater strength of recommendation for rituximab over cyclophosphamide for relapsing disease. The evidence for this exists for patients who relapsed after cyclophosphamide. For patients who relapse post-rituximab maintenance therapy – we may still need to use rituximab, especially if there was a contraindication to cyclophosphamide, necessitating the use of rituximab.

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) [59] <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%) [60]. An increase in the prednisolone dosage led to remission in 35 (80%) cases, but 31 had a second relapse (14 severe) [60]. 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 [60]. 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 [61-63]. 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 [43]. Long-term follow-up and analysis of this trial has also been published [64]. 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) [43]. 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 [65]. 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 [66]. 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) [67]. 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 [67]. 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 ($p < 0.05$) [67]. 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 [67]. 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 [68]:

- 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 rituximab 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 [63, 69].

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

- *Azathioprine*
    - *Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 94%.*
- *Rituximab*
    - *Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 59%.*
- *Methotrexate*
    - *Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 53%*
- *Mycophenolate mofetil*
    - *Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 53%*

EGPA

- *Azathioprine*
    - *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 [19-21]. Azathioprine (2 mg/kg/day) is safer than oral cyclophosphamide but as effective at 18 months in preventing relapse [42, 70]. 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) [71, 72]. Leflunomide (20–30 mg/day) may be more effective than methotrexate in remission maintenance but is associated with more

adverse effects [73]. Therefore leflunomide is considered for second-line treatment in cases of intolerance to azathioprine, methotrexate, mycophenolate mofetil or rituximab. Early cessation of therapy is associated with an increased risk of relapse [40].

Long-term follow-up of the CYCAZAREM study which recruited 155 participants with AAV (95 GPA, 60 MPA) was published in 2014 [74]. 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 [42]. 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 [74].

The WEGENT trial compared methotrexate to azathioprine and recruited 126 participants with AAV (GPA 96 and MPA 30) [75]. 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 [75]. 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 [75]. 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 methotrexate group. The hazard ratio for the risk of relapse among methotrexate vs azathioprine was 0.92 (95% CI, 0.52 to 1.65; P = 0.78).

The MAINRITSAN trial compared rituximab to azathioprine for remission maintenance [76]. 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 [76]. 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 azathioprine was between 1.5 and 1 mg/kg/day and the rest once azathioprine stopped), 3 in the rituximab group (at months 8, 22 and 24). Renal relapses occurred in 8/17 major relapses in the azathioprine group and 0/3 in the rituximab group [76].

Azathioprine is preferred over mycophenolate mofetil for remission maintenance, primarily because of the results from the IMPROVE trial [77]. 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 mycophenolate mofetil (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 [77]. The primary end point was relapse-free survival from the time remission was first achieved. Relapses were noted in 42 participants treated with mycophenolate mofetil (55.3%; 18 major and 24 minor) and in 30 participants in the azathioprine 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 [78]. 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 [78, 79]. 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* [80].

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 [8]:

- 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 [7, 31, 81, 82]. 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 [83].

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 [84]. 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 [85]. 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) [85].

For patients who fail to achieve remission and have persistent low activity, adjunctive therapy with intravenous immunoglobulin may help patients achieve remission [86-88]. 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 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 is associated with repeated use of cyclophosphamide and rituximab and is dependent on the cumulative dose of the drugs used. 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 [89]. Pulsed cyclophosphamide 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 (rituximab) treatment in patients who had previously received cyclophosphamide resulted in a further decline in Ig levels from pre rituximab IgG 9.84 g/L (8.71-11.60) to 7.11 g/L (5.75-8.77; $p=0.007$), from pre rituximab IgM 0.84 g/L (0.63-1.18) to 0.35 g/L (0.23-0.48; $p<0.001$) and from pre rituximab 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 rituximab. Treatment with rituximab 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 cyclophosphamide followed by rituximab were started on immunoglobulin replacement because of severe bronchopulmonary infections and serum IgG concentrations below 5 g/L. In patients with AAV, treatment with cyclophosphamide also leads to a decline in immunoglobulin concentrations. Subsequent treatment with rituximab 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 rituximab infusions worsen the immunodeficiency. Surveying patients with AAV post cyclophosphamide and rituximab treatment for serum immunoglobulin concentrations and persisting hypoimmunoglobulinaemia is warranted [89]. 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 [90].

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 [91, 92]. In addition patients with GPA show an adequate immune response to influenza vaccination [93]. Vaccination against herpes zoster (follow local guidelines because this is a live vaccine which may be contraindicated in immunosuppressed patients), 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 [94].

