EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update

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ABSTRACT

Background: Since the publication of the European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in 2016, several randomized clinical trials have been published that have the potential to change clinical care and support the need for an update.

Methods: Using EULAR standardized operating procedures, the EULAR task force undertook a systematic literature review and sought opinion from 20 experts from 16 countries. We modified existing recommendations and created new recommendations.

Results: Four overarching principles and 17 recommendations were formulated. We recommend biopsies and ANCA-testing to assist in establishing a diagnosis of AAV. For remission induction in life- or organ-threatening AAV, we recommend a combination of high-dose glucocorticoids (GC) in combination with either rituximab or cyclophosphamide. We recommend tapering of the GC dose to a target of 5 mg prednisolone equivalent/day within 4-5 months. Avacopan may be considered as part of a strategy to reduce exposure to GC in granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA). Plasma exchange may be considered in patients with rapidly progressive glomerulonephritis. For remission maintenance of GPA/MPA we recommend rituximab. In patients with relapsing or refractory eosinophilic granulomatosis with polyangiitis, we recommend the use of mepolizumab. Azathioprine and Methotrexate are alternatives to biologics for remission maintenance in AAV.

Conclusions: In the light of recent advancements, these recommendations provide updated guidance on AAV management. As substantial data gaps still exist, informed decision making between physicians and patients remains of key relevance.

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BACKGROUND

The ANCA associated vasculitides (AAV) include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA).[1-3] AAV represent a subgroup within the spectrum of primary systemic vasculitis defined by the Chapel Hill consensus conference nomenclature.[4]

In 2009, the European Alliance of Associations for Rheumatology (EULAR) developed its first recommendations for managing small and medium vessel vasculitis.[5] An update focusing on AAV was published in 2016.[6] These recommendations provided guidance to clinicians and researchers and have been widely cited. Recent landmark studies on the role of plasma exchange (PLEX), standardization of glucocorticoid (GC) dosing, use of rituximab (RTX) for maintenance therapy, complement 5a receptor (C5aR)-targeted and anti-interleukin-5 (IL5) therapy in EGPA make this an opportune time to update the 2016 guidelines.

These recommendations address the diagnosis and treatment of adult patients with AAV and are intended to give advice to clinicians, other health professionals, pharmaceutical companies, and regulatory organizations.

METHODS

The recommendations were drafted according to the 2014 update of the EULAR standardized operating procedures (SOPs) for the development of EULAR-endorsed recommendations[7] and the updated version of the Appraisal of Guidelines for Research & Evaluation (AGREE II) recommendations,[8] where applicable (see supplementary file for a full description of methods). The task force consisted of 20 clinical experts including rheumatologists (MC, BH, JH, OK, RL, AJM, CM, JM, PM, GT, DV), internists (AM,DB, BT) and nephrologists (AK, ML, MS, OT, AV, DJ), from 15 European countries, and the USA (PM), two methodologists (RL; GT), convenor (BH) and co-convenor (DJ), two delegates of the EULAR young rheumatologists' network EMEUNET (AB, SM), two fellows (BA, JS), one health professional (NH) and two patient representatives (PV, FPK).

Based on results of a Delphi survey among the task force, we defined 14 key research questions addressing the management of AAV. For the update domains the systematic literature review (SLR) was restricted to literature published from 01/02/2015 (the date of the last set of recommendations) onwards. For new domains and drugs not included in last update the search was unrestricted. The following databases were used: PubMed, EMBASE and Cochrane Library. Each article was assigned a level of evidence (LoE) according to the standards of the Oxford Centre for Evidence-Based Medicine (2009) and was systematically assessed for bias.[7] The methods and results of the SLR are published separately.[9 10]

During a face-to-face meeting, task force members independently voted on each recommendation. Agreement on each recommendation and on the overarching principles on a scale of 0–10 (10 meaning full agreement) was given anonymously after the meeting by electronic mail. A research agenda was formulated based on controversial issues and evidence gaps. The final manuscript was approved by the EULAR Executive Committee.

RESULTS

General aspects

Definitions of disease activity states in AAV differed across clinical trials. For the purpose of these recommendations, we propose consensus definitions for disease activity states in AAV (**Table 1**), which are based on the concept of activity states developed for the EULAR recommendations for conducting clinical trials in AAV[11] that have been validated for use in clinical trials.[12] ACR/EULAR criteria for treatment response in AAV are now in development which are expected to replace these definitions in the future.

Table 1. EULAR consensus definitions for disease activity states in AAV

Activity State	**EULAR Consensus Definition**
Active disease	Presence of typical signs, symptoms or other features (such as glomerulonephritis or pulmonary nodules) of active AAV
Remission	Absence of typical signs, symptoms, or other features of active AAV with or without immunosuppressive therapy
Sustained remission	Absence of typical signs, symptoms, or other features of active AAV over a defined time period with or without immunosuppressive therapy
Response	≥50% reduction of disease activity score and absence of new manifestations
Relapse	Recurrence of active AAV after a period of remission
Refractory	Unchanged or increased signs, symptoms, or other features of active AAV after a period of standard induction therapy. Damage, infections, side effects of treatment or co-morbidities as potential causes of the persistent or worsened disease manifestations need to be ruled out.

AAV, antineutrophil cytoplasmic antibody associated vasculitis.

Patients with AAV have previously been subdivided into those with “severe” and “non-severe” disease, or “generalized” versus “non-generalized" and some guidelines have adopted this categorization.[13-16] However, the terms “severe/non-severe”, “limited” or “early-systemic” are variably defined and misleading in clinical practice. Patients who appear to have less severe disease may receive less intense treatment yet are at risk of developing organ- or life-threatening manifestations.[17] [18] In most recent RCTs this concept has been discarded and patients with different stages of disease severity were assigned the same intensity of induction treatment.[19-21] As patients with “non-severe” AAV are at risk of being under treated, this task force decided not to change the categorization of the 2016 recommendations that distinguishes patients with and without organ- or life-threatening disease (**Table 2**), instead of adapting the terminology of “severe” and “non-severe” AAV.

Table 2. Examples for organ-/life-threatening and not organ-/life-threatening manifestations in patients with AAV

Examples for potentially organ-/life-threatening manifestations*	**Examples for manifestations that are not ultimately organ-/life-threatening***

glomerulonephritis pulmonary hemorrhage meningeal involvement central nervous system involvement retro-orbital disease cardiac involvement mesenteric involvement mononeuritis multiplex	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 episcleritis

*These are just examples of typical disease manifestations and many other manifestations of AAV exist. Assessment of severity in the individual patient may differ (e.g. scleritis can become organ-threatening under certain circumstances)

Overarching principles

In line with other recent EULAR recommendations [22-24], general principles deemed fundamental for the management are now added to the AAV recommendations (**Table 3**). These principles were consensus-based and did not result directly from the SLR. Statements 1, 13, 14, and 15 of the 2016 update addressed topics based on low-quality evidence specific to AAV. Therefore, these statements have been moved into overarching principles B, C, and D while the content remains mostly unchanged.

A. *Patients with AAV should be offered best care which must be based on shared decision making between the patient and the physician considering efficacy, safety, and costs.*

This highlights the importance of shared decision-making between patients and physicians. Adherence to effective therapies is crucial to prevent permanent organ damage related to uncontrolled inflammation in AAV. Therefore, the committee considers efficacy, safety, and tolerability as important factors in the decision-making process. This includes other factors such as kidney or liver function, fertility and pregnancy, lifestyle/smoking habits, or concomitant interacting medications. Costs of treatment also need to be considered as access to expensive medication may be restricted in some countries.

Table 3. EULAR recommendations for the management of AAV – 2022 Update

		LoE	**SoR**	**FV (%)**	**LoA (0-10)**
	Overarching principles				
A	Patients with AAV should be offered best care which must be based on shared decision making between the patient and the physician considering efficacy,	n.a.	n.a.	n.a.	9.6±0.5

	safety, and costs.				
B	Patients with AAV should have access to education focusing on the impact of AAV and its prognosis, key warning symptoms and treatment (including treatment-related complications).	n.a.	n.a.	n.a.	9.8±0.6
C	Patients with AAV should be periodically screened for treatment-related adverse effects and co-morbidities. We recommend prophylaxis and life-style advice to reduce treatment-related complications and other co-morbidities.	n.a.	n.a.	n.a.	9.8±0.6
D	AAV are rare, heterogeneous, and potentially life-and organ-threatening diseases and thus require multidisciplinary management by centres with, or with ready access to, expertise in vasculitis.	n.a.	n.a.	n.a.	9.8±0.5
	Recommendations				
1	A positive biopsy is strongly supportive of a diagnosis of vasculitis and we recommend biopsies to assist in establishing a new diagnosis of AAV and for further evaluation of patients suspected of having relapsing vasculitis.	3b	C	90	8.7±1.9
2	In patients with signs and/or symptoms raising suspicion of a diagnosis of AAV, we recommend testing for both, PR3- and MPO-ANCA using a high-quality antigen-specific assay as the primary method of testing.	1a	A	100	10.0±0
3	For induction of remission in patients with new-onset or relapsing GPA or MPA with organ- or life-threatening disease, we recommend treatment with a combination of glucocorticoids and either rituximab or cyclophosphamide.* Rituximab is preferred in relapsing disease.§	*1a §2b	*A §B	100	9.6±0.8
4	For induction of remission of non-organ- or non-life-threatening GPA or MPA, treatment with a combination of glucocorticoids and rituximab is recommended. Methotrexate or mycophenolate mofetil can be considered as alternatives to rituximab.	1b	B	90	9.2±0.8
5	As part of regimens for induction of remission in GPA or MPA we recommend treatment with oral glucocorticoids at a starting dose of 50 - 75 mg	1b	A	100	9.4±0.8

