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ORIGINAL RESEARCH

Systematic literature review informing the 2022 update of the EULAR recommendations for the management of ANCA-associated vasculitis (AAV): part 1—treatment of granulomatosis with polyangiitis and microscopic polyangiitis

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ABSTRACT

Objective To summarise and update evidence to inform the 2022 update of the EULAR recommendations for the management of antineutrophil cytoplasm antibody-associated vasculitis (AAV).

Methods A systematic literature review (SLR) was performed to identify current evidence regarding treatment of AAV. PubMed, EMBASE and the Cochrane library were searched from 1 February 2015 to 25 February 2022. The evidence presented here is focused on the treatment of granulomatosis with polyangiitis and microscopic polyangiitis.

Results 3517 articles were screened and 175 assessed by full-text review. Ninety articles were included in the final evidence synthesis. Cyclophosphamide and rituximab (RTX) show similar efficacy for remission induction (level of evidence (LoE) 1a) but RTX is more effective in relapsing disease (LoE 1b). Glucocorticoid (GC) protocols with faster tapering result in similar remission rates but lower rates of serious infections (LoE 1b). Avacopan can be used to rapidly taper and replace GC (LoE 1b). Data on plasma exchange are inconsistent depending on the analysed trial populations but meta-analyses based on randomised controlled trials demonstrate a reduction of the risk of end-stage kidney disease at 1 year but not during long-term follow-up (LoE 1a). Use of RTX for maintenance of remission is associated with lower relapse rates compared with azathioprine (AZA, LoE 1b). Prolonged maintenance treatment results in lower relapse rates for both, AZA (LoE 1b) and RTX (LoE 1b).

Conclusion This SLR provides current evidence to inform the 2022 update of the EULAR recommendations for the management of AAV.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Since the publication of the previous EULAR recommendations for the management of antineutrophil cytoplasm antibody (ANCA)-associated vasculitis in 2016, several landmark trials have been published and refined treatment strategies in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).

INTRODUCTION

Since the 2016 update of the EULAR recommendations for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV),[1] several high-impact clinical trials have broadened the repertory of available treatments for granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) and refined management strategies in daily routine care.[2–7]

Cyclophosphamide (CYC) and glucocorticoids (GC) have been the mainstay of remission induction treatment in AAV.[8] Even though successful strategies to reduce the exposure of CYC and GC, including the use of rituximab (RTX) have been in use for several years now,[9 10] the toxicity and sequelae caused by these substances remain an unsolved issue in AAV.[11 12] The optimal management and duration of immunosuppressive treatment balancing risk of relapse and risk of treatment-induced complications is an ongoing challenge during long-term follow-up. Biomarkers guiding the intensity or duration of immunosuppression are not

WHAT THIS STUDY ADDS

⇒ This review highlights new evidence derived from randomised controlled trials and meta-analyses regarding remission induction, glucocorticoid dosing, plasma exchange and maintenance treatment for ANCA-associated vasculitis (AAV).
⇒ Cyclophosphamide and rituximab have overall similar efficacy for induction treatment but rituximab shows superior capacity in relapsing patients.
⇒ Glucocorticoid-sparing protocols are non-inferior to conventional tapering schemes in terms of efficacy and have lower serious infection rates.
⇒ Avacopan can be used to rapidly taper and replace glucocorticoids during induction treatment.
⇒ Available data on the effect of plasma exchange are conflicting.
⇒ Recent meta-analyses suggest that plasma exchange may lower the risk of end-stage kidney disease at 12 months (but not during long-term follow-up) in renal vasculitis.
⇒ The available data demonstrate no efficacy of plasma exchange to reduce mortality.
⇒ Use of rituximab for maintenance of remission is associated with lower relapse rates compared with azathioprine.
⇒ Prolonged maintenance treatment results in lower relapse rates.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this systematic literature review will shape the treatment approaches for patients with GPA and MPA.
⇒ The 2022 update of the EULAR recommendations for the treatment of AAV have been based on this evidence synthesis.

yet established. Since the last update, new information is available on (i) the use of mycophenolate mofetil (MMF) for remission induction,[5 13] (ii) reduced-dose GC schemes,[2 6] (iii) GC-sparing treatment with avacopan,[4] (iv) the efficacy of plasma exchange (PLEX),[2] (v) dosing and duration of remission maintenance treatment with conventional immunosuppressives and RTX[3 7 14] and (vi) pooled evidence from meta-analyses on several areas of the management of AAV.[15 16]

We conducted a systematic literature review (SLR) focused on treatment of GPA and MPA. The results presented here will provide the available evidence to the task force of the 2022 update of the EULAR recommendations for the management of AAV.[17] A second complementary article will cover the treatment of eosinophilic granulomatosis with polyangiitis as well as diagnostic procedures and general management of AAV.[18]

METHODS

The SLR was performed according to the EULAR standard operating procedures (SOP) for EULAR-endorsed recommendations.[19] A methods protocol was established prior to the conduct of the review. Based on a Delphi survey administered to the whole task force (including field expert physicians, one healthcare professional and two patient representatives), eight research questions in the patient, intervention, comparator, outcome (PICO) format were developed to address treatment of GPA and MPA (online supplemental file 1). An electronic search focusing on treatment of AAV was performed in PubMed, EMBASE and the Cochrane Library databases (including trial registries clinicaltrials.gov and the WHO Clinical Trial Registry platform). Search strings were developed in collaboration with an experienced librarian. The search was performed as an update starting with the end date of the SLR of the previous recommendations (1 February 2015)[1] and included studies up to 25 February 2022. For treatments not included in the last recommendations, a search without time restrictions was done. Randomised controlled trials (RCTs) and non-randomised intervention studies were included in the review. Congress abstracts of the international meetings of EULAR, the American College of Rheumatology (ACR), the American Society of Nephrology, the European Renal Association/European Dialysis and Transplant Association and the Vasculitis and ANCA Workshop were additionally screened for abstracts of RCTs. Detailed PICO questions, search strategies and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram are provided in the online supplemental file 1.

The SLR was performed by two independent reviewers (BS-A and JHS) under supervision of two methodologists (RAL, GT). Articles delivered by the electronic database search were screened by review of title and abstract (10% in duplicate with >80% agreement) and relevant articles selected for full-text review. Both reviewers agreed on the included studies by consensus and disagreements were resolved by discussion. Included articles were summarised in piloted summary of evidence tables during full-text review (50% in duplicate). Data and quality of evidence of studies included in the final data synthesis were agreed on by both reviewers. Disagreements were resolved by discussion. In case of uncertainties, methodologists were consulted to resolve open questions. Case reports, editorials, retrospective studies with mixed populations (not mainly consisting of patients with AAV), retrospective studies with <50 patients with GPA/MPA and prospective studies with <10 patients with AAV were excluded. The SLR was limited to articles in English language.

The 2009 Oxford Centre for Evidence-Based Medicine levels of evidence (LoE) were assigned to included studies.[20] Risk of bias (RoB) was assessed using the AMSTAR 2[21] tool for systematic reviews and meta-analyses, RoB 2 for randomised trials,[22] ROBINS-I for non-randomised intervention studies[23] and the Newcastle-Ottawa Scale for case series or intervention studies without control group ('self-controlled before-after').[24]

RESULTS

The search strategy identified 3517 articles (after deduplication). One hundred and seventy-five articles were selected for full-text review. Details are provided in the online supplemental file 1. Ninety articles[2–7 11 13–16 25–103] addressing GPA and MPA treatment were included for evidence synthesis (online supplemental file 2).