EUVAS membership vote:

The EUVAS membership was surveyed and asked to grade the strength of recommendation (A highest, D lowest) based on the strength of evidence (1 highest, 4 lowest). This was carried out for the recommendations to have the greatest representation amongst their intended users. Members of the taskforce who were EUVAS members were not invited to vote again. Of the 161 EUVAS members, 88 voted (55%). When statements were formed from expert opinion (i.e. from the taskforce) the EUVAS membership were not surveyed since only grade D can be given.

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 EUVAS vote 75%.

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 EUVAS vote 83%.

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*
    - *level of evidence 1A for GPA and MPA; grade of recommendation A; strength of EUVAS vote 87%.*
    - *level of evidence 3 for EGPA; grade of recommendation C; strength of EUVAS vote 85%.*
- *Rituximab*
    - *level of evidence 1B for GPA and MPA; grade of recommendation A; strength of EUVAS vote 60%.*

- *level of evidence 3 for EGPA; grade of recommendation D; strength of EUVAS vote 55%.*

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.

- *Methotrexate*
  - *Level of evidence 1B; grade of recommendation B; strength of EUVAS vote 51%.*
- *Mycophenolate mofetil*
  - *Level of evidence 1B; grade of recommendation C; strength of EUVAS vote 38%.*

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.

- *Rituximab*
  - *level of evidence 1B for GPA and MPA; grade of recommendation A; strength of EUVAS vote 76%.*
  - *level of evidence 4 for EGPA; grade of recommendation D; EUVAS members not surveyed.*
- *Cyclophosphamide*
  - *level of evidence 1A for GPA and MPA; grade of recommendation A; strength of EUVAS vote 59%.*
  - *level of evidence 3 for EGPA; grade of recommendation C; strength of EUVAS vote 82%.*

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 EUVAS vote 56%.

Plasma exchange can also be considered for the treatment of severe diffuse alveolar haemorrhage. Level of evidence 3; grade of recommendation C; strength of EUVAS vote 82%.

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

- *Azathioprine*
    - *Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of EUVAS vote 76%.*
- *Rituximab*
    - *Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of EUVAS vote 55%.*
- *Methotrexate*
    - *Level of evidence 1B for GPA and MPA; grade of recommendation B; strength of EUVAS vote 49%*
- *Mycophenolate mofetil*
    - *Level of evidence 1B for GPA and MPA; grade of recommendation B; strength of EUVAS vote 49%*

EGPA

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

Statement Eight

Grade of evidence D – EUVAS members not surveyed.

Statement Nine

For patients with refractory ANCA-associated vasculitis 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 EUVAS vote 83%.

Statement Ten

Grade of evidence D – EUVAS members not surveyed.

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 EUVAS vote 93%.

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 EUVAS vote 77%.

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 EUVAS vote 53%.

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 EUVAS vote 77%.

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 Data Supplement.

Statement Fifteen

Grade of evidence D – EUVAS members not surveyed

Organ Specific Modules

Organ specific modules for ophthalmic and otorhinolaryngological manifestations of AAV are discussed below.

EYE DISEASE IN AAV:

Lead: Nilüfer Yalcindag, Consultant Ophthalmologist - Department of Ophthalmology, School of Medicine, Ankara University, Ankara, Turkey

Ophthalmic manifestations in AAV are numerous (See below Table S3) and can be the first presenting sign of systemic disease [95, 96]. AAV should be kept in mind in the differential diagnosis of almost all forms of ocular disease. However, ophthalmic findings seen in AAV are not pathognomonic of AAV and may also be associated with other vasculitic, inflammatory or infectious diseases [97].

Ocular disease in AAV can also occur in the absence of systemic disease [98-101]. ANCA can be negative in some patients with disease limited only to the eye [102, 103]. In the limited form of GPA, ANCA have been reported to be positive in only 50-65% of patients. Although eye involvement occurs less frequently in MPA and EGPA, ocular findings have been reported in 29% to 60% of patients with GPA, being the presenting feature in 8-16% of patients [104-110]. Ocular involvement may be because of primary inflammation or due to contiguous spread from neighbouring structures. It is important to recognise ophthalmic manifestations of AAV as some can cause irreversible visual impairment and blindness if not promptly diagnosed and treated. The diagnosis of diverse eye findings can be challenging for non-ophthalmologists and patients with ophthalmic symptoms and signs should be referred to an ophthalmologist. These patients require a multidisciplinary approach to management and periodic long-term follow-up.