	prednisolone-equivalent/day, depending on body weight. We recommend stepwise reduction in glucocorticoids according to **Table 4** and achieving a dose of 5 mg prednisolone equivalent per day by 4 to 5 months.				
6	Avacopan in combination with rituximab or cyclophosphamide may be considered for induction of remission in GPA or MPA, as part of a strategy to substantially reduce exposure to glucocorticoids.	1b	B	100	9.0±0.9
7	Plasma exchange may be considered as part of therapy to induce remission in GPA or MPA for those with a serum creatinine > 300 µmol/L due to active glomerulonephritis.* Routine use of plasma exchange to treat alveolar hemorrhage in GPA and MPA is not recommended.§	*1a §1b	*B §B	*95 §90	8.0±1.7 8.8±1.3
8	For patients with GPA or MPA with disease refractory to therapy to induce remission, we recommend a thorough reassessment of disease status and comorbidities and consideration of options for additional or different treatment. These patients should be managed in close conjunction with, or referred to, a center with expertise in vasculitis.	5	D	100	9.9±0.5
9	For maintenance of remission of GPA and MPA, after induction of remission with either rituximab or cyclophosphamide, we recommend treatment with rituximab. Azathioprine or methotrexate may be considered as alternatives.	1b	A	100	9.3±1.0
10	We recommend that therapy to maintain remission for GPA and MPA be continued for 24 to 48 months following induction of remission of new-onset disease.* A longer duration of therapy should be considered in relapsing patients or those with an increased risk of relapse, but should be balanced against patient preferences and risks of continuing immunosuppression.§	*1a §4	B D	100	9.1±1.4
11	For induction of remission in new-onset or relapsing EGPA with organ- or life-threatening manifestations we recommend treatment with a combination of high-dose glucocorticoids and cyclophosphamide. A combination of high-dose glucocorticoids and rituximab may be considered as an alternative.	2b	B	100	9.6±0.8

12	For induction of remission in new-onset or relapsing EGPA without organ- or life-threatening manifestations we recommend treatment with glucocorticoids.	2b	B	95	9.3±0.9
13	For Induction of remission in patients with relapsing or refractory EGPA without active organ- or life-threatening disease, we recommend the use of mepolizumab.	1b	B	70	8.9±1.3
14	For maintenance of remission of EGPA after induction of remission for organ- or life-threatening disease, treatment with methotrexate[§], azathioprine[&], mepolizumab[&], or rituximab[&] should be considered.[§] For maintenance of remission of relapsing EGPA after induction of remission for non-organ- or life-threatening manifestations at the time of relapse we recommend treatment with mepolizumab.*	[§]2b [&]4 *1b	B C A	85	8.8±1.5
15	In the management of patients with AAV we recommend that structured clinical assessment, rather than ANCA and/or CD19+ B cell testing alone, should inform decisions on changes in treatment.	1b	B	95	9.3±1.1
16	In patients with AAV receiving rituximab we recommend measurement of serum immunoglobulin concentrations prior to each course of rituximab to detect secondary immunodeficiency.	1b	B	100	9.2±1.4
17	For patients with AAV receiving rituximab, cyclophosphamide, and / or high doses of glucocorticoids we recommend the use of trimethoprim–sulfamethoxazole as prophylaxis against Pneumocystis jirovecii pneumonia and other infections.	3b	B	100	9.5±1.1

The level of evidence was determined for different parts of each recommendation (referred to with different signs such as * or [§]). The level of agreement was computed on a 0-10 scale.

FV, final vote (% of expert panel members that agreed to the recommendation); LoA, level of agreement on scale of 0 to 10; LoE, level of evidence; n.a., not applicable; SoR, strength of recommendation.

B. *Patients should have access to education focusing on the impact of AAV and its prognosis, key warning symptoms, and treatment (including treatment-related complications).*

Patients with AAV should be given a clear explanation of the nature of their disease, the treatment options, side effects of treatment, and their short and long-term prognosis. This statement is

unchanged from the 2016 update (formerly statement No. 14) and has been moved to an overarching principle. Structured education programs in patients with AAV increase knowledge in areas such as treatment and side effects.[25 26] Patients should be informed on how to reach a vasculitis patient organization.

C. *Patients with AAV should be periodically screened for treatment-related adverse effects and co-morbidities. We recommend prophylaxis and life-style advice to reduce treatment-related complications and other co-morbidities.*

Statements 11, 13, and 15 of the 2016 update have been transferred to principle C. As the use of cyclophosphamide (CYC) is associated with an increased risk of bladder cancer,[27] all patients treated with CYC should have periodic urinalysis for the duration of their follow-up. In the presence of hematuria confirmed on urine microscopy that is not due to glomerulonephritis, a urology opinion must be sought. In common with other chronic inflammatory diseases, increased cardiovascular risk for patients with AAV is not explained by traditional risk factors alone and the risk of cardiovascular events is related to the burden of AAV disease activity.[28 29] Additionally, as a result of damage due to AAV and its treatment, the frequency of cardiovascular risk factors such as diabetes and hypertension are increased.[30] Therefore, both adequate control of vascular inflammation, and screening for and treatment of traditional cardiovascular risk factors, are important.[31] Screening for and management of other treatment- and disease-related comorbidities, such as osteoporosis or chronic kidney disease (CKD), should also be conducted. While the available evidence is insufficient to recommend an AAV-specific evaluation of comorbidities, several EULAR and other recommendations[31-35] provide general guidance.

D. *AAV are rare, heterogeneous, and potentially life-and organ-threatening diseases and thus require multidisciplinary management by centres with, or with ready access to, specific vasculitis expertise*

This is based on statement 1 of the 2016 recommendations. Since AAV are rare, expertise in their management is more likely to be available in specialized centres. Accurate diagnosis, assessment of disease severity and differentiation between active vasculitis, infection or other complication or comorbidity, can be challenging and often requires rapid and low-threshold access to multidisciplinary diagnostic evaluation and treatment. In view of the limited number of formally approved therapies, access to treatment with novel drugs within clinical trials can be important, particularly in patients with relapsing or refractory AAV. Appropriately trained nurses and other health care providers experienced in AAV can support patients and provide education. These and other services can be bundled in dedicated vasculitis centers, such as the vasculitis centers within the European Reference Network for rare immune disorders (www.ern-rita-org). Better outcomes of patients with centre-based management compared to earlier cohorts has been reported from single-centre cohorts[36-38], but high-quality evidence on this topic is still lacking.

Recommendations

1. 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.

This recommendation (former statement No.2), and additional guidance related to the role of biopsies outlined in the 2016 update[6] , has not been revised, as the key evidence supporting this recommendation is unchanged. In addition to supporting a clinical diagnosis, biopsies (particularly from the kidney) can be helpful for distinguishing active disease from damage as the cause of clinical decline. A clinicopathologic renal risk score gives prognostic information for end-stage kidney disease but histopathologic subtypes are insufficient to guide treatment decisions.[39-41-34 42 43 44] Repeat kidney biopsy may differentiate recurrent or refractory disease activity from damage or alternative diagnoses.[45]

This task force acknowledges that it may not be feasible to obtain a biopsy in every patient with suspected AAV and initiation of treatment should not be delayed while awaiting histologic information.[46] Barriers to biopsies may include difficulty accessing tissue (e.g. retro-orbital mass in GPA), unjustified risk of procedure (e.g. patients who are on anticoagulant therapy), and anticipated low yield (e.g. the diagnostic sensitivities of upper airway and transbronchial biopsies are only 30 % and 12%, respectively).[47 48] In patients with pulmonary lesions that cannot be clearly attributed to active AAV, thoracoscopic or open lung biopsies can be considered.[49-51] When obtaining or interpreting a biopsy is challenging, surrogate markers can support a clinical diagnosis of AAV that is based on a typical clinical presentation and positive PR3- or MPO-ANCA serology.[52] Such surrogate parameters can be either clinical (such as mononeuritis multiplex confirmed by electrophysiologic studies), laboratory data (such as red blood cell casts in the urine suggestive of glomerulonephritis), or findings on imaging.[52]

No studies have investigated the diagnostic accuracy of imaging compared to a definite clinical diagnosis or a positive biopsy in AAV.[10] Therefore, no evidence-based recommendations on the use of imaging for the diagnosis of AAV can be made. However, imaging is recommended as an integral part of the diagnostic evaluation to detect organ involvement and to identify potential biopsy sites. Computed tomography (CT) of the chest is more sensitive than conventional radiographs and helps to distinguish disease manifestations of AAV from infection and other comorbidities,[53-56] and to detect interstitial lung disease in patients with MPA.[54 55] Magnetic resonance imaging (MRI) can detect central nervous system lesions, pachymeningitis, retro-orbital lesions, or subglottic inflammation in GPA or cardiac disease in EGPA.[57-60] F-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) with CT (PET/CT) allows detection of occult sites of disease activity, concomitant malignancy, and chronic infection.[61-63] Endoscopy contributes to the management of certain organ-specific manifestations, such as subglottic or bronchial stenosis, or vasculitis of the gastrointestinal tract.[64-66] Bronchoalveolar lavage contributes to the evaluation of pulmonary infiltrations, particularly alveolar hemorrhage or eosinophilic alveolitis, and microbiological analysis of the lower respiratory tract.