Remission induction treatment with immunosuppressives

Cyclophosphamide

Three meta-analyses of RCTs were identified that reported pooled estimates from comparing intravenous pulsed and continuous oral CYC.[15 16 71] The main results are summarised in table 1. Two meta-analyses[15 71] compared remission rates and found them not significantly different between the CYC regimens. Two meta-analyses compared relapse risk between the regimens and found them to be higher in patients treated with intravenous pulsed CYC compared with oral CYC. Risk of leucopenia (a well-defined risk factor for infectious complications) was lower in patients treated with intravenous pulsed CYC.[15 16]

One new RCT comparing different CYC regimens was identified since the 2016 AAV EULAR recommendations. The CORTAGE trial included a mixed population of necrotising vasculitides (mainly GPA and MPA but also EGPA and polyarteritis nodosa (PAN)) aged ≥65 years and compared an induction regimen with reduced dose and duration and a conventional treatment (table 2).[73] The intervention group received GC that were tapered and discontinued at 9 months combined with fixed-dose 500 mg intravenous CYC pulses for induction (given until remission, maximum six pulses), afterwards switched to maintenance treatment with azathioprine (AZA), methotrexate (MTX) or MMF. The conventional treatment (control) group received higher doses of GC that were reduced over a longer period (discontinued by 26 months) combined with CYC, dosed according to body surface area (500 mg/m^2) followed by three consolidation pulses, then the same maintenance treatment as in the intervention group. Patients with EGPA or PAN and a 1996 Five-Factor Score of 0 in the control group received only GC. The primary outcome was the occurrence of ≥1 serious adverse event (SAE) over 3 years, which occurred less frequently in the intervention arm compared with the conventional treatment arm. Relapses were not significantly (p=0.15), but numerically more frequent in the reduced-dose arm (20 of 45; 44%) compared with the control arm (12 of 41; 29%).

Supplementary studies from the 'General Management' section in the second SLR manuscript report dose-dependent increase of malignancy risk and early menopause under CYC treatment that need to be considered when choosing agents for induction treatment.[18]

In summary, continuous oral and intravenous pulsed CYC combined with GC show similar efficacy in the induction of remission (LoE 1a). Continuous oral CYC is associated with a lower rate of relapse but a higher rate of leucopenia, a well-known risk factor for serious infections (LoE 1a). Reduced-dose CYC and GC for induction treatment in elderly patients reduces the rate of SAEs (LoE 2b) but that could come at the cost of lower efficacy in preventing relapses.

Rituximab

A Cochrane Review and meta-analysis reported pooled estimates from two RCTs comparing RTX and CYC induction treatment and showed no differences for achieving remission at 6 months (risk ratio (RR 1.02, 95% CI 0.79 to 1.32), relapse at 12 months (RR 1.43, 95% CI 0.18 to 11.31) nor risk of death at 6 months (RR 1.00, 95% CI 0.21 to 4.70). There was no difference in serious infections (RR 0.89, 95% CI 0.62 to 1.92) and SAEs (RR 1.11, 95% CI 0.72 to 1.71) between the treatments.[15]

No new RCTs comparing RTX with another remission induction treatment were identified since the last update. A post hoc analysis[94] of the randomised controlled double-blind RAVE trial[9] that compared RTX and CYC for remission induction in AAV, identified subgroups of importance regarding the efficacy of RTX. The main results from the RAVE trial reported overall non-inferiority of remission induction treatment with RTX compared with CYC (+AZA). RTX induction was superior in those patients with relapsing disease at baseline, 6 and 12, but not at 18 months of follow-up.[9 104] Furthermore, higher rates of relapse were reported for patients with proteinase 3 (PR3)-ANCA (compared with Myeloperoxidase (MPO)), patients with GPA (compared with MPA) and those with relapsing (compared with new-onset) disease. The post hoc analysis grouped patients by ANCA specificity and diagnoses.[94] The odds of being in complete remission at 6 months (but not at 12 or 18 months) were higher in patients with PR3-ANCA (including newly onset and relapsing patients) treated with RTX compared with those treated with CYC/AZA (OR 2.11, 95% CI 1.04 to 4.30). When relapsing patients with PR3-ANCA were analysed, the likelihood of being in remission were higher in those treated with RTX compared with CYC/AZA at 6 months (OR 3.57, 95% CI 1.43 to 8.93), 12 (OR 4.32, 95% CI 1.53 to 12.15) and 18 months (OR 3.06, 95% CI 1.05 to 8.97), even though RTX-treated patients received no additional maintenance treatment in the RAVE trial. No difference for remission rates after RTX or CYC/AZA induction was shown for GPA, MPA, newly diagnosed PR3-AAV or newly diagnosed MPO-AAV. Furthermore, high remission rates (90%) after induction treatment of relapsing AAV with RTX are reported in the induction phase of the RITAZAREM trial (no control group in the induction phase of the trial).[85]

No RCTs comparing different doses of RTX were identified. A systematic review of available studies, mainly consisting of non-randomised studies including case reports, reported comparable effect sizes of reaching complete remission of 85% (70% to 96%) and 91% (79% to 99%) for induction regimens with RTX 4×375 mg/m^2 weekly vs 2×1000 mg biweekly with significant RoB resulting from heterogeneity of included reports.[28]

In summary, RTX shows similar efficacy for remission induction in AAV compared with CYC (LoE 1a) but RTX leads to longer lasting remission rates compared with CYC in patients with relapsing disease course (LoE 2b). No difference in efficacy of four-infusion and two-infusion protocols of RTX has been shown, yet (LoE 4), but high-quality evidence is lacking.

Table 1 Meta-analyses of remission induction treatment with pulsed versus continuous oral CYC in GPA and MPA

Study ID	Intervention	Control	Outcome	Included studies	No. of participants	Summary estimate	Effects size	Heterogeneity
Death								
Nagasaka *et al*[71]	Pulse CYC	Continuous CYC	Death at 1 year	3 RCT	246	RR (95% CI)	0.47 (0.23 to 0.99)	I^2=0%
Springer *et al*[16]	Pulse CYC	Continuous CYC	Mortality	4 RCT	296	OR (95% CI)	0.56 (0.29 to 1.07)	I^2=0%
Walters *et al*[15]	Pulse CYC	Continuous CYC	Death at final FU	4 RCT	278	RR (95% CI)	0.77 (0.44 to 1.32)	I^2=15%
Remission								
Nagasaka *et al*[71]	Pulse CYC	Continuous CYC	Remission	3 RCT	246	RR (95% CI)	1.07 (0.96 to 1.19)	I^2=15%
Walters *et al*[15]	Pulse CYC	Continuous CYC	Remission at 6 months	2 RCT	176	RR (95% CI)	1.03 (0.93 to 1.13)	I^2=0%
Relapse								
Springer *et al*[16]	Pulse CYC	Continuous CYC	Relapse	4 RCT	284	OR (95% CI)	2.04 (1.11 to 3.75)	I^2=0%
Walters *et al*[15]	Pulse CYC	Continuous CYC	Relapse at end of FU	4 RCT	235	RR (95% CI)	1.79 (1.11 to 2.87)	I^2=0%
Leucopenia								
Springer *et al*[16]	Pulse CYC	Continuous CYC	Leucopenia	3 RCT	250	OR (95% CI)	0.37 (0.20 to 0.69)	I^2=16%
Walters *et al*[15]	Pulse CYC	Continuous CYC	Leucopenia	4 RCT	278	RR (95% CI)	0.53 (0.36 to 0.77)	I^2=0%
Serious infection								
Nagasaka *et al*[71]	Pulse CYC	Continuous CYC	Serious infection	3 RCT	246	RR (95% CI)	0.56 (0.37 to 0.86)	I^2=0%
Walters *et al*[15]	Pulse CYC	Continuous CYC	Serious infection	4 RCT	278	RR (95% CI)	0.71 (0.38 to 1.33)	I^2=71%

I^2 refers to the proportion of overall variability that rises from between-study heterogeneity.
CYC, cyclophosphamide; FU, follow-up; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; RCT, randomised controlled trial; RR, risk ratio.