Although there have been no RCTs for the management of eye manifestations in AAV, some case reports or case series suggest the efficacy of cyclophosphamide, azathioprine, mycophenolate mofetil, and methotrexate (combined with glucocorticoids) [111, 112]. There is no consensus on dosing, tapering or duration of therapy. Orbital disease is a resistant manifestation and associated with irreversible visual loss, local destruction and perforation into adjacent tissues. Although some authors reported successful use of rituximab in the treatment of refractory orbital

disease, the role of rituximab in treatment of orbital disease in AAV remains to be evaluated [7, 113-116].

Topical corticosteroids should be reserved for patients with episcleritis, conjunctivitis and anterior uveitis and are considered ineffective in the treatment of keratitis in systemic vasculitides. Treatment of peripheral ulcerative keratitis requires systemic immunosuppression but also topical antibiotic coverage and frequent use of artificial tears should be used. Adhesive glue or corneal grafts may be necessary in cases with marked corneal thinning and potential corneal perforation.

Artificial tears may provide some relief in cases with dry eyes. Conservative measurements *for corneal protection against exposure keratopathy secondary to marked proptosis include artificial tears, lubricating ointment, and* eyelid taping overnight when necessary.

In necrotising scleritis, the risk of scleral thinning and perforation can be exacerbated by secondary infection. In addition to systemic immunosuppression, aggressive topical antibiotic therapy and even scleral patch grafts can be required in patients with necrotising scleritis.

In cases with intermediate uveitis, sub-conjunctival steroid injections might be indicated but systemic steroids and other immunosuppressant drugs may be required in refractory cases. Indomethacin may be the initial treatment choice in cases of anterior scleritis. Oral steroids should be considered if this therapy is ineffective, or in cases of posterior and necrotising scleritis. In most cases of necrotising scleritis, an immunosuppressive such as cyclophosphamide should be added.

In cases of severe orbital inflammation, especially if the optic nerve is at risk of compression, orbital decompression surgery should be considered to relieve pressure in the orbit [117, 118]. In patients with nasolacrimal duct obstruction or dacryocystitis secondary to GPA, dacryocystorhinostomy has been shown successful [119, 120].

Table S3. Ophthalmic manifestations in AAV

CATEGORISATION OF THE TYPES OF OCULAR INVOLVEMENT		
SITE OF INVOLVEMENT	**CLINICAL MANIFESTATIONS**	**SYMPTOMS AND SIGNS**

GLOBE INVOLVEMENT	• Conjunctival ulcer
	• Conjunctivitis
	• Conjunctival nodule / granuloma
	• Episcleritis
	• Scleritis:
	  ○ Anterior scleritis (diffuse, nodular or necrotising)
	  ○ Posterior scleritis
	• Keratitis (peripheral ulcerative keratitis or interstitial keratitis)
	• Sclerokeratitis
	• Sclerouveitis
	• Uveitis
	• Choroidal granuloma with exudative retinal detachment
	• Choroiditis
	• Retinitis
	• Retinal vasculitis
		• Pain
		• Tearing
		• Blurred vision
		• Red eye
		• Floaters
		• Photophobia
		• Mild irritation / Discomfort

ORBITAL DISEASE (Orbital involvement may be due to primary inflammation (LOCAL DISEASE) or results from extension of disease from neighboring paranasal sinuses or nasopharynx (CONTIGUOUS DISEASE))	• Orbital cellulitis • Orbital inflammatory disease • Orbital socket contracture and enophthalmos (a late sequelae of chronic orbital inflammation) • Inflammatory lacrimal gland masses • Orbital mass lesions / granuloma • Lacrimal gland involvement / dacryoadenitis • Orbital bruit (EGPA) • Myositis	• Orbital pain / cephalalgia • Red eye • Eyelid swelling • Restriction of motility of the eye • Diplopia (may be due to the mass effect itself or vasculitis of vessels supplying the extraocular muscles) • Epiphora • Eye dryness • Ptosis • Proptosis