2. *In patients with signs and/or symptoms raising suspicion of a diagnosis of AAV, we recommend testing for both, PR3- and MPO-ANCA using a high-quality antigen-specific assay as the primary method of testing.*

This recommendation was added due to the increasing relevance of ANCA for the diagnosis and classification of AAV and new data on the methodology of ANCA testing. ANCA are detectable in most patients with newly-diagnosed GPA and MPA and contribute to the diagnosis. Although

ANCA are a sensitive and specific tool to support a diagnosis of AAV, the diagnosis should not be made on ANCA serology alone, as ANCA can be found in other inflammatory diseases and infections, or may be drug-induced.[67 68] Antigen-specific immunoassays have better diagnostic accuracy than indirect immunofluorescence (IIF).[69] The 2017 international consensus statement on testing of ANCA in GPA and MPA recommended high-quality immunoassays for PR3 and MPO-ANCA as the preferred screening method for diagnosis.[67] If the immunoassay is negative, but the clinical suspicion for AAV is still high, a second test (either another immunoassays and/or IIF) is advised. A negative ANCA does not exclude a diagnosis of AAV, as a small proportion of patients with disease limited to the respiratory tract, or with renal-limited vasculitis, are ANCA-negative.[70] The 2017 international consensus statement contains detailed advice regarding other aspects of ANCA testing in GPA and MPA, such as indications for testing, the role of antibody levels, and laboratory methodology. Additional testing for antibodies against glomerular basement membrane (anti-GBM) is advisable in the context of pulmonary-renal syndrome, as patients with anti-GBM/AAV overlap have a lower renal survival[71 72] and may benefit from routine use of PLEX.

With a prevalence of 30% at diagnosis, ANCA are less frequent in patients with EGPA, in whom MPO-ANCA is the predominant serotype.[73 74] EGPA with PR3-ANCA shares clinical features with GPA.[75] A genome-wide association study reported that ANCA-positive and ANCA-negative EGPA are genetically different syndromes.[73] Glomerulonephritis and neuropathy occur more frequently in ANCA-positive EGPA while pulmonary infiltrates and cardiomyopathy are more frequent in ANCA-negative patients.[73] The international consensus statement on testing of ANCA in EGPA stated that the presence of MPO-ANCA is neither sensitive nor specific enough to identify whether a patient should be subclassified as having “vasculitic” or “eosinophilic” EGPA.[76] Furthermore, no differences in response to treatment between ANCA positive and ANCA-negative patients were seen in two recent randomized controlled clinical trials (RCTs) examining the use of RTX or mepolizumab in EGPA.[77 78]

ANCA serology is also relevant for the sub-classification of AAV. In a large multicenter cohort study PR3-ANCA were detected in 84-85 % of patients with GPA and 2-27 % of patients with MPA, while MPO-ANCA were found in 16 % of patients with GPA and 75-97 % with MPA.[79] Patients with PR3- and MPO-ANCA have distinct genetic backgrounds and differ in the frequency of some clinical manifestations, relapse rates and other clinical outcomes.[79 80] The 2012 Chapel Hill consensus conference recommended adding the prefix to the name to indicate ANCA reactivity (i.e., MPO-ANCA, PR3-ANCA, or ANCA-negative), while the presence of PR3 or MPO-ANCA is weighted highly in the 2022 ACR/EULAR classification criteria for GPA, MPA, and EGPA.[1-3] Therefore, ANCA serotype is emerging as a key clinical classification criterion.

3. *For induction of remission in patients with new-onset or relapsing GPA or MPA with organ- or life-threatening disease, we recommend treatment with a combination of glucocorticoids and either rituximab or cyclophosphamide. Rituximab is preferred in relapsing disease.*

The two major changes of this recommendation wording are the recommendation for a preferential use of RTX in relapsing GPA or MPA and the exclusion of EGPA, for which separate recommendations have been created.

Recent trials of induction therapy with CYC- or RTX-based regimens in GPA and MPA included both new-onset and relapsing patients.[19 81] In the largest trial comparing RTX and CYC for remission induction, remission rates at 6 and 12 months in relapsing patients were higher for RTX. This superiority of RTX over CYC did not extend to month 18,[81 82] probably because there was no maintenance treatment in the RTX-arm whereas patients in the CYC-arm were switched to receive azathioprine for 12 to 15 months. Therefore, we favor treatment with RTX in relapsing patients. The recently published data from the induction part of the RITAZAREM study have shown that RTX can effectively restore remission in patients with relapsing AAV.[20] There are limited data on use of CYC in patients relapsing after induction with RTX and the risk of malignancy increases when repeated courses of CYC are given.[27]

In new-onset GPA or MPA, RTX was non-inferior to CYC for induction of remission in two high-quality RCTs.[81 83] Additional RCTs comparing both of these agents for induction of remission in new-onset GPA or MPA have not been published since the last update, nor have new data been released showing differences in long-term outcomes between them. There has been an increasing preference for RTX over CYC, mostly because of concerns about long-term safety of CYC.[84] As CYC reduces ovarian reserve and increases the risk of premature ovarian failure and male infertility,[85 86] RTX is preferable in patients who wish to preserve their reproductive potential. CYC has been associated with development of bladder cancer, bone marrow failure, myelodysplastic syndrome (MDS), and other malignancies.[27 87-90] The use of RTX is lowering CYC exposure and reducing the risk of malignancy in patients with AAV.[91]

A recent meta-analysis that included retrospective studies found that efficacy and safety outcomes do not differ between the RTX protocol used in the RAVE trial (375 mg /m^2 per week for 4 weeks) which is approved for induction of remission in GPA and MPA in the EU and the two-dose protocol (1 g in weeks 0 and 2~~)~~ approved for rheumatoid arthritis.[92] Recent retrospective studies found similar efficacy of RTX and RTX biosimilars in patients with AAV.[93-95] Until recently, experience with RTX without concomitant CYC in patients with severe kidney failure has been limited to data from retrospective studies.[96] The recent PEXIVAS study included patients with severe renal disease and/or diffuse alveolar hemorrhage (DAH) treated with RTX and outcomes appear not to differ compared to CYC, but the study was not sufficiently powered to demonstrate non-inferiority of RTX over CYC in this subgroup.[97] Although pharmacokinetics and mode of action of RTX do not suggest inferior efficacy in patients with renal failure or DAH, some task force members prefer CYC over RTX in this setting. No RCTs have assessed the benefit of RTX/CYC combination over RTX. However, the RTX/CYC combination has been shown to be CYC reducing in RITUXVAS[83] and retrospective studies[98-101] have indicated the possibility of GC minimization and improved responses that require investigation in an RCT (NCT03942887).

The MYCYC trial showed that MMF was non-inferior to CYC for remission induction in new-onset MPA or GPA.[21] There was no safety benefit of MMF demonstrated and the study subjects in the MMF group who were PR3-ANCA positive had a much higher relapse rate.[21] Thus, use of MMF for remission induction should be limited to situations where RTX and CYC are not tolerated or are contraindicated.

4. *For induction of remission of non-organ- or non-life-threatening GPA or MPA, treatment with a combination of glucocorticoids and rituximab is recommended. Methotrexate or mycophenolate mofetil can be considered as alternatives to rituximab.*

AAV EULAR Recommendations, R1, 13.02.23

In contrast to the 2016 update, this recommendation now includes RTX. Although, there are no RCTs comparing the use of RTX to other agents in patients with non-organ threatening AAV, the RAVE trial and recent trials using RTX for induction therapy included such patients. Efficacy and safety outcomes were not inferior compared to those who had more severe disease at baseline.[19-21 81]

With respect to MTX and MMF, this statement refers to new-onset disease only. The MYCYC study also included patients without organ-threatening manifestations.[21] Another RCT comparing CYC and MMF in AAV found numerically lower disease-free survival rates in the MMF group at 2 and 4 years, respectively.[102] Two smaller RCTs, primarily focusing on MPA, concluded equivalence of CYC and MMF for remission induction and safety.[103 104] Given the probable lower long-term efficacy in patients with PR3-ANCA positive AAV, the lack of superiority in safety, and the lack of formal approval for use in AAV, there is insufficient evidence to support the routine use of MMF as a treatment of first choice for new-onset GPA or MPA over RTX or CYC. MMF can be considered as an alternative to RTX-based-regimens, particularly in patients with intolerance or contra-indications to RTX.