Table 2 Randomised controlled trials of induction treatments in GPA and MPA

Study ID	Included patients	N	Intervention (I)	Control	Primary end point	Result intervention	Result control	Significance
Mycophenolate for remission induction								
Jones *et al* (MYCYC trial)[5]	GPA and MPA, newly diagnosed	140	MMF	Pulse CYC	Remission by 6 months	47 of 70 (67%)	43 of 70 (61%)	RD 5.7%, 90% CI 7.5 to 19%), non-inferior
Tuin *et al*[13]	PR3- and MPO-AAV, relapsing (enrolment stopped early)	84	MMF	Continuous CYC	Remission at 6 months	27 of 41 (66%)	35 of 43 (81%)	P=0.11
Remission induction in age ≥65 years								
Pagnoux *et al* (CORTAGE)[73]	GPA, MPA, EGPA, PAN, age ≥65 years, newly diagnosed	104	GC discontinued at 9 months, max. 6× pulse CYC 500 mg until remission, maintenance with MTX/AZA/MMF	GC discontinued at 26 months, pulse CYC 500 mg/m^2, maintenance with MTX/AZA/MMF. Patients with EGPA or PAN and FFS=0 received only GC	≥1 SAE	32 of 53 (60%)	40 of 51 (78%)	P=0.04 HR 0.61 (95% CI 0.38 to 0.98)
GC treatment								
Furuta *et al* (LoVAS)[6]	GPA, MPA, RLV, newly diagnosed	140	Reduced-dose GC starting at 0.5 mg/kg/day+RTX	High-dose GC starting at 1 mg/kg/day+RTX	Remission rate at 6 months	49 of 69 (71%)	45 of 65 (69.2%)	RD 1.8% (one-sided 97.5% CI −13.7 to ∞) P=0.003 for non-inferiority
Walsh *et al* (PEXIVAS)[2]	GPA, MPA, newly diagnosed or relapsing, active renal involvement or pulmonary haemorrhage	704	Reduced-dose GC (+remission induction with CYC/RTX±PLEX)	Standard-dose GC (+remission induction with CYC/RTX±PLEX)	Death or ESKD	92 of 330 (27.9%)	83 of 325 (25.5%)	RD 2.3% (90% CI, −3.4 to 8.0; 95% CI −4.5 to 9.1), non-inferiority
Avacopan								
Merkel *et al* (CLASSIC)[64]	GPA, MPA, newly diagnosed or relapsing	42	Group 1: 10 mg avacopan twice daily+SOC Group 2: 30 mg avacopan twice daily+SOC	Placebo + SOC (induction with RTX or CYC+GC)	AEs (safety)	Group 1: 11 of 13 (85%) Group 2: 15 of 16 (94%)	13 of 13 (100%)	Similar AE rates

Continued

Table 2 Continued

Study ID	Included patients	N	Intervention (I)	Control	Primary end point	Result intervention	Result control	Significance
Jayne *et al* (CLEAR)[53]	GPA, MPA, newly diagnosed or relapsing	67	Group 1: 30 mg avacopan twice daily+prednisone 20 mg starting dose+RTX or CYC Group 2: 30 mg avacopan twice daily+placebo+RTX or CYC	Placebo+prednisone 60 mg starting dose+RTX or CYC	≥50% BVAS reduction (week 12) without worsening in any body system	Group 1: 19 of 22 (86.4%) Group 2: 17 of 21 (81.0%)	14 of 20 (70%)	Group 1: P=0.002 (Difference 16.4%; 90% CI –4.3% to 37.1%) Group 2: P=0.01 (Difference 11.0%; 90% CI -11.0% to 32.9%). Non-inferiority.
Jayne *et al* (ADVOCATE)[4]	GPA, MPA, newly diagnosed or relapsing	331	30 mg avacopan twice daily+placebo GC+RTX or CYC	Avacopan-placebo+GC 60 mg (tapered)+RTX or CYC	End point 1: remission (week 26) End point 2: sustained remission (week 52)	End point 1: 120 of 166 (72.3%) End point 2: 109 of 166 (65.7%)	End point 1: 115 of 164 (70.1%) End point 2: 90 of 164 (54.9%)	End point 1: P<0.001 for non-inferiority (Difference 3.4%; 95% CI –6.0 to 12.8) End point 2: P=0.007 for superiority (Difference 12.5%; 95% CI 2.6 to 22.3)
Plasma exchange								
Walsh *et al* (PEXIVAS)[2]	GPA, MPA, newly diagnosed or relapsing, active renal involvement or pulmonary haemorrhage	704	PLEX (+remission induction with CYC/RTX+GC)	No PLEX (+remission induction with CYC/RTX+GC)	Death or ESKD	100 of 352 (28.4%)	109 of 352 (31.0%)	P=0.27 HR 0.86 (95% CI 0.65 to 1.13)

AE, adverse event; AZA, azathioprine; BVAS, Birmingham Vasculitis Activity Score; CYC, cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; ESKD, end-stage kidney disease; FFS, Five-Factor Score; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; PAN, polyarteritis nodosa; PLEX, plasma exchange; RCT, randomised controlled trial; RD, risk difference; RLV, renal limited vasculitis; RR, risk ratio; RTX, rituximab; SAE, serious adverse event; SOC, standard of care.

Combination treatment with rituximab and cyclophosphamide

Only one RCT (RITUXVAS) compared the combination of CYC and RTX with a regimen consisting of intravenous CYC (followed by AZA maintenance) for remission induction treatment in 44 patients with renal AAV.[10 54] Rates of remission/relapse, SAEs, infections and deaths were not significantly different between intervention and control group at 1 and 2 years. SAEs (CYC+RTX: 20 of 33, 61%; CYC 4 of 11, 36%) and serious infections (CYC+RTX 11 of 33, 33%; CYC: 2 of 11, 18%) were numerically higher in the CYC+RTX group after 2 years. Some retrospective studies reported high rates of remission, low relapse rates, slow progression towards permanent kidney failure and reduced GC use as compared with earlier published cohorts when combining CYC, RTX and in one cohort also PLEX. Other retrospective studies reported increased rates of neutropenia or infections when CYC and RTX were combined.[36 47 62 74 92 103] Due to the lack of a randomised control group, multiple therapeutic interventions and settings, variable individual GC doses, a relevant RoB remains. A randomised trial comparing induction treatment with a combination of RTX and CYC with RTX without CYC is ongoing (NCT03942887).

In summary, available data preclude solid conclusions regarding efficacy and safety of induction treatment with combined RTX and CYC, as compared with induction treatment with either CYC or RTX, yet.

Mycophenolate mofetil

Four meta-analyses pooled results from four RCTs that compared MMF and CYC for remission induction (table 3).[29 55 86 99] No differences were reported for rates of remission, relapse, death, infection, nor leucopenia. The meta-analyses included two RCTs comparing MMF and CYC for remission induction that were published since the 2016 EULAR recommendations for AAV (table 2).

The MYCYC trial compared MMF with intravenous pulsed CYC (both combined with GC and followed by AZA maintenance) in new-onset non-severe AAV.[5] Remission at 6 months was not different between the intervention and control groups and fulfilled the criteria for non-inferiority. However, relapses were observed more frequently in the MMF group (incidence rate ratio 1.97, 95% CI 0.96 to 4.23), this effect was driven by patients with PR3-positive disease (two RCTs published before the start date of our SLR update included mainly patients with MPA that were MPO-ANCA positive[105 106]).

Tuin et al compared MMF with continuous oral CYC in relapsing AAV.[13] The primary end point was stable remission at month 6 which was reached in 66% in MMF group and 81% in CYC group (numerical difference not reaching statistical significance). No significant difference in relapse was observed.

All four mentioned RCTs excluded patients with imminently life-threatening disease and three of them also excluded patients with most severe renal disease.

In summary, there is evidence that the efficacy of MMF combined with GC to induce remission is similar to CYC combined with GC in GPA and MPA without imminently life-threatening vasculitis (LoE 1a). However, there seem to be higher relapse rates in PR3-ANCA-positive patients treated with MMF compared with CYC.

Induction treatment of organ-threatening or life-threatening versus non-organ-threatening or life-threatening disease

The NORAM trial is usually viewed as the primary example of a trial investigating induction regimens in non-organ-threatening or life-threatening disease.[107] No new RCTs were identified since the last update, which investigated treatment agents exclusively in non-organ-threatening or non-life-threatening AAV. However, there is no overarching definition of organ-threatening or life-threatening disease that is uniformly used in clinical trials and several newly identified trials included mixed populations with and without potentially organ-threatening or life-threatening manifestations.[5 6 13 85] Increased relapse rates after induction with MTX or MMF (LoE 1b) compared with more potent treatments must be considered when choosing induction treatment.[5 107] Adverse drug effects also have to be considered (studies on malignancy risk and infertility associated with CYC are discussed in the second corresponding SLR article).