		• Vision loss • May be asymptomatic
NEURO-OPHTHALMIC MANIFESTATIONS	• Optic neuropathy (compressive, ischemic or inflammatory) • Amorosis fugax • Cranial nerve palsies (3,4,6→GPA/ 3,4→EGPA) • Horner syndrome (Rarely) • Optic perineuritis • Optic nerve edema • Optic atrophy	• Diplopia • Ophthalmoplegia • Relative afferent pupillary defect (RAPD) • Blurred vision • Amaurosis fugax
NASOLACRIMAL DISEASE	• Nasolacrimal duct obstruction • Canalicular involvement • Dacryocystitis • Lacrimal sac mucocele	• Epiphora
VASCULAR INVOLVEMENT	• Central retinal artery occlusion (CRAO) • Branch retinal artery occlusion (BRAO) • Retinal vein occlusion	• Vision loss

As an internist or general physician:

ANCA-associated vasculitides can manifest themselves by diverse eye manifestations which may sometimes be the most evident disease manifestation at presentation and during relapse. Therefore any patients with eye findings should be evaluated by an ophthalmologist. Eye findings *can occur* as one sided (*unilateral*) or two sided (*bilateral*).

Red flags a general physician should look out for:

- Red eye
- A reduction in visual acuity
- Proptosis (subacute painful proptosis is the most commonly reported presentation of GPA involving the orbit)
- Lid swelling / erythema

- Diplopia
- Pain of the orbital region
- Ophthalmoplegia (disturbances in eye movement)
- Epiphora
- Eye dryness (grittiness, pain, redness, photophobia)

Vasculitis may be the reason for these findings and they require further examination of an ophthalmologist.

As an ophthalmologist:

Ophthalmologists must be able to recognise the patient whose eye disease might be the presenting feature of a life-threatening systemic vasculitis. A *multidisciplinary approach* on the *diagnosis and treatment* decisions of these patients may save the vision and even the life of the patient. A delay in diagnosis may contribute to a higher rate of severe GPA manifestations such as necrotising scleritis which can pose a major threat to the integrity of the globe.

Although any part of the eye can be affected, orbital involvement has the worst prognosis among ocular manifestations of the disease. Poor vision in orbital inflammatory disease may result from ischemic or compressive optic neuropathy, exposure keratopathy secondary to proptosis, neuropathic keratopathy and glaucoma.

The diagnosis of ocular GPA is particularly difficult as its clinical manifestations often overlap with other inflammatory conditions such as sarcoidosis and idiopathic inflammatory orbital disorders.

Although histopathologic findings are often diagnostic for GPA in renal disease, this is not the case for orbital disease. Histopathologic features of orbital GPA are diverse and can mimic other forms of orbital inflammation. Classic histopathologic findings are present in less than a third of patients.

OTORHINOLARYNGOLOLICAL INVOLVEMENT IN AAV:

Lead: Martin Laudien - Department of Otorhinolaryngology, Head and Neck Surgery, University of Kiel, Kiel, Germany

Otorhinolaryngological (ear, nose and throat) involvement is common in AAV (in up to 80% of the patients in the course of the disease) [121, 122]. Often otorhinolaryngological manifestations are the first and may be the only manifestation (up to 2%) [123]. In order of frequency, the nose/paranasal sinus, ear, throat and other regions (e.g. salivary gland, neck) are affected [124, 125].

Otorhinolaryngological involvement can be life-threatening (e.g. subglottic stenosis, skull base involvement) and often impairs physiological function (e.g. breathing, olfactory system, auditory system). Destruction is common (e.g. septal perforation, saddle nose deformity, oronasal/orbitonasal fistula, scar formation) [125].

Diagnosis is challenging because signs and symptoms are ambiguous and completely different concerning the AAV entities (e.g. nasal polys in EGPA and ulcers, crusts and granulation in GPA). Therefore an Otorhinolaryngologist with experience in AAV should be integrated in the interdisciplinary management of the disease [126]. Clinical evaluation should be structured using available tools [127]. In GPA biopsies may be helpful but should be restricted to more harmless regions like the lateral part of the common nasal cavity. Biopsies of the subglottic region might accelerate scar tissue formation and stenosis. Most meaningful biopsies seem to be achieved from suspicious lesions [128-130]. In EGPA biopsies of the nasal mucosa give little information concerning AAV but might be helpful in excluding differential diagnoses. Functions should be followed clinically and with subjective/objective testing (e.g. olfactory test, audiogram, lung function) [131].

Follow-up should be done on a regular basis to detect early subtle changes and adapt therapy [126].

Local complications may make a rapid surgical intervention necessary (e.g. active disease at the larynx/subglottic region with (seldom) necessity for temporary tracheostomy) [7, 132].