The NORAM trial comparing oral CYC versus oral MTX in new-onset GPA found no difference in remission rates and safety at 6 months,.[105 106] However, around 50 % of patients in the MTX arm had either not attained remission or experienced a relapse by month 12 despite continued MTX and high GC exposure (starting dose 1 mg/kg, slow taper to 15 mg per day by months 3), had a shorter time to first relapse and developed additional relapse in the absence of maintenance therapy after months 12. Both NORAM and MYCYC employed GC regimens with higher doses than are currently recommended (see recommendation #5) which increased the chance of demonstrating non-inferiority. In contrast, recent data from the induction phase of the RITAZAREM trial showed that 66 of 69 patients with GPA or MPA without organ-threatening manifestation who were treated with RTX were in remission at month 4 despite the use of a lower-dose GC regimen with a starting dose of 30 mg prednisolone per day.[20] In summary, the use of RTX over MTX or MMF should be considered in patients with GPA and MPA even without organ-threatening manifestations as RTX-based induction and remission regimens are associated with higher rates of sustained remission and lower GC exposure. (see statement #5).

CYC is associated with long-term complications and should not be used as a first-line option in non-organ threatening disease. It may be considered for remission-induction in non-organ-threatening disease when the alternatives RTX, MTX, and MMF cannot be used or are ineffective.

5. As part of regimens for induction of remission in GPA or MPA we recommend treatment with oral glucocorticoids at a starting dose of 50 -75 mg prednisolone-equivalent/day, depending on body weight. We recommend stepwise reduction in glucocorticoids according to Table 4 and achieving a dose of 5 mg prednisolone-equivalent per day by 4 to 5 months.

Long-term follow-up of 535 patients with MPA or GPA and a broad spectrum of severity stages revealed an increased mortality ratio of 2.6 (95% CI 2.2 to 3.1) compared with an age- and sex-matched general population. The main causes of death within the first year were infection (48%) and active vasculitis (19%).[107] High-dose GC contributes to the risk of infections,[108-110] and patients are concerned about adverse effects of GC[111], thus reducing GC exposure in AAV without compromising control of vasculitis is a priority.

The PEXIVAS trial compared two GC taper regimens in 704 patients with GPA and MPA and active organ- or life-threatening disease [97]. The reduced-dose prednisone regimen (**table 4**) resulted in a 40% reduction in oral GC exposure in the first six months (**Figure 1**), it was not inferior for the primary efficacy endpoint but led to a reduction of serious infections during the first year. We recommend tapering GC according to the PEXIVAS reduced GC regimen.[112]

Table 4. Glucocorticoid dosing (mg/day, prednisolone equivalent) with rituximab or cyclophosphamide-based regimens for remission induction in GPA or MPA according to the PEXIVAS-study.[93]

Weeks	**Body weight (kg)**		
	< 50	50-75	>75
1*	50	60	75
2	25	30	40
3-4	20	25	30
5-6	15	20	25
7-8	12.5	15	20
9-10	10	12.5	15
11-12	7.5	10	12.5
13-14	6	7.5	10
15-18	5	5	7.5
19-52	5	5	5
>52	Individual taper	Individual taper	Individual taper

*consider use of IV methylprednisolone at a cumulative dose of 1-3 grams on days 1-3 in patients with severely active disease, including but not limited to renal involvement with a documented estimated glomerular filtration rate <50 mL/min/1.73m^2 and/or diffuse alveolar hemorrhage

The RITAZAREM trial of 190 patients with GPA/MPA at relapse permitted physician selection of either 0.5mg/kg/day or 1.0mg/kg/day starting dose of GC in conjunction with RTX.[20] Although the GC dosing regimens were non-randomized, when patients were stratified for 'major' or 'minor' relapse, no differences in efficacy were seen for either severity subgroup between the two doses.[20] A recent randomized, open-label multicenter trial in patients with predominantly MPA excluding severe kidney disease and/or alveolar hemorrhage compared a reduced GC starting dose (0.5 mg/kg) with a standard starting dose (1 mg/kg) for induction of remission in combination with RTX. At 6 months, remission rates were similar in both groups, but serious adverse events and infections occurred less frequently with the reduced dose. It is premature to give a general recommendation to use lower GC starting doses of 0.5 mg/kg for remission induction in all

patients with active AAV. However, these data encourage further research of lower GC starting doses in cohorts with a broader spectrum of risk factors for unfavorable disease outcomes. For now, lower GC starting doses of 0.5 mg/kg/day may be considered on an individual basis in selected patients without life- or organ-threatening disease.

Administration of intravenous methylprednisolone (MP) pulses in doses of 1000-3000 mg has been used in induction protocols including the RAVE, MEPEX, and PEXIVAS trials[81 97 113] and is common practice in many institutions, without an evidence base. No head-to-head trials have studied the role of MP pulses in AAV, the best available evidence being derived from indirect comparison across different trials. Observational studies have reported no efficacy benefit but increased rates of infections with the use of higher initial doses GC, including MP pulses.[108 109 114 115] Taken together, there is no compelling evidence to support the routine use of MP pulse therapy in addition to oral GC induction therapy and there is a need for further research on this topic. In view of this limitations, and based on the evidence from PEXIVAS trial, MP pulse therapy should be limited to treatment of severe organ-threatening manifestations, particularly either active renal involvement with a documented estimated glomerular filtration rate (eGFR) of <50 mL/min/1.73/m^2, or DAH.

6. Avacopan, in combination with rituximab or cyclophosphamide, may be considered for induction of remission in GPA or MPA as part of a strategy to substantially reduce exposure to glucocorticoids.

This is a new recommendation based on results of the ADVOCATE RCT in 331 patients with newly-diagnosed or relapsing MPA or GPA that compared the use of the oral complement C5a receptor inhibitor avacopan (30 mg twice daily) to a GC regimen tapering from 1mg/kg/day to zero by 21 weeks (a GC withdrawal time similar to the RAVE-trial[81]) as part of a standard induction protocol (RTX or CYC).[19] The primary endpoint (remission at week 26) was reached at similar rates with avacopan (72.3 %) and GCs (70.1 %). Patients with active glomerulonephritis at baseline had greater recovery of kidney function compared to patients treated with GCs. The cumulative GC dose in the avacopan group over one year was 2.3 g lower than in the prednisone group and GC-induced toxic effects measured by the Glucocorticoid Toxicity Index at week 26 were lower in the avacopan compared to the prednisone group. The incidence of adverse events, severe adverse events and infections was not different between groups. There are no data on use of avacopan beyond one year, so longer-term use cannot be recommended. We recommend consideration of avacopan in those subgroups that are likely to have enhanced benefit compared to GC therapy, i.e. patients at risk for development or worsening of GC-related adverse effects and complications or patients with active glomerulonephritis (GN) and rapidly deteriorating kidney function who had better recovery of kidney function with avacopan.[19]

In ADVOCATE remission sustained until week 52 (the second primary endpoint) was reached at a higher rate in the avacopan (65.7 %) compared to the GC treatment groups (54.9 %). Thus, avacopan appears to have efficacy for maintenance of remission. Future studies are needed to evaluate the role of avacopan for this purpose beyond one-year, for patients presenting with a GFR < 15ml/min/1.73 m^2, and for those with refractory disease, and whether avacopan can be stopped when RTX is given for maintenance of remission.

7. *Plasma exchange may be considered as part of therapy to induce remission in GPA or MPA for those with a serum creatinine > 300 µmol/L due to active glomerulonephritis. Routine use of plasma exchange to treat alveolar hemorrhage in GPA and MPA is not recommended.*

Compared to the 2016 update, the strength of recommendation supporting the use PLEX for patients with active glomerulonephritis has been reduced ("may be considered" compared to "we recommend"). While the cut-point serum creatinine qualifying for PLEX has been lowered from 500 to 300 µmol/L (3.41-5.68 mg/dL), the routine use of PLEX to treat alveolar hemorrhage in GPA and MPA is not routinely recommended.