Refractory disease

The open-label ALEVIATE trial reported safety and efficacy of two different doses of alemtuzumab in a cohort with refractory AAV (n=12) or Behçet's disease (n=11). Nine (75%) and five (41.6%) patients with AAV had complete or partial response at 6 and 12 months, respectively (LoE 4). The search strategy for this SLR identified the data in form of an abstract (the trial has now been fully published).[46 108]

Overall, data reporting efficacy of treatment for refractory disease is scarce and this situation requires expert consultation and individualised treatment.

Glucocorticoid dosing

Two RCTs compared different GC regimens (table 2). The PEXIVAS trial included patients with severe (defined by active renal involvement and estimated glomerular filtration rate <50 mL/min/1.73 m^2 or pulmonary haemorrhage) GPA or MPA and compared a reduced-dose GC regimen to a standard regimen[2] (table 4), combined with induction treatment with either CYC or RTX with or without additional PLEX. All patients received intravenous methylprednisolone (MP) pulse treatment for 1–3 days (cumulative maximum dose 3 g), before receiving one of the two oral GC regimens. The reduced-dose GC regimen was non-inferior compared with the standard-dose regimen for the primary composite end point, which was death of any cause or end-stage kidney disease (ESKD). HR for sustained remission was not significantly different for the reduced versus the standard-dose GC regimen (HR 1.04, 95% CI 0.92 to 1.19) but risk of serious infections at 1 year was lower (HR 0.69, 95% CI 0.52 to 0.93).

Table 3 Meta-analyses of remission induction treatment with mycophenolate versus cyclophosphamide in GPA and MPA

Study ID	Intervention	Control	Outcome	Included studies	No. of participants	Summary estimate	Effects size	Heterogeneity
Remission								
Berti *et al*[29]	MMF	CYC	Remission induction	4 RCT	300	OR (95% CI)	1.06 (0.74 to 1.52)	I^2=0%
Kuzuya *et al*[55]	MMF	CYC	Remission at 6 months	4 RCT	300	RR (95% CI)	1.09 (0.86 to 1.38)	I^2=60%
Song and Lee[86]	MMF	CYC	Remission	4 RCT	300	RR (95% CI)	1.311 (0.570 to 3.017)	I^2=57.4%
Xiong *et al*[99]	MMF	CYC	Remission	4 RCT	290	OR (95% CI)	1.30 (0.56 to 3.04)	I^2=57%
Relapse								
Kuzuya *et al*[55]	MMF	CYC	Relapse	2 RCT	189	RR (95% CI)	1.36 (0.80 to 2.31)	I^2=45%
Song and Lee[86]	MMF	CYC	Relapse	2 RCT	224	RR (95% CI)	1.331 (0.497 to 3.568)	I^2=63.4%
Leucopenia								
Kuzuya *et al*[55]	MMF	CYC	Leucopenia	3 RCT	160	RR (95% CI)	0.45 (0.16 to 1.32)	I^2=0%
Xiong *et al*[99]	MMF	CYC	Leucopenia	3 RCT	150	OR (95% CI)	0.38 (0.12 to 1.21)	I^2=0%
Infection								
Kuzuya *et al*[55]	MMF	CYC	Infection	4 RCT	300	RR (95% CI)	1.26 (0.79 to 2.01)	I^2=0%
Song and Lee[86]	MMF	CYC	Infection	4 RCT	300	RR (95% CI)	0.958 (0.561 to 1.634)	I^2=28.5%
Xiong *et al*[99]	MMF	CYC	Infection	4 RCT	290	OR (95% CI)	0.82 (0.35 to 1.91)	I^2=49%
Other outcomes								
Kuzuya *et al*[55]	MMF	CYC	Death	4 RCT	300	RR (95% CI)	1.05 (0.40 to 2.74)	I^2=0%
Kuzuya *et al*[55]	MMF	CYC	Severe infection or death	4 RCT	300	RR (95% CI)	0.87 (0.31 to 2.50)	I^2=0%
Kuzuya *et al*[55]	MMF	CYC	ESKD	2 RCT	181	RR (95% CI)	0.66 (0.15 to 2.79)	I^2=0%
Kuzuya *et al*[55]	MMF	CYC	Malignancy	2 RCT	224	RR (95% CI)	1.04 (0.27 to 3.98)	I^2=0%
Song and Lee[86]	MMF	CYC	SAE	4 RCT	300	RR (95% CI)	1.232 (0.754 to 2.014)	I^2=0%

I^2 refers to the proportion of overall variability that rises from between-study heterogeneity. Bayesian network meta-analysis of RCTs comparing CYC, RTX and MMF induction reported in online supplemental file 2.[57]
CYC, cyclophosphamide; ESKD, end-stage kidney disease; GPA, granulomatosis with polyangiitis; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; RCT, randomised controlled trial; RR, risk ratio; SAE, serious adverse event.

Table 4 Glucocorticoid dosing schemes from randomised controlled trials in GPA and MPA

PEXIVAS[2]							LoVAS[6]		
	Standard dose			Reduced dose					
Week	<50 kg	50–75 kg	>75 kg	<50 kg	50–75 kg	>75 kg	Weeks	High dose	Reduced-dose
	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse			
1	50 mg	60 mg	75 mg	50 mg	60 mg	75 mg	1–2	1.0 mg/kg/day	0.5 mg/kg/day
2	50 mg	60 mg	75 mg	25 mg	30 mg	40 mg			
3–4	40 mg	50 mg	60 mg	20 mg	25 mg	30 mg	3–4	0.8 mg/kg/day	0.25 mg/kg/day
5–6	30 mg	40 mg	50 mg	15 mg	20 mg	25 mg	5–6	0.7 mg/kg/day	7.5 mg/day*
7–8	25 mg	30 mg	40 mg	12.5 mg	15 mg	20 mg	7–8	0.5 mg/kg/day	5 mg/day*
9–10	20 mg	25 mg	30 mg	10 mg	12.5 mg	15 mg	9–10	0.4 mg/kg/day	4 mg/day*
11–12	15 mg	20 mg	25 mg	7.5 mg	10 mg	12.5 mg	11–12	0.35 mg/kg/day	3 mg/day*
13–14	12.5 mg	15 mg	20 mg	6 mg	7.5 mg	10 mg	13–16	15 mg/day*	2 mg/day*
15–16	10 mg	10 mg	15 mg	5 mg	5 mg	7.5 mg			
17–18	10 mg	10 mg	15 mg	5 mg	5 mg	7.5 mg	17–20	12.5 mg/day*	1 mg/day*
19–20	7.5 mg	7.5 mg	10 mg	5 mg	5 mg	5 mg			
21–22	7.5 mg	7.5 mg	7.5 mg	5 mg	5 mg	5 mg	21 to 24	10 mg/day*	0 mg/day*
23–52	5 mg	5 mg	5 mg	5 mg	5 mg	5 mg			
>52	Investigator's local practice			Investigator's local practice					
							Prednisolone doses rounded up in 5 mg increments for low-dose group in weeks 1–4 and high-dose group in weeks 1–12.		
							In low-dose group, reduction to 5 mg (initiating tapering and discontinuing GC in 14 weeks) could be postponed in case of BVAS >0 or not normalised CRP or ANCA values.		

*No adjustment for body weight.
ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; CRP, C reactive protein; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis.

The LoVAS trial included newly diagnosed patients with GPA, MPA or renal limited vasculitis (RLV).[6] All subjects received remission induction treatment with RTX and were randomised to receive either reduced-dose GC or high-dose GC treatment (table 4). Subjects with severe glomerulonephritis (glomerular filtration rate (GFR) <15 mL/min/1.73 m^2 or alveolar haemorrhage requiring >2 L oxygen/min) were excluded. MP pulse treatment was not allowed in either group. The trial demonstrated that the reduced-dose regimen is non-inferior compared with the high-dose regimen with regard to remission at 6 months. SAEs and severe infections were significantly less frequent in the reduced-dose compared with the high-dose group.