Attention should be given towards restoring function (e.g. local therapy, hearing aids or cochlear implant).

AAV is a systemic disease and usually has to be treated with systemic immunomodulatory therapy. However, local manifestation might be positively influenced by local therapy. In accordance with national and international guidelines and albeit weak data out of case reports and small case series, local immunomodulatory therapy (e.g. corticosteroids and mitomycin c applied intralesional or on the mucosa) as well as saline water rinsing and ointment of the nasal mucosa and phytotherapy in GPA might be beneficial at least for quality of life [133-135].

Reconstruction of damage should be performed with surgical expertise concerning the diseases and attention towards timing (e. g. time since remission, since immunomodulatory therapy) and techniques (e.g. special attention to scar tissue in saddle nose deformity) [136, 137].

Whenever treatment is unsuccessful and/or disease course is unusual, a second opinion should be obtained, best achieved in a centre-based structure.

Lay Summary

Newly updated advice on the treatment of patients with AAV.

INTRODUCTION

A central focus of newly updated recommendations on treating ANCA-associated vasculitis (AAV) is shared decision-making between patients and doctors. The updated recommendations, produced by a collaboration between the European League Against Rheumatism (EULAR) and European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), taking account of recent research on the benefits and safety treatments for AAV.

WHAT DO WE KNOW ALREADY?

When someone has ANCA-associated vasculitis (AAV), their immune system -which normally fights infection – mistakenly attacks their blood vessels. This can compromise the tissues which the blood vessels supply, leading to a whole range of signs and symptoms including: bleeding and crusting from the nose, cough and shortness of breath, tiredness, aching in muscles, loss or blurring of vision and double vision which may also be associated with eye pain, swollen, stiff, and painful joints, pain or numbness in arms and legs and confusion.

Immunosuppressive drugs can help stop this happening by reducing damage to the blood vessels and helping prevent irreversible damage and disability.

Immunosuppressive drugs are the main treatment for AAV, and there are many different types including:

- Older, standard types, which are manufacturered chemically: cyclophosphamide, steroids, azathioprine, methotrexate and mycophenolate.
- Newer types, often called ‘biologics’. The main drug of this type used to treat AAV is rituximab.

In certain situations giving patients blood proteins via a drip or even removing the immune proteins via a machine that ‘washes’ the blood may be appropriate.

With so many options to consider, deciding on a treatment approach can be a challenge, particularly since research does not provide clear answers on which works best and is safest. To help with this, the European groups of both EULAR and ERA-EDTA convened a task force of doctors specialising in AAV, nurses and patient representatives to review the current research and provide guidance. They have now released their recommendations which are an update of those published in 2009.

WHAT DO THE RECOMMENDATIONS SAY?

The updated recommendations emphasise the importance of doctors, nurses and patients working together to find the best care approach, stressing that treatment must be based on shared decisions between the patient and their doctor. Other key principles are:

- Specialists who have a special interest and expertise in AAV should primarily care for people with AAV.
- Biopsy of an affected organ (most commonly the kidney) can be helpful in confirming a new diagnosis of AAV and in those patients having a relapse.

- The aim of the treatment should be remission.
- Doctors should monitor patients using structured clinical assessment and make use of validated tools to monitor for complications of AAV and also the drugs used to treat it.
- A combination of steroid and either cyclophosphamide or rituximab should be the first-line treatment doctors and patients to consider for newly diagnosed organ or life-threatening AAV.
- Patients and doctors can consider using steroids (glucocorticoids), as part of patients' initial treatment (along with immunosuppressive drugs) but these drugs should be reduced and stopped as soon as possible.
- If the first treatment approach doesn't work well enough, patients should be referred to an expert centre for ongoing management and enrolment in clinical trials.
- For patients who relapse with either an organ or life-threatening disease, a combination of steroid and either cyclophosphamide or rituximab should be the first-line treatment doctors and patients consider.
- When a patient has been successfully treated for their initial disease or relapse then a period of treatment with remission-maintenance should occur. The drug choices include: azathioprine, rituximab, methotrexate and mycophenolate. The precise drug will depend both on the type of AAV you have and which drug was used to bring about remission in the first place.
- If a patient's AAV is not active (in remission) then the immunosuppressive drugs including the steroids should be reduced. However treatment with remission-maintenance therapy should be continued for at least 24 months in those patients in stable remission (i.e. have not suffered relapses during that period). This is a decision that should be carefully considered by the patient and their doctor.
- When treatment needs to be adjusted, other things need to be taken into account, along with a patient's disease activity and ANCA titre result, include any other illnesses, possible side effects of current or previous treatment and the development of damage over time.