The 2016 statement was based on the results of the MEPEX trial[113] that included only patients with severe GN defined by a serum creatinine > 500 µmol/L. In view of a meta-analysis[116] which suggested that the evidence supporting PLEX was not robust, but there may be benefit in less severe presentations, the PEXIVAS trial was conducted to evaluate the efficacy of PLEX as an adjunct to standard induction therapy in patients with newly diagnosed or relapsing MPA or GPA, with positive PR3 or MPO-ANCA who had active kidney involvement with an eGFR <50mL/min/1.73m^2 or DAH.[97] After a median follow-up of 2.9 years no difference for the primary composite endpoint of death of any cause or end-stage kidney disease (ESKD) was found between patients randomized to PLEX (28%) compared with those randomized to no PLEX (31%).

A meta-analysis of 9 RCTs[97 113 117-124] confirmed that PLEX had no effect on all-cause mortality.[125] Outcome data for ESKD were reported in 999 patients of which 597 came from PEXIVAS and meta-analysis revealed that PLEX reduced the risk of ESKD at 12 months (relative risk 0.62 (95% CI 0.39 to 0.98). As baseline serum creatinine predicts ESKD risk, subgroups based on baseline creatinine with low risk (≤ 200 µmol/L), low to moderate risk (>200-300 µmol/L), moderate to high risk (> 300-500 µmol/L) and high risk (>500 µmol/L) were analyzed. While little absolute risk reduction of ESKD was observed following use of PLEX in the low- and low-moderate risk groups, a 4.6% absolute reduction of ESKD at 12 months was estimated for the moderate-high risk group and 16.0% for the high risk group.[125 126] This translates into a number of patients to treat with PLEX of 21.7 for the moderate to high risk group and 6.25 for the high risk group to prevent one case of ESKD at 12 months. The impact of PLEX on ESKD risk diminished over a 3-year follow-up (relative risk 0.79 (95% CI 0.58 – 1.08). PLEX increased the risk of serious infections at 12 months by 8.5% in the moderate-high risk group, and 13.5% in the high-risk group or patients and no effect on quality of life was found.[125] Thus, treating 14 patients with PLEX will result in 1 serious infection. Two retrospective studies involving 251 and 188 patients with AAV and severe kidney disease, respectively, found no efficacy of PLEX on death or ESKD.[127 128]

Thus, PLEX may reduce the risk of ESKD 12 months but may increase the risk of severe infection. This benefit declines over longer follow-up, suggesting that PLEX might prolong the time to dialysis. Balancing the reported benefit in a subgroup of patients at high risk of ESKD against the risk of severe infection the cost and risks of the procedure, PLEX may be considered as an adjunctive treatment of GPA and MPA for selected cases with a serum creatinine > 300 µmol/L, after discussion of the risks and benefits with the patient.

The SLR and recent meta-analysis revealed no evidence for a clinically relevant benefit of PLEX in patients with AAV and DAH.[125] A small open-label study reported survival in 19 of 20 patients with DAH of whom 9 had severe DAH,[129] while an observational study of 73 patients with DAH of which 34 required mechanical ventilation did not find a benefit of PLEX on mortality or other outcomes.[130] In PEXIVAS, DAH was present in 191 patients and was associated with hypoxia in 61.

No significant effect of PLEX on the combined endpoint of death from any cause or development of ESKD was found in these patients even after adjustment for the severity of DAH, but this sub-study was under-powered for this endpoint and further analysis of the impact of PLEX on DAH mortality is ongoing. As isolated DAH is rare in AAV, the driver for PLEX in those with DAH is usually the degree of associated renal impairment, and there is insufficient evidence to make a recommendation for or against PLEX in isolated DAH.

PLEX is recommended for those patients with AAV also positive for anti-GBM antibodies.[131] Although high-quality evidence for this small subgroup is lacking, most clinicians follow management recommendations for both anti-GBM disease and AAV in their initial treatment of these dual-positive patients.[132] There is low level of evidence derived from a prospective randomized trial that included 62 patients with either EGPA or PAN for a lack of short- and long-term efficacy of PLEX on remission and mortality in patients with EGPA.[133 134]

8. *For patients with GPA or MPA with disease refractory to therapy to induce remission, we recommend a thorough reassessment of disease status and comorbidities and consider options for use of additional or different treatment. These patients should be managed in close conjunction with, or referred to, a centre with expertise in vasculitis.*

Given new options it is too narrow to limit the recommendation for refractory disease to switching from to CYC to RTX or vice versa, as stated in 2016. Time to a treatment response varies individually in the early treatment phase (weeks 0-4). Raising the GC dose for some time can be reasonable strategy, particularly if only minor symptoms persist. The combination of RTX and CYC is used in patients with refractory organ- or life-threatening disease by many centres, but data on this approach in true refractory AAV are lacking. Adding intravenous immunoglobulins can be an option for persistent disease manifestations, particularly in patients with increased risk of infection.[135] No controlled studies on the management of refractory GPA or MPA have been published since the last update. Refractory disease is rare, and management should include review of the diagnosis and careful assessment of disease activity. Refractory AAV needs to be distinguished from infections, other co-morbidities, and alternative diagnoses. Therefore, patients with suspected refractory severe AAV should be managed at centres of expertise.

9. *For maintenance of remission of GPA and MPA, after induction of remission with either rituximab or cyclophosphamide, we recommend treatment with rituximab. Azathioprine or methotrexate may be considered as alternatives.*

This recommendation was changed towards favoring RTX in view of consistent results from two high-quality RCTs confirming a higher efficacy of RTX compared to AZA[136 137] and other recent prospective trials on the use of RTX for maintenance of remission.[138 139]

In the MAINRITSAN trial, patients who attained remission after induction therapy with GC and CYC, repeat-dose RTX (500mg x 2 at 6 months then 500mg every 6 months x 3) over 2 years was associated with a lower relapse rate than treatment with AZA, with comparable safety.[136] Long-term data of this trial showed that the rate of sustained remission remained superior over 60 months with repeat-dose RTX, with better overall survival.[140] First results (abstract) of another multicenter RCT (RITAZAREM) now confirm the higher efficacy of RTX (1g every 4 months x 5) compared with AZA for patients receiving RTX induction therapy for relapsing disease.[137] Results

of MAINRITSAN and RITAZAREM complemented each other with similar findings despite methodological differences (i.e. type of induction therapy, duration and dose of AZA, inclusion of relapsing patients, RTX dose, and dosing interval).[9] RTX is considered cost-effective by preventing costs associated with the occurrence of relapses, particularly since RTX biosimilars have become available.[141] In a RCT, "tailored" RTX maintenance treatment based on biomarkers (rise of ANCA concentration, switch from negative to positive ANCA, or repopulation of CD19+ lymphocytes) was associated with a higher but not statistically different relapse rate (17.3 %) compared to the approved fixed regimen (9.9 %).[139] As the anticipated and observed relapse rates differed substantially, the trial was considered underpowered to exclude inferiority of the biomarker-triggered regimen. In view of these uncertainties, this task force favors the use of the 500 mg q 6 months RTX maintenance regimen. The higher dose of 1g or shorter dosing interval of 4 months or both may be considered for patients who relapse on the 500 mg every 6 months regimen.

RTX impairs humoral responses to vaccination[142-144] and there is increasing information concerning the risks of secondary immunodeficiency in patients with GPA/MPA receiving RTX.[145] [146] Patients should be counseled about the risk of hypogammaglobulinemia (see also recommendation # 14) and further research is required into the safety, duration and dosing of repeated RTX in this disease.

Evidence regarding the use of conventional immunosuppressive agents has not changed substantially since the last update. AZA and MTX are similarly effective maintenance agents in AAV[147] and can be used if RTX is contraindicated (e.g. previous allergic reaction to RTX) or appears inappropriate (e.g. urgent need for vaccination, severe hypogammaglobulinemia). Doses lower than those recommended for AZA and MTX (**supplementary Table S1**) have been associated with higher relapse rates.[136] [147] [148] MTX can be continued in patients in whom it was used to induce remission. MMF was associated with a higher relapse rate compared to AZA in the only phase III RCT[149] and can be considered in patients with intolerance or contraindications to RTX, AZA, or MTX. In patients with GPA, leflunomide can be considered in patients with intolerance to all the above mentioned drugs.[150] Results of two recent meta-analyses revealed that trimethoprim–sulfamethoxazole (T/S) does not reduce relapse risk in patients with GPA.[151] [152] The addition of belimumab to an AZA-based maintenance regimen did not improve relapse-free survival in a RCT which was stopped early due to slow recruitment and had a low relapse rate in the placebo group making a positive result with belimumab unlikely to be detected.[153]

Since there is little evidence to guide low-dose GC therapy during remission in AAV,[154] duration and dosage needs to be individualized on a shared decision basis, taking into account the patient`s individual disease course, risk for or presence of GC-related co-morbidities and patient preferences. There is lower quality evidence that GC withdrawal increases relapse risk,[154] but high-quality prospective studies on the role of GC are yet lacking. Regular screening for GC-related co-morbidities during continued low-dose GC-therapy is recommended according to EULAR recommendations for monitoring adverse events of low-dose glucocorticoid therapy.[34]

10. *We recommend that therapy to maintain remission for GPA and MPA be continued for 24 to 48 months following induction of remission of new-onset disease. Longer durations of therapy should be considered in relapsing patients or those with an increased risk of relapse, but should be balanced against patient preferences and risks of continuing immunosuppression.*

For the 2016 update, this statement was based on low-quality evidence derived from observational studies or long-term follow-up of RCTs.[105 155 156] Since then, three trials[138 157 158] have directly compared the duration of maintenance regimens and this recommendation has therefore been changed accordingly. In the REMAIN study, 117 patients received AZA for a total of 24 months after induction therapy with CYC. Patients were to withdrawal of AZA/GC or continued dosing for an additional 24 months. Those treated for 4 years had fewer relapses (22%) than those treated for 2 years (63%).[157] Four patients in the withdrawal group developed ESKD versus none in the group treated for another 2 years (P=0.012). A meta-analysis of REMAIN and the smaller AZA-ANCA trial concluded that prolonged administration of AZA reduced the risk of relapse.[152] Results of the open label randomized MAINRITSAN-3 trial showed that more patients remain relapse-free after an additional 18 months of RTX maintenance therapy than after treatment for only 18 months.[138] Prolonged therapy with RTX was not associated with an excess of serious adverse events or infections.