Both trials had differences in the included populations and the regimens they propose may be convenient for different patient groups: while the PEXIVAS trial included also patients at severe disease stages, the LoVAS trial, that used an even lower GC dosing scheme, excluded patients with most severe renal and pulmonary involvement and the majority of patients in LoVAS were MPO-ANCA positive (which may be a factor associated with lower relapse risk). These trials are the only RCTs identified by a systematic review of studies comparing GC regimens in AAV.[98]

The non-controlled SCOUT study reported even shorter GC taper over 8 weeks in patients treated with RTX.[66] The patients achieved remission rates compatible with controls from the RAVE trial (OR 1.31, 95% CI 0.26 to 6.56) and median adverse events (AEs) per patient were less frequent (2 vs 8, p<0.001) but consecutive relapse rate was higher (30% vs 7%, p=0.03), highlighting the previously described association of prolonged GC treatment with less relapses.[109]

No RCTs informing about benefits and risks of intravenous GC pulses were identified. A retrospective cohort study suggests that GC pulses may increase the risk of infections and diabetes while showing no difference in survival, renal recovery or relapse.[32] One article reported GC pulse treatment to be associated with the ability to stop maintenance treatment,[48] while other authors report no significant effect of GC pulse treatment given in patients with AAV on dialysis at disease onset with regard to survival, renal recovery or AEs.[49] The SLR for general management reported in the second complementary SLR manuscript included risk factors on infections: GC pulse treatment is reported to be associated with infection by some retrospective studies[110–114] identified in the supplementary SLR, while no significant associations (or associations not reaching statistical significance) is reported by others.[115–117] Randomised studies are needed to compare efficacy of pulse GC (eg, fast and durable remission in patients with organ-threatening or life-threatening disease) and potential harms in AAV.

In summary, reduced-dose GC regimens reduce the rate of infectious complications while showing similar efficacy to conventional GC regimens when combined with remission induction treatments (LoE 1b for both studied regimens used in different populations). The benefits and risks of GC pulse treatment remain not well defined.

Avacopan

Three RCTs reported on the use of the complement C5 receptor antagonist avacopan for GPA and MPA (table 2). The phase II CLASSIC trial compared 10 mg avacopan twice daily and 30 mg avacopan twice daily with placebo (all groups combined with induction treatment consisting of GC and RTX or CYC), the primary end point was safety. AE and infection rates were similar among groups.[64] The phase II CLEAR trial compared efficacy of placebo+prednisone (starting at 60 mg/day), avacopan 30 mg twice daily+prednisone (starting at 20 mg/day) and avacopan+placebo.[53] All groups received induction treatment with CYC or RTX. The primary efficacy outcome (response at week 12) was reached by 70% in the control arm, 86.4% in the avacopan+reduced-dose GC arm and 81.0% in the avacopan+placebo arm (non-inferiority for both avacopan arms compared with standard GC). The AE rate was similar between trial arms. The phase III ADVOCATE trial enrolled newly diagnosed or relapsing GPA and MPA to receive either avacopan 30 mg twice daily (with maximum 20 mg prednisone initially, tapered and stopped within 4 weeks) for 52 weeks or a prednisone tapering scheme starting at 60 mg (lower in persons weighing <55 kg) that was tapered and discontinued at week 21. In contrast to the 21-week GC course in the control group, avacopan was continued up to week 52 in the intervention group. Both groups received additional remission induction treatment with RTX or CYC (intravenous or oral), followed by AZA maintenance if CYC was given. Avacopan met the non-inferiority criterion for remission at week 26 and the superiority criterion for remission at week 52. The difference of sustained remission at week 52 between patients randomised to GC or avacopan was low if CYC was used for remission induction (CYC+GC: 52.6%, CYC+avacopan: 55.9%) but pronounced in those that receivedRTX for induction treatment (RTX+GC: 56.1%, RTX+avacopan: 71.0%). However, patients treated with RTX induction did not receive maintenance treatment and GC were given for a shorter period than avacopan in this trial. The lower GC exposure in the avacopan group translated into less GC-related toxicity. Recovery of renal function seemed to be higher in the avacopan-treated group (mean eGFR 7.3 mL/min/1.73 m^2), compared with the GC group (mean eGFR 4.1 mL/min/1.73 m^2), mean difference between groups 3.2 mL/min/1.73 m^2 (95% CI 0.3 to 6.1). This was pronounced in the subgroup of patients with worse renal function (GFR <30 mL/min/1.73 m^2), mean difference 5.6 mL/min/1.73 m^2 (95% CI 1.7 to 9.5).

In summary, there is good quality evidence that the use of avacopan instead of high-dose GC in CYC-based or RTX-based protocols leads to similar rates of remission and is associated with less GC-related toxicity (LoE 1b).

Plasma exchange

The PEXIVAS trial (table 2) compared the efficacy of adjunctive PLEX in addition to remission induction (GC and CYC or RTX) in 704 patients with new-onset or relapsing GPA or MPA with active renal involvement or alveolar haemorrhage.[2] The primary end point was the composite of death from any cause or ESKD. PEXIVAS found no difference between treatment arms (induction treatment with or without adjunctive PLEX) with respect to neither the primary outcome death of any cause or ESKD nor the secondary outcomes when these were analysed independently. The primary outcome of combined death or ESKD was also not significantly reduced in subgroup analyses for alveolar haemorrhage (in two subgroups with oxygen saturation >85% or ≤85% on room air/invasive ventilation).

Several meta-analyses[15 16 27 96 100 101] have addressed the potential benefit of PLEX (table 5). None of the meta-analyses showed a benefit with respect to mortality[15 16 27 96 100 101] nor identified a subgroup of patients with AAV for which PLEX decreases the risk of death. Regarding potential benefit of PLEX for preventing ESKD, the meta-analyses provide somewhat conflicting results (table 5): two meta-analyses including RCTs only (but no observational studies) found the risk of ESKD to be reduced at 1 year. The only meta-analysis that included data from the PEXIVAS trial (total seven RCTs) but no non-randomised observational studies in the 12-month analysis found that PLEX decreased the risk of ESKD at 1 year but not at long-term follow-up (median 3 years).[96] A lower risk of dialysis dependence at 1 year was also reported in a Cochrane Review by *Walters et al* that did not include PEXIVAS (total six RCTs). Three meta-analyses that included a low number of subjects[100] or included non-randomised observational studies[27 101] found that PLEX did not reduce the overall risk of ESKD at 1 year. Two meta-analyses found that benefit of PLEX may be highest in patients at high risk of ESKD.[16 96] *Walsh et al*[96] grouped patients according to baseline creatinine as risk factor for subsequent ESKD (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 or dialysis dependency) and calculated a risk reduction of 4.6% in the moderate-risk to high-risk group and of 16.0% in the high-risk group. Other studies have investigated subgroups that might be of importance with respect to potential benefit of PLEX.[72] However, biomarker-defined subgroups that may be more likely to benefit from PLEX have not been investigated in prospective trials.

Two meta-analyses (those including the largest number of RCTs) found that PLEX increases the risk of severe infections,[15 96] whereas four (with overall lower numbers of RCTs included in the analysis or analysis was based on pooled data from RCTs and non-randomised studies) reported no significantly increased infection risk.[16 27 100 101]

In summary, the results of the most recent and largest trial (PEXIVAS) did not demonstrate a significant reduction of mortality and ESKD in patients with organ-threatening or life-threatening AAV (LoE 1b). Some, but not all, meta-analyses suggest a benefit of PLEX with respect to ESKD at 1 year (but not during long-term follow-up), especially so among those with severely impaired kidney function. This potential benefit of PLEX in AAV must be counterbalanced against the presumably increased risk of severe infections associated with PLEX (LoE 1a). There is no evidence that PLEX improves outcomes related to Diffuse alveolar hemorrhage (LoE 1b).

Remission maintenance treatment

Maintenance treatment with conventional immunosuppressives

A meta-analysis (table 6) pooled results from two RCTs that investigated prolonged remission maintenance treatment with AZA and demonstrated a reduction of relapse risk but not mortality for prolonged AZA maintenance.[15] Both included RCTs were also identified by the SLR update: the REMAIN trial[3] and the AZA-ANCA trial[81] (table 7).