HOW RELIABLE ARE THE RECOMMENDATIONS?

These recommendations are based on a thorough review of the current research and knowledge, as well as discussions among experts and patient representatives. They should provide reliable guidance on the best approach to treating AAV.

WHAT DOES THIS MEAN FOR ME?

If you have AAV, these recommendations should provide useful insight into what treatments you are likely to be offered and when. They also emphasise that as a patient, you should have a voice in your treatment. If you have any questions or concerns, be sure to speak with your specialist.

From: Yates M, Watts RA, Bajema IM, *et al*. EULAR and ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Annals of the Rheumatic Diseases 2015;

Date prepared: September 2015

Audit Tool for EULAR and ERA-EDTA 2015 AAV Recommendations.

Criterion 1	For patients suspected or confirmed as having AAV there should be access to a multidisciplinary team or recognised specialist network with expertise in managing AAV.
Exceptions	None
Settings	All
Standard	100%
Definitions	Includes physician(s) with an interest in systemic vasculitis to look after all aspects of the disease and a specialist nurse.
Criterion 2	For patients suspected of having AAV: There should be access to blood testing including inflammatory markers and ANCA.
Exceptions	None
Settings	All
Standard	100%
Definitions	None
Criterion 3	For patients suspected of having AAV: There should be a documented management plan which is agreed with the patient.
Exceptions	None
Settings	All
Standard	100%
Definitions	None
Criterion 4	For patients receiving cyclophosphamide there should be access to IV infusion facilities.
Exceptions	None
Settings	Secondary and tertiary care centers
Standard	100%
Definitions	None

Criterion 5	For patients receiving cyclophosphamide there should be dose adjustments should be made based on age and renal function.
Exceptions	People for whom the use of cyclophosphamide is contraindicated
Settings	Secondary and tertiary care centers
Standard	100%
Definitions	None
Criterion 6	For those people prescribed IV pulsed cyclophosphamide: Documentation of assessment of hydration status and decision regarding the need for IV fluids and / or MESNA.
Exceptions	People for whom the use of MESNA is contraindicated
Settings	Secondary and tertiary care centers
Standard	100%
Definitions	Hydration status should be stated biochemically (urea and electrolytes) and clinically – (e.g. skin turgor, tongue moistness, JVP).
Criterion 7	For those patients receiving cyclophosphamide: Discussion about potential for infertility.
Exceptions	None
Settings	All
Standard	100%
Definitions	None
Criterion 8	For those patients receiving cyclophosphamide: Documentation of decision regarding need for vaccination and action taken.
Exceptions	None
Settings	All
Standard	100%
Definitions	None
Criterion 9	For those patients receiving cyclophosphamide:

	Documentation of decision regarding need for pneumocystis pneumonia (PCP) prophylaxis.
Exceptions	People for whom the use of PCP prophylaxis is contraindicated
Settings	All
Standard	100%
Definitions	None
Criterion 10	Percentage of patients offered evidence-based written information about: • their illness or condition • treatment and care • the service providing their treatment and care
Exceptions	None
Settings	All
Standard	100%
Definitions	Patient should be offered written information to help them make informed decisions about their healthcare. This should cover the condition, treatments and the health service providing the care. Information should be available in formats appropriate to the individual, taking into account, age, language, and physical, sensory or learning difficulties.
Criterion 11	Decision on switch to remission maintenance therapy based on recording of disease activity (e.g. BVAS).
Exceptions	None
Settings	All
Standard	100%
Definitions	None

Criterion 12	Tapering of immunosuppressive adjunct agents should begin after two years of disease remission or there should be documentation of a conscious decision to continue immunosuppression due to risk factors for relapse.
Exceptions	None
Settings	All
Standard	100%
Definitions	None
Criterion 13	Periodic monitoring for complication such as cardiovascular disease (CVD) should be performed using standard risk calculators.
Exceptions	None
Settings	All
Standard	100%
Definitions	None
Criterion 14	Referral to urology for non-glomerular haematuria.
Exceptions	None
Settings	All
Standard	100%
Definitions	None
Criterion 15	For those patients receiving regular glucocorticoids there should be monitoring for complications such as diabetes, osteoporosis and hypertension.
Exceptions	None
Settings	All
Standard	100%
Definitions	None

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