The clinical disease type (GPA vs. MPA), ANCA serotype (PR3-ANCA vs. MPO-ANCA), and ANCA status (positive vs. negative) have all been associated with the risk of relapse. In several studies, a higher risk of relapse was observed in patients with GPA than in patients with MPA.[159-161] Regardless of the clinical phenotype, patients with positive PR3 ANCA at diagnosis are at higher risk of relapse than MPO ANCA-positive.[80 140 156 162 163] Persistent ANCA positivity despite clinical remission[164-166], or seroconversion from negative to positive ANCA[164], are also each associated with an increased risk of relapse. B-cell repopulation within 12 months of RTX[164] and persistent hematuria[167] have been identified as risk factors for relapse in individual studies. The intensity of induction therapy also impacts the risk of relapse. Lower cumulative CYC doses or induction therapy with MTX or MMF instead of CYC have been associated with an increased risk of relapse.[105 156 168 21]

There is low- to moderate-level evidence that patients with renal-limited vasculitis and patients positive for MPO-ANCA have a lower relapse risk compared to PR3-ANCA-positive patients and patients with respiratory tract involvement.[169 170] In a series of 228 patients with ESKD, the proportion of patients with ANCA-associated vasculitis in remission off immunosuppression increased with time spent on dialysis and patients were far less likely to relapse from their vasculitis than to display serious infectious or cardiovascular events.[171] Therefore, the benefit of relapse prevention should be weighed against the risk of complications resulting from immunosuppressive therapy in patients with renal limited MPO-ANCA-associated vasculitis and some task force members do not routinely use maintenance therapy in these patients. Patients with drug-induced AAV rarely relapse and do not require routine immunosuppressive therapy after remission is achieved and the implicated drug is discontinued.[172]

In summary, there is no consistent high-quality evidence available to guide decisions about the duration of maintenance therapy based on biomarkers such as ANCA or other factors alone (see also recommendation no. 14).[9] While there is now consistent evidence from two RCTs that extending maintenance therapy for longer than 24 months reduces relapse risk, we recommend considering individual risk factors for relapse and damage as well as patient preferences for decisions about the length of maintenance treatment.

11. *For induction of remission in new-onset or relapsing EGPA with organ- or life-threatening manifestations we recommend treatment with a combination of high-dose glucocorticoids and*

cyclophosphamide. A combination of high-dose glucocorticoids and rituximab may be considered as an alternative.

Since the last update of these recommendations, results of three RCTs enrolling only or mainly patients with EGPA have been reported,[77 78 173] which allowed the development of separate recommendations for EGPA for this update.

The Five Factor Score (FFS) is used for prognostic assessment of EGPA.[174] Particularly, cardiac involvement has been associated with increased mortality in EGPA.[36 175 176] However, under optimized management in centers of expertise, the prognosis of cardiac involvement appears to be better than previously reported. This may reflect more frequent diagnosis of milder forms of cardiac disease through use of cardiac MRI and a greater awareness among physicians regarding cardiac disease in EGPA.[177] In a recent series from the French Vasculitis Study Group of 70 patients with EGPA with cardiac manifestations treated with high-dose GC, mostly along with CYC, no patient died as a consequence of cardiac involvement during a 10-year observation period.[178] With the aim of preventing permanent organ damage due to EGPA, patients with severe involvement of the kidneys, central and peripheral nervous system, or gastrointestinal tract are also considered to be candidates for treatment with CYC (**Table 2**) [179]. In a randomized, open-label trial in patients with EGPA and poor prognosis (FFS ≥ 1), 12 compared to 6 pulsed doses of CYC was associated with a lower rate of minor relapses but did not improve response rate or reduce severe relapses.[180] Therefore, we recommend treatment be switched to a less intensive remission maintenance therapy after 6 pulses of CYC if remission is achieved, and the GC dose is reduced by then to approximately 7.5 mg per day (see **supplementary Table S2** for protocols).

A RCT examining the use of RTX in EGPA (REOVAS) included 105 patients with new-onset or relapsing EGPA of whom 42 had life- or organ-threatening disease (FFS ≥ 1) (abstract).[77] Patients with FFS ≥ 1 received high-dose GCs plus either 2 x 1 g RTX (day 1 and 15) or 9 pulses of CYC over 13 weeks. The primary endpoint of on-treatment remission was reached at similar frequencies at days 180 and 360 in both groups, but the limited number of patients, the superiority-design, and the lack of fully published results do not allow for strong conclusions regarding non-inferiority. Adverse events, cumulative prednisone doses and quality of life were not different between groups. Results were similar in both newly-diagnosed and relapsing disease. In contrast to earlier observational studies,[181 182] the response to RTX was not higher in MPO-ANCA-positive patients compared to ANCA-negative patients, consistent with consensus recommendations on ANCA-testing that treatment decisions in EGPA should not be influenced solely by ANCA-status.[76] Keeping in mind that the results of the REOVAS trial have not been fully published yet, the data reported so far are deemed sufficiently strong to consider RTX as an alternative to CYC, particularly in patients in which exposure to CYC needs to be avoided, and are consistent with earlier observational reports (see recommendation #3).

In contrast to GPA and MPA, no studies have compared different GC tapering strategies in the treatment of EGPA. In the absence of data to support an evidence-based recommendation on GC tapering in EGPA, recommendations made for GPA and MPA (statement #4) can be used as an orientation. However, asthma and ENT exacerbations increase the GC requirement in patients with EGPA, leading to prolonged tapering.[183] Therefore, interdisciplinary management involving pulmonologists and/or otorhinolaryngologists is recommended aimed at optimizing treatment (including topical agents) of asthma, polyposis, and sinusitis.

12. *For induction of remission in new-onset or relapsing EGPA without organ- or life-threatening manifestations we recommend treatment with glucocorticoids.*

Patients with EGPA without adverse prognostic factors (FFS=0) treated with GC only achieve remission > 90% of the time, but relapses are common once GC are tapered.[174 184] Therefore, clinicians frequently combine GCs with other immunosuppressants or biologics. However, the SLR revealed that evidence supporting GC-sparing therapy in newly-diagnosed patients with EGPA without organ- or life-threatening manifestations is low.[10] A prospective placebo-controlled study showed that therapy with AZA for 1 year in addition to GC had no effect on the risk of relapse, cumulative GC requirement, or the rate of asthma and sinusitis exacerbations compared with GC monotherapy in EGPA without poor prognostic factors (FFS=0).[173] Recent long-term study data also showed that, within 5 years, 48% of all patients experienced vasculitis relapses, and prior therapy with AZA did not reduce this risk.[184] The REOVAS trial included 63 new-onset or relapsing patients with EGPA with a FFS of 0 who were randomized to receive high-dose GCs together with either 2 x 1 g RTX (day 1 and 15) or placebo. Efficacy and safety outcomes after 180 and 360 days were not different between RTX and placebo group. Because the trial was not designed as a non-inferiority trial and since it has been reported only in abstract format so far, the data preclude from making strong conclusions but provide no support for use of RTX for remission induction in this subgroup of patients. No RCTs are available on the use of MTX, MMF, or leflunomide in EGPA. Small observational studies on the use of MTX or MMF did not include control groups and carry a high risk of bias.[185 186] As the evidence to support immunosuppression beyond GCs in new-onset EGPA without risk factors for worse outcome is low,[10] decisions on the use of GC-sparing therapy in this subset of patients may be made on an individual basis considering risk-factors of GC-related morbidity.