The REMAIN trial randomised GPA, MPA or RLV with a history of renal involvement or other organ-threatening manifestations that were in stable remission under AZA and GC after successful remission induction with CYC.[3] The intervention group received continued AZA and GC until 48 months from diagnosis, in the control group AZA and GC were withdrawn by 24 months. Relapses were significantly more common in the withdrawal than in the continued maintenance group. Major relapses were significantly more common in the withdrawal group (35.3%) than in the continued maintenance group (13.5%). The decrease of renal function (compared with initial function) was significantly more distinct in the withdrawal group but not in the prolonged maintenance group (where renal function slightly increased). Four (7.8%) in the withdrawal group but no patients in the prolonged maintenance group developed ESKD (p=0.012). AEs, infections and cytopenias were numerically higher in the continued maintenance group but the difference did not reach statistical significance. However, the trial may be underpowered to detect significant differences for AEs.

The AZA-ANCA trial included patients that achieved remission within 6 months after induction treatment with CYC and GC for newly diagnosed PR3-AAV.[81] Those with a C-ANCA titre ≥1:40 (by indirect immunofluorescence) at switch to AZA maintenance (after 3 months of stable remission) were randomised to receive AZA with an 'extended' (until 4 years after diagnosis and tapered afterwards) or 'standard' (until 1 year after diagnosis with successive tapering by 25 mg every 3 months) duration regimen. Five of 21 patients in the extended group and 11 of 24 patients in the 'standard' group relapsed within 4 years. Relapses were numerically more frequent in the 'standard' compared with the 'extended' group, but the difference did not reach statistical significance. These results have to be interpreted in the context of early closing of trial enrolment.

The POWERCIME trial (table 7) included patients with active (newly diagnosed or relapsing/refractory)

Table 5 Meta-analyses of plasma exchange in GPA and MPA

Study ID	Intervention	Control	Outcome	Included studies	No. of participants	Summary estimate	Effects size	Heterogeneity
Mortality at 1 year								
Bellos *et al*[27]	PLEX	No PLEX	Mortality (12 months)	3 RCT, 4 NRIS	427	RR (95% CI)	0.73 (0.40 to 1.34)	I^2=10%
Walters *et al*[15]	PLEX	No PLEX	Death (1 year)	5 RCT	267	RR (95% CI)	1.04 (0.57 to 1.92)	I^2=19%
Walsh *et al*[96]	PLEX	No PLEX	Mortality (12 months)	6 RCT	857	RR (95% CI)	0.90 (0.64 to 1.27)	I^2=0%
Yamada *et al*[100]	PLEX	No PLEX	Mortality (1 year)	3 RCT	123	RR (95% CI)	0.71 (0.27 to 1.86)	I^2=7%
Zhu *et al*[101]	PLEX	No PLEX	Mortality (1 year)	4 RCT, 5 NRIS	1272	OR (95% CI)	0.83 (0.60 to 1.14)	I^2=9%
Mortality (any timepoint)								
Bellos *et al*[27]	PLEX	No PLEX	Overall mortality (time-to-event)	2 RCT, 2 NRIS	965	HR (95% CI)	0.96 (0.72 to 1.29)	I^2=0%
Springer *et al*[16]	PLEX	No PLEX	Mortality	6 RCT	251	RR (95% CI)	1.15 (0.78 to 1.70)	I^2=0%
Walters *et al*[15]	PLEX	No PLEX	Death at any timepoint	6 RCT	957	RR (95% CI)	0.96 (0.72 to 1.29)	I^2=0%
Walsh *et al*[96]	PLEX	No PLEX	Mortality (long-term FU, median 3 years)	8 RCT	1028	RR (95% CI)	0.93 (0.73 to 1.19)	I^2=0%
Yamada *et al*[100]	PLEX	No PLEX	Mortality (whole FU)	4 RCT	827	RR (95% CI)	0.93 (0.70 to 1.24)	I^2=0%
Zhu *et al*[101]	PLEX	No PLEX	Mortality (end of FU)	1 RCT, 3 NRIS	512	OR (95% CI)	1.18 (0.78 to 1.79)	I^2=0%
ESKD at 1 year								
Bellos *et al*[27]	PLEX	No PLEX	ESKD (12 months)	3 RCT, 5 NRIS	489	RR (95% CI)	1.32 (0.53 to 3.25)	I^2=66%
Walters *et al*[15]	PLEX	No PLEX	Dialysis at 1 year	6 RCT	235	RR (95% CI)	0.45 (0.29 to 0.72)	I^2=0%
Walsh *et al*[96]	PLEX	No PLEX	ESKD (12 months)	7 RCT	829	RR (95% CI)	0.62 (0.39 to 0.98)	I^2=15%
Yamada *et al*[100]	PLEX	No PLEX	Renal failure (death-censored, 1 year)	2 RCT	84	RR (95% CI)	0.40 (0.11 to 1.50)	I^2=9%
Zhu *et al*[101]	PLEX	No PLEX	ESKD (12 months)	4 RCT, 4 NRIS	1168	OR (95% CI)	0.90 (0.40 to 2.03)	I^2=66%
ESKD (any timepoint)								
Bellos *et al*[27]	PLEX	No PLEX	Overall ESKD (time-to-event)	4 RCT, 2 NRIS	1007	HR (95% CI)	0.71 (0.55 to 0.92)	I^2=0%
Springer *et al*[16]	PLEX	No PLEX	ESKD	2 RCT	841	HR (95% CI)	0.67 (0.40 to 1.11)*	I^2=49%
Springer *et al*[16]	PLEX	No PLEX	ESKD	2 RCT	841	HR (95% CI)	0.72 (0.53 to 0.98)†	I^2=49%
Springer *et al*[16]	PLEX	No PLEX	ESKD	6 RCT	251	RR (95% CI)	0.61 (0.42 to 0.90)	I^2=20%
Walsh *et al*[96]	PLEX	No PLEX	ESKD (long-term FU, median 3 years)	7 RCT	996	RR (95% CI)	0.79 (0.58 to 1.08)	I^2=14%
Yamada *et al*[100]	PLEX	No PLEX	Renal failure (death-censored, overall FU)	4 RCT	827	RR (95% CI)	0.85 (0.57 to 1.28)	I^2=27%
Zhu *et al*[101]	PLEX	No PLEX	ESKD (end of FU)	1 RCT, 3 NRIS	462	OR (95% CI)	1.15 (0.56 to 2.36)	I^2=57%
ESKD or death (composite)								
Yamada *et al*[100]	PLEX	No PLEX	ESKD or death (overall FU)	3 RCT	795	RR (95% CI)	0.97 (0.80 to 1.18)	I^2=0%
Yamada *et al*[100]	PLEX	No PLEX	ESKD or death (1 year)	2 RCT	756	RR (95% CI)	0.81 (0.62 to 1.06)	I^2=0%
Infections								
Bellos *et al*[27]	PLEX	No PLEX	Overall incidence of infections	2 RCT, 5 NRIS	498	RR (95% CI)	1.05 (0.63 to 1.76)	I^2=53%

Continued

Table 5 Continued

Study ID	Intervention	Control	Outcome	Included studies	No. of participants	Summary estimate	Effects size	Heterogeneity
Springer *et al*[16]	PLEX	No PLEX	Severe infections	4 RCT	887	RR (95% CI)	1.19 (0.99 to 1.43)	I^2=0%
Walters *et al*[15]	PLEX	No PLEX	Serious infections	5 RCT	956	RR (95% CI)	1.26 (1.03 to 1.54)	I^2=0%
Walsh *et al*[96]	PLEX	No PLEX	Serious infection (12 months)	4 RCT	647	RR (95% CI)	1.27 (1.08 to 1.49)	I^2=0%
Walsh *et al*[96]	PLEX	No PLEX	Serious infection (long-term FU, median 3 years)	6 RCT	957	RR (95% CI)	1.13 (1.03 to 1.24)	I^2=0%
Yamada *et al*[100]	PLEX	No PLEX	Infections	2 RCT	756	RR (95% CI)	1.20 (0.98 to 1.46)	I^2=0%
Zhu *et al*[101]	PLEX	No PLEX	Serious infections	2 RCT, 4 NRIS	1011	OR (95% CI)	1.25 (0.77 to 2.01)	I^2=36%
Adverse events								
Bellos *et al*[27]	PLEX	No PLEX	SAEs	2 RCT, 5 NRIS	498	RR (95% CI)	1.04 (0.59 to 1.81)	I^2=71%
Springer *et al*[16]	PLEX	No PLEX	SAEs	3 RCT	183	RR (95% CI)	1.04 (0.74 to 1.46)	I^2=0%
Yamada *et al*[100]	PLEX	No PLEX	Adverse events (whole FU)	2 RCT	756	RR (95% CI)	1.10 (0.73 to 1.68)	I^2=37%
Zhu *et al*[101]	PLEX	No PLEX	SAEs	2 RCT, 2 NRIS	1020	OR (95% CI)	1.07 (0.57 to 2.03)	I^2=67%
Remission/Relapse								
Springer *et al*[16]	PLEX	No PLEX	Remission	2 RCT	736	RR (95% CI)	1.34 (0.64 to 2.8)	I^2=72%
Yamada *et al*[100]	PLEX	No PLEX	Relapse (overall FU)	3 RCT	775	RR (95% CI)	0.81 (0.55 to 1.18)	I^2=0%

I^2 refers to the proportion of overall variability that rises from between-study heterogeneity.
*Random effects model.
†Fixed effects model.
ESKD, end-stage kidney disease; FU, follow-up; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; NRIS, non-randomised intervention study; PLEX, plasma exchange; RCT, randomised controlled trial; RR, risk ratio; SAE, serious adverse event.

Table 6 Meta-analyses of remission maintenance treatment in GPA and MPA

Study ID	Intervention	Control	Outcome	Included studies	No. of participants	Summary estimate	Effects size	Heterogeneity
Prolonged maintenance treatment								
Walters *et al*[15]	Extended AZA	Standard AZA	Death	2 RCT	162	RD (95% CI)	0.06 (−0.01 to 0.13)	I^2=0%
Walters *et al*[15]	Extended AZA	Standard AZA	Relapse	2 RCT	162	RR (95% CI)	0.41 (0.26 to 0.64)	I^2=0%
TMS for maintenance treatment								
Walters *et al*[15]	TMS	Placebo	Remission at 1 year	2 RCT	111	RR (95% CI)	1.14 (0.98 to 1.33)	I^2=0%
Monti *et al*[67]	TMS	No treatment	Relapse	2 RCT, 2 NRIS	357	RR (95% CI)	0.69 (0.46 to 1.05)	I^2=0%
Monti *et al*[67]	TMS	Immunosuppression	Relapse	3 NRIS	131	RR (95% CI)	1.87 (0.35 to 10.04)	I^2=82%
Monti *et al*[67]	TMS	All comparators	Relapse	2 RCT, 5 NRIS	488	RR (95% CI)	1.15 (0.51 to 2.55)	I^2=79%

I^2 refers to the proportion of overall variability that rises from between-study heterogeneity. Bayesian network meta-analysis of RCTs comparing RTX, MMF, MTX, CYC, AZA for maintenance reported in online supplemental file 1.[58]
AZA, azathioprine; CYC, cyclophosphamide; GPA, granulomatosis with polyangiitis; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; NRIS, non-randomised intervention study; RCT, randomised controlled trial; RD, risk difference; RR, risk ratio; RTX, rituximab; TMS, trimethoprim-sulfamethoxazole.

AAV (GPA, MPA or EGPA).[61] The patients received induction treatment with oral CYC and GC and, after achieving remission, were randomised to receive maintenance treatment with either MTX or continued oral CYC. The primary end point (relapse at month 12 from start of maintenance treatment) did not differ between groups (neither in the whole trial population including EGPA, nor in the subgroup analysis including 41 patients diagnosed with GPA or MPA). The interpretation of results is limited by a premature closure of enrolment.

The SLR retrieved no further new RCTs on the use of MMF or other conventional immunosuppressive agents for remission maintenance. In an earlier RCT (WEGENT), AZA and and MTX showed similar efficacy for remission maintenance treatment.[118] The IMPROVE trial showed higher relapse risk for remission maintenance treatment with MMF as compared with AZA (HR 1.69; 95% CI 1.06 to 2.70; p=0.03).[119]

In summary, prolonged AZA treatment significantly reduces relapse rate (LoE 1a) and seems to be associated with better renal prognosis. AZA and MTX have similar efficacy for remission maintenance treatment (LoE 1b), whereas relapse risk is higher for maintenance treatment with MMF as compared with AZA (LoE 1b).

Maintenance treatment with rituximab

Several RCTs on the use of RTX for remission maintenance have been published since the 2016 EULAR recommendations for AAV.

In the RITAZAREM trial (table 7), patients with relapsing GPA or MPA received remission induction treatment with RTX and GC. Those achieving disease control by month 4 were randomised to receive maintenance treatment with either 1000 mg RTX at months 4, 8, 12, 16 or AZA (and standardised GC tapering). The SLR identified preliminary data (published as abstract only[84]) but the full publication became recently available.[120] The trial results demonstrate relapse risk to be significantly lower in the RTX compared with the AZA group. This supports the findings of the MAINRITSAN trial comparing RTX for 18 months and AZA for 22 months for remission maintenance treatment after induction treatment with CYC and GC. The MAINRITSAN trial reported RTX to be more efficacious than AZA to prevent relapses at 28 months (HR 6.61; 95% CI 1.56 to 27.96; p=0.002).[121] Major relapse-free survival remained better in the RTX group (71.9%; 95% CI 61.2% to 84.6%) compared with the AZA group (49.4%; 95% CI 38.0% to 64.3%; p=0.003) at 60 months of follow-up.[90]

The MAINRITSAN 2 trial (table 7) randomised patients with GPA or MPA that were in remission after induction treatment with CYC, RTX or MTX to receive either biomarker 'tailored' or fixed interval remission maintenance treatment with RTX.[14] The 'tailored' arm received 500 mg RTX at randomisation and afterwards only if CD19-positive B cells or previously negative ANCA (by indirect immunofluorescent test (IFT) or ELISA) reappeared, or if ANCA levels significantly

Table 7 Randomised controlled trials of remission maintenance treatments in GPA and MPA

Study ID	Included patients	N	Intervention	Control	Primary end point	Result intervention	Result control	Significance	Comment
Conventional immunosuppressives									
Karras *et al* (REMAIN)[3]	GPA, MPA, RLV in stable remission on AZA+GC 18–24 months from diagnosis	117	Continued AZA and GC	Withdrawal of AZA and GC	Relapse	13 of 59 (22.0%)	32 of 51 (62.7%)	OR 5.96 (95% CI 2.58 to 13.77) P<0.0001	
Maritati *et al* (POWERCIME)[61]	GPA, MPA, EGPA, newly diagnosed or relapsing/refractory	71	MTX (+GC) after induction with CYC	CYC (+GC) after induction with CYC	Relapse frequency by month 12	3 of 38 (8%)	3 of 33 (9%)	P=1.00 Relapse-free survival P=0.99	Premature closure of enrolment
Sanders *et al* (AZA-ANCA)[81]	PR3-positive GPA, newly diagnosed, remaining C-ANCA positive after induction	45	AZA until 4 years after diagnosis (after CYC induction)	AZA until 1 year after diagnosis, then tapered (after CYC induction)	Relapse-free survival at 4 years	Relapse in 5 of 21 (23.8%)	Relapse in 11 of 24 (45.8%)	RR 0.65 (95% CI 0.24 to 1.75) P=0.40	Premature closure of enrolment
Rituximab									
Charles *et al* (MAINRITSAN 2)[14]	GPA or MPA, newly diagnosed or relapsing in complete remission after induction with CYC or RTX or MTX and GC	162	Tailored RTX (retreatment on reappearance of CD19+B cells or ANCA or rising ANCA titre until month 18)	Fixed interval RTX (every 6 months until month 18)	Relapses (month 28)	14 relapses in 13 of 81 patients	8 relapses in 8 of 81 patients	P=0.22	
Charles *et al* (MAINRITSAN 3)[7]	GPA or MPA, in remission at month 28 after 18 months RTX maintenance	97	RTX	Placebo	Relapse-free survival (month 28)	48 of 50 (96%)	35 of 47 (74%)	HR 7.5 (95% CI 1.67 to 33.7) P=0.008	
Zonozi *et al* (MAINTANCAVAS)[102]	MPO-AAV or PR3-AAV, in remission under RTX-induced B cell depletion for ≥24 months	113 at interim analysis	RTX on increasing ANCA titre	RTX on B cell return	Relapse-free survival	43 of 57 (76%)	51 of 56 (91%)	HR 3.85 (95% CI 1.40 to 10.60) P=0.024	Interim analysis Abstract
Smith *et al* (RITAZAREM)[84]	GPA and MPA, relapsing	170	RTX (+GC; after RTX induction)	AZA (+GC; after RTX induction)	Time to relapse	11 of 85 (13%) relapsed	32 of 85 (38%) relapsed	HR 0.36 (95% CI 0.23 to 0.57) P<0.001	Abstract Preliminary data
Belimumab									
Jayne *et al* (BREVAS)[52]	GPA and MPA, newly diagnosed and relapsing	105	BEL (+AZA+GC; after RTX or CYC induction)	Placebo (+AZA+GC; after RTX or CYC induction)	Protocol-specified composite event (BVAS ≥6 or ≥1 major BVAS item or receipt of prohibited medication)	10 of 53 (18.9%)	11 of of 52 (21.2%)	HR 1.07 (95% CI 0.44 to 2.59) p=0.884	Initially planned as superiority phase III trial, truncated later

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; AZA, azathioprine; BEL, belimumab; BVAS, Birmingham Vasculitis Activity Score; CD19, cluster of differentiation 19 (B-lymphocyte antigen CD19); CYC, cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MTX, methotrexate; PAN, polyarteritis nodosa; PLEX, plasma exchange; PR3, proteinase 3; RCT, randomised controlled trial; RLV, renal limited vasculitis; RR, risk ratio; RTX, rituximab.

increased (≥2 dilution steps in IFT or doubled quantitative ELISA for MPO or PR3-ANCA). These biomarkers were measured in 3 monthly intervals. The treatment phase was 18 months. Patients in the fixed arm received 500 mg RTX on days 0 and 14 and at months 6, 12 and 18. The primary end point was the number of relapses at month 28. The number of relapses was not significantly different but numerically higher in patients receiving tailored RTX compared with the fixed-dose group. Since the number of relapse events was lower than anticipated, the trial is underpowered to exclude non-inferiority of a tailored approach. Two hundred forty-eight RTX infusions compared with 381 RTX infusions were given in the tailored versus fixed-dose group (n=81 subjects in each group). Of 22 relapsing patients, 7 (31.8%) had negative ANCA throughout the trial, 11 (50%) had always negative circulating B cell counts and 4 (18.2%) had negative ANCA and no detectable circulating B cells.

In the ongoing MAINTANCAVAS trial (table 7), patients with AAV in remission under RTX-induced continuous B cell depletion for 2 years were included and randomised to receive RTX maintenance treatment either at B cell return or at significant rise of ANCA levels.[102] An interim analysis published as abstract reported relapse-free survival to be significantly higher in the B cell-driven compared with the ANCA-driven RTX treatment group.

The MAINRITSAN 3 trial (table 7) re-randomised patients from the MAINRITSAN 2 trial that were in remission at month 28 (including those with a minor relapse during MAINRITSAN 2 that required only increase of GC) to receive RTX 500 mg or placebo at months 0, 6, 12 and 18. Relapse-free survival at month 28 after randomisation was significantly higher in the RTX compared with the placebo group with similar rates of AEs.

Reduced levels of immunoglobulins have been reported in patients with AAV treated with RTX, which in some cases makes treatment with intravenous immunoglobulins necessary.[7 37 84 122] Low baseline immunoglobulin levels seem to increase the risk of subsequent hypogammaglobulinaemia under treatment.

In summary, efficacy of RTX is higher than AZA for remission maintenance in AAV (LoE 1b). Prolonged RTX maintenance treatment for 36 months is more effective than 18 months (LoE 1b). Available evidence is insufficient to rule out inferiority of a biomarker-driven RTX treatment compared with a fixed administration at 6 months intervals. Hypogammaglobulinaemia (in some cases requiring immunoglobulin substitution) can develop under treatment with RTX (LoE 1b).

Maintenance treatment with belimumab

The randomised BREVAS trial (table 7) compared belimumab and placebo added to maintenance treatment with AZA and GC after remission induction with GC and RTX or CYC.[52] The BREVAS trial did not demonstrate a significant difference in relapse rates, but relapse rates were low in the placebo group limiting the possibility of showing benefit of belimumab. The trial was terminated early.

In summary, the use of belimumab has not been shown to reduce relapse rates in GPA and MPA (LoE 1b).

Maintenance treatment with trimethoprim-sulfamethoxazole

Two meta-analyses (table 6) assessed the effect of trimethoprim-sulfamethoxazole (TMS) for remission maintenance treatment in GPA. *Walters et al* compared data from two RCTs,[15] whereas *Monti et al* also included non-randomised intervention studies.[67] No significant difference in remission rate or relapse risk of GPA was reported with both meta-analytical strategies.

In summary, pooled data from meta-analyses show no efficacy of TMS for maintenance treatment in GPA (LoE 1a).

DISCUSSION

Several landmark trials that improved the treatment strategies in AAV have been published since the last update of the EULAR recommendations for the management of AAV.[1]

For several areas of disease treatment evidence has accumulated: several meta-analyses comparing remission induction for AAV have been published. Continuous oral CYC and intravenous pulsed CYC show a similar efficacy for initial remission induction.[15 16] The benefit of lower relapse risk with oral CYC comes at the cost of some increased toxicity. Meta-analyses also demonstrate similar overall efficacy for remission induction with RTX or MMF when compared with CYC. Several lessons on remission induction have been provided by the evidence since the 2016 version of the AAV recommendations: first, two RCTs comparing MMF and CYC[5 13] suggest that MMF may not be as effective as CYC, which may be especially important to consider in patients with organ-threatening or life-threatening disease or higher relapse risk (eg, PR3-positive patients). Second, RTX is more effective than CYC for remission induction in patients with relapsing AAV.[94] Third, two RCTs have demonstrated low- or reduced-dose GC schemes to be non-inferior to high-dose or standard-dose schemes, resulting in similar remission rates but lower rates of infectious complications.[2 6] Fourth, a novel therapeutic agent, avacopan, has been demonstrated to allow rapid tapering and discontinuation of GCs during induction treatment, resulting in lower GC-induced adverse reactions.[53]

The role of PLEX for AAV remains controversial. Negative results of the PEXIVAS trial are in contrast to earlier RCTs like the MEPEX trial, which found PLEX to reduce the rate of death or ESKD.[2 123] Meta-analyses pooling RCTs of PLEX in AAV reported contradictory results (table 5).[15 16 27 96 100 101] Their results are dependent on methodology and inclusion criteria. The inclusion of observational non-randomised studies in some meta-analyses results in higher heterogeneity and increases the RoB. Meta-analyses that are limited to RCTs, including the results of PEXIVAS, suggest a lowered risk of ESKD at 1 year, but not during long-term follow-up, and an increased risk of infectious complications associated with

PLEX used in active renal AAV. However, potential sources of bias remain: some of the included RCTs predate the classification criteria or diagnostic tests (ANCA) used to define trial populations nowadays. Furthermore, the introduction of new agents and treatment strategies may reduce the visible effect of PLEX additional to that achieved by drug treatment, which may result in less pronounced effects of PLEX in more recent trials. To summarise, the evidence on PLEX that has accumulated since the 2016 EULAR recommendations has decreased the enthusiasm for this treatment modality in AAV.

Evidence to refine maintenance treatment strategies for AAV has continued to accumulate. First, the superiority of RTX compared with AZA as maintenance treatment that was established after induction treatment with CYC by the MAINRITSAN trial,[121] has now been expanded to situations when remission is induced with RTX.[84] Prolonged maintenance