13. *For induction of remission in patients with relapsing or refractory EGPA without active organ- or life-threatening disease, we recommend the use of mepolizumab.*

The interleukin-5 (IL-5) inhibitor mepolizumab was evaluated in a randomized double-blind placebo-controlled phase III study (MIRRA) that included 136 patients with relapsing or refractory EGPA with a disease duration of at least 6 months[78] The study protocol allowed the inclusion of patients without vasculitic manifestations while patients with active life- or organ-threatening manifestations were excluded. After treatment with prednisolone at a stable dose ≥ 7.5 mg per day prior to baseline, 54 % of patients in the mepolizumab arm and 71 % of patients in the control arm had active disease at randomization with a BVAS > 0. Patients were randomized 1:1 to continuation of standard therapy (including other conventional immunosuppressive agents in more than 50 % of patients in each arm) or standard therapy plus mepolizumab at a dose of 300 mg every 4 weeks s.c. Both co-primary endpoints (the number of weeks in remission on a prednisolone dose reduced to 4 mg and the proportion of patients in remission at weeks 36 and 48) were met in favor of mepolizumab.[78] A post-hoc analysis showed that treatment with mepolizumab was associated with additional clinically-relevant endpoints, such as remission and GC reduction of >50%, in over half of the patients treated with mepolizumab.[187] Based on its association with clinically meaningful improvement of disease control and reduction of GC demand, and good safety profile compared to conventional immunosuppressants, this task force recommends the use of mepolizumab with relapsing or refractory, non-organ- or life-threatening EGPA. Mepolizumab has recently been approved for this indication in many European countries.

Data from studies using mepolizumab for treatment of life- or organ-threatening or new-onset EGPA are currently lacking.[10]

Other IL-5- or IL-5-receptor inhibitors (reslizumab, benralizumab) showed efficacy in small open-label pilot studies in EGPA,[188 189] but data from RCTs using these agents are not yet available. In a retrospective multicenter series, anti-IgE targeted therapy with omalizumab appeared to be less effective than mepolizumab.[190] As discussed above, data showing improved outcomes with other biologic or conventional drugs for non-severe relapsing or refractory EGPA are lacking. In patients for whom mepolizumab is not be effective or not tolerated, AZA, MTX, MMF, or RTX can be considered on an individual basis.[184-186 190-192]

A true refractory course of EGPA with life- and organ-threatening manifestations is rare if patients are treated with high-dose GC and a CYC- or RTX-based induction regimen.[77 180] Data guiding treatment decisions in this small subgroup of patients are scarce and true refractory severe EGPA needs to be carefully distinguished from infections and co-morbidities. Therefore, patients with suspected refractory severe EGPA should be managed at centres of expertise.

14. *For maintenance of remission of relapsing EGPA after induction of remission for non-organ- or life-threatening manifestations at the time of relapse we recommend treatment with mepolizumab. For maintenance of remission of EGPA after induction of remission for organ- or life-threatening disease, treatment with methotrexate, azathioprine, mepolizumab, or rituximab should be considered.*

In view of the relapsing nature of EGPA requiring long-term use of GCs in most patients, other agents for maintenance of remission are commonly prescribed in an attempt to be GC-sparing. In a RCT (MIRRA, see recommendation #13 for details) that enrolled patients with EGPA who had relapsing or refractory disease, rates of severe and non-severe relapses were significantly lower and the median GC dose throughout the study was lower in the mepolizumab group compared to the control group.[78] Adverse events occurred at similar rates in the mepolizumab group and the placebo group, while serious adverse events were somewhat more common in the placebo group (18% vs. 26%). In view of its efficacy and good safety profile, the use of mepolizumab after induction of remission for non-organ- or life-threatening manifestations at the time of relapse is recommended. In a RCT that enrolled 51 patients with EGPA and no organ- or life-threatening manifestations, AZA for 1 year in addition to GC had no effect on the risk of relapse, cumulative GC requirement, or the rate of asthma and sinusitis exacerbations compared with GC monotherapy.[173] There is little evidence to recommend routine use of other immunomodulatory agents for maintenance of remission in EGPA without organ- or life-threatening manifestations.[10]

The SLR identified only one prospective study addressing remission maintenance strategies in patients with EGPA who attained remission after treatment for life- or organ-threatening disease.[10] A single-centre prospective randomized trial compared oral CYC to MTX for one year after remission induction with CYC in different subtypes of AAV.[193] In the subgroup of 30 patients with EGPA who had either a FFS > 1 or peripheral neuropathy, no difference in relapse rates between the two treatment arms was observed. Although no excess in adverse events was found in this study, we do not recommend CYC for remission maintenance in view of its toxicity. However, this study provides rationale for use of MTX for maintenance of remission in EGPA, although the small sample size of patients with EGPA precludes a strong recommendation. As

observational studies reported favorable outcomes on the use of AZA, mepolizumab, and RTX for maintenance of remission,[36 190] these agents can also be considered for remission maintenance in EGPA after induction of remission for organ- or life-threatening manifestations. In view of its efficacy in eosinophilic asthma, mepolizumab should also be considered for patients with EGPA with residual GC-dependent asthma who achieved remission of major organ involvement.

15. *In the management of patients with AAV we recommend that structured clinical assessment, rather than ANCA and/or CD19+ B cell testing alone, should inform decisions on changes in treatment.*

This recommendation (former statement #10) has been amended to include CD19+ B cell testing but is otherwise unchanged as data from recent RCTs have confirmed earlier studies on this topic. Although ANCA status is associated with relapse,[165 194-196] prospective trials on maintenance of remission showed conflicting results in ANCA status or CD19+ B cells counts to predict future relapses at a level deemed insufficient to guide treatment decisions for individual patients.[138 139] Administration of RTX for maintenance of remission based on changes of ANCA-status and/or B cell counts were associated with a non-significantly higher rate of relapses compared to regular treatment at 6 months intervals, while adverse events occurred at a similar rate.[139] Regarding the role of ANCA-measurements for monitoring in AAV we also refer readers to the recent international consensus statements on ANCA testing.[67 76] Further prospective studies are clearly necessary to identify predictive markers of relapse.

As AAV involves multiple organs and relapses are frequent, a structured clinical assessment during follow-up at regular intervals is recommended. The Birmingham Vasculitis Activity Score (BVAS)[197] has been used in different variants in the majority of RCTs in AAV and can be helpful in clinical practice to document response to treatment in a systematic fashion. Damage resulting from AAV, or its treatment needs to be distinguished from active disease to avoid unnecessarily escalating treatment. The Vasculitis Damage Index (VDI)[198] is a validated instrument to record damage in AAV and provides definitions that help distinguish damage from active disease.

16. *In patients with AAV receiving rituximab we recommend measurement of serum immunoglobulin concentrations prior to each course of rituximab to detect secondary immunodeficiency.*

The SLR revealed no data published since the last update that suggested a change of this recommendation,[10] but wording has been rephrased to highlight the purpose of immunoglobulin measurement. Results of the MAINRITSAN-3 study have shown that long-term treatment of patients with GPA or MPA with RTX over 36 months was associated with the development of hypogammaglobulinemia (IgG < 5 g/L) in 21 % of patients, confirming earlier reports on decreased IgG levels following treatment with RTX or CYC in AAV.[199 200] For further details on risk factors for secondary immunodeficiency after RTX, monitoring, indications, dosage and discontinuation of immunoglobulin replacement therapy, we refer readers to evidence-based consensus recommendations. [201]

17. *For patients with AAV receiving rituximab, cyclophosphamide, and / or high doses of glucocorticoids we recommend the use of trimethoprim–sulfamethoxazole as prophylaxis against Pneumocystis jirovecii pneumonia and other infections.*

This is a new recommendation based on results of an observational study in 192 patients with AAV treated with RTX, showing that the prophylactic use of trimethoprim–sulfamethoxazole (T/S) was associated with a lower frequency of severe infections (HR 0.30, 95% CI 0.13 to 0.69).[202] In an earlier RCT investigating the role of T/S in therapeutic dosage (960 mg twice a day for 2 years) a reduction in respiratory tract infections and a trend towards fewer non-respiratory tract infections compared with placebo had been observed.[203] Thus, available evidence suggests that T/S not only reduces the risk for *Pneumocystis jirovecii* pneumonia (PJP), but is also associated with a reduction of the overall risk of infection. T/S also reduced the 1-year incidence of PJP and related mortality in a cohort of 1092 patients with various rheumatic diseases treated with ≥30 prednisolone mg/day for ≥4 weeks.[204] For patients treated with ≥ 15 to < 30 mg/day of prednisone per day for ≥4 weeks, the risk of PJP and benefit of T/S are lower, but in a subgroup of patients with lymphopenia at baseline and those receiving GC pulse treatment, the number needed to treat to prevent one PJP was lower than the number needed to harm by serious adverse events.[205] As infections are the leading cause of death within the first year of induction therapy in patients with AAV,[206] infection prophylaxis with T/S (800/160 mg on alternate days or 400/80 mg daily) is recommended for all patients with AAV receiving CYC or RTX and patients where treatment with GCs at a dose of ≥30 mg/day for 4 weeks or longer is envisioned, irrespective of other concomitant immunosuppressants. Although there have been concerns about synergistic toxicities to T/S given at therapeutic doses and MTX, recent studies found no evidence for an interaction between MTX and T/S at prophylactic doses.[207], but data on the safety of this combination in patients with rheumatic diseases are lacking. While there are insufficient data to guide the total duration of prophylaxis with T/S it seems reasonable to continue this drug for the estimated duration of the biologic effect of CYC and RTX of around 3 and 6 months after the last dose or B-cell reconstitution, respectively. For patients treated with GCs in combination with immunosuppressants other than CYC or RTX, T/S may be stopped once GC doses have been tapered to 15 mg/day, but that strong consideration should be given to continuing it until lower doses are achieved if other risk factors such as pulmonary disease or hypogammaglobulinemia are present [208] Patients who develop adverse reactions often tolerate re-introduction of T/S if the dose is gradually increased according to published regimens.[209] [210] Alternatives for patients who cannot tolerate T/S are dapsone,[211] atovaquone[212] [213] or aerosolized pentamidine.[214]

Vaccinations are an integral part of infections prophylaxis in patients with autoimmune diseases receiving immunosuppressive therapy. Since the approach to vaccination in patients with AAV does not differ from other rheumatic diseases treated with a similar intensity of immunosuppression, we refer to the 2019 EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases and local guidelines.[215]

DISCUSSION

Since the publication of the 2016 EULAR recommendations on the management of AAV several high-quality RCTs have expanded our knowledge about these complex diseases and allowed updates of previous recommendations. We have made substantial alterations, including the introduction of overarching principles and new recommendations on ANCA-testing, therapy with

GC, use of agents with novel modes of action (C5aR inhibition, IL-5 blockade) and prophylaxis against infections. Whilst most of the original recommendations addressed AAV in general, new data allowed us to devise separate recommendations for GPA/MPA and EGPA for some management principles.

Given the complexity and variability of multi-organ involvement in AAV, we emphasize that these recommendations are not intended to propose a "one size fits all" strategy. Co-morbidities, the individual patient's history, toxicities, local availability and costs of medication, and patient preferences should all be considered in the process of informed decision making. High quality evidence of management of AAV in pregnancy is lacking and we refer readers to EULAR recommendations for the management of family planning, assisted reproduction, pregnancy, and menopause in patients with systemic lupus erythematosus and other rheumatic diseases.[216 217] In addition, many of the organ manifestations such as severe kidney disease, MPO-ANCA-associated interstitial lung disease, bronchial/subglottic stenosis, orbital mass, severe ear, nose and throat manifestations, cardiac involvement in EGPA, and CNS disease or vasculitic neuropathy may require specific pharmacologic and non-pharmacologic interventions. Recognition and supportive management of organ damage is another important aspect. However, the level of evidence guiding management of these organ manifestations or organ damage in AAV is mostly low. Thus, it was beyond the scope and format of these EULAR recommendations to specifically address these important areas of management.

The COVID-19 pandemic has had a major impact on patients with AAV and influences their management.[218] In the light of changing virus variants, availability of vaccinations and antiviral treatments, conditions affecting the management of patients with AAV in the pandemic change rapidly. Therefore, specific recommendations for management of patients with AAV in the pandemic are beyond the scope of this project, since these would to be outdated at the time these recommendations are published. Instead, we refer to the most recent national guidelines and EULAR points to consider on the use of immunomodulatory therapies and vaccinations in COVID-19.[219 220]

Given the relative rarity of AAV and the limitations of the published studies, particularly in terms of outcome assessment and long-term follow-up, important questions remain unanswered. We have listed key issues in a research agenda (**Table 5**) and encourage investigators to use them as a basis for conducting future high-quality research in the field of AAV.

In conclusion, we substantially revised the recommendations for the management of AAV. Despite progress over the past 10 years, we acknowledge that some recommendations had to be made based on low-quality evidence. Nevertheless, the level of agreement for each recommendation was consistently high among the task force members. We encourage clinicians to implement these recommendations into their clinical practice to effectively manage AAV and to improve the patients' quality of care.

Table 5 Research agenda

A. Diagnosis and Classification

- Develop data-driven diagnostic criteria for AAV
- Develop data-driven definitions for disease activity states (remission, response, relapse) and standardization of outcome measures, including patient-reported outcomes, for use in trials in AAV.
- Develop data-driven definitions of disease subtypes of importance
- Identify reliable biomarkers and risk factors for relapsing disease and damage
- Identify reliable biomarkers including imaging and biopsies to assess subclinical disease activity and monitor treatment response

B. Treatment

- Evaluate benefits and harms of higher dose GC therapy (e.g. intravenous MP) compared to standard starting dosing (1 mg/kg/day) for patients with different subtypes, severity stages, and risk factors for adverse outcomes
- Evaluate benefits and harms of reduced starting doses of GC (e.g. 0.5 mg/day) compared to standard starting doses (1 mg/kg/day) in patients with different ANCA subtypes, severity stages, and risk factors for adverse outcomes
- Investigate optimal duration of therapy with GC
- Study benefit of the combination of RTX and CYC vs RTX only
- Investigate the safety and optimum schedule of repeat-dose rituximab maintenance therapy
- Investigate the effect of immunomodulators with novel modes of action (e.g. JAK inhibitors)
- Study long-term outcomes after induction therapy with avacopan and its efficacy for maintenance therapy, in combination with and/or compared to standard therapy
- Further study the potential of C5a blockade to fully replace GCs for induction of remission and for extended use
- Study efficacy and safety of IL-5 inhibitors in newly-diagnosed patients with EGPA and patients with organ-threatening manifestations compared to other types of induction therapy (CYC, RTX)
- Study maintenance therapies for EGPA
- Study the optimal duration and dosage of with T/S or other agents for prophylaxis at against infection
- Management of AAV during conception and pregnancy and potential impact on fertility

C. Long-Term Outcome and Biomarkers

- Identify biomarkers to predict drug toxicity
- Identify predictors for good response, remission, or relapse

- Define and validate use of patient-reported outcomes for management of AAV in clinical practice
- Study the impact of long-term GC therapy on GC-related adverse effects and co-morbidities

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CONTRIBUTORS

BS and JS conducted the SLR. DJ, GT, SM, and RL were members of the steering committee and provided substantial methodological advice. BH drafted the first version of the manuscript and subsequent revisions. All authors were involved in the formulation and discussion of the recommendations, reviewed the manuscript and made extensive comments and changes to it. The final version of the manuscript was approved by all authors.

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FIGURE LEGENDS

Figure 1. Protocol target glucocorticoid (GC) doses in AAV induction trials[81 106 221-227] (black line), illustrating how these compare with the reduced GC group from the PEXIVAS trial (red line). The line and error bars represent the mean and 95% confidence intervals across a range of weights, genders and ages.

Figure 2. The 2022 EULAR algorithm for treatment of granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA). Dashed lines indicate supplementary action to consider. GC doses are provided as prednisolone equivalent. [1]See **table 2** for examples for organ-/life-threatening and not organ-/life-threatening manifestations; [2]see **table 4** and recommendation #5 for details and consider AAV EULAR Recommendations, R1, 13.02.23

lower starting dose of 0.5 mg/kg/day in individual patients without organ- or life-threatening manifestations; [3]as part of a strategy to substantially reduce exposure to glucocorticoids (see recommendation #6 for details); [4]prefer RTX over CYC in relapsing disease and patients (m/f) with child-bearing potential or previous exposure to CYC at an individual cumulative dosage considered to be associated with an increased risk of complications; [5]in selected patients with serum creatinine > 300 µmol/L due to active glomerulonephritis plasma exchange may be considered taken into account individual risk for end stage kidney disease and patient preferences; [6] stop avacopan after a duration of treatment of 6-12 months; there are no data on use of avacopan beyond one year, so longer-term use cannot be recommended. Abbreviations: AZA, azathioprine; CYC, cyclophosphamide; GC, glucocorticoid; MMF, mycophenolate mofetil; MTX, methotrexate; RPGN, rapid progressive glomerulonephritis; RTX, rituximab.

Figure 3. The 2022 EULAR algorithm for treatment of eosinophilic granulomatosis with polyangiitis (EGPA). [1]See **table 2** for examples for organ-/life-threatening and not organ-/life-threatening manifestations; [2]see **table 4** as an example for GC dosing (note: validated in MPA and GPA only). [3]consider use of RTX over CYC in patients (m/f) with child-bearing potential or previous exposure to CYC at an individual cumulative dosage considered to be associated with an increased risk of complications; [4]individualized duration of maintenance treatment; [5]in patients with relapsing or refractory EGPA without organ-threatening manifestations at the time of relapse MEPO is preferred for maintenance of remission and AZA, MTX or RTX can be used as alternatives if MEPO is not tolerated or ineffective. Abbreviations: AZA, azathioprine; CYC, cyclophosphamide; GC, glucocorticoid; MTX, methotrexate; MEPO, mepolizumab; RTX, rituximab.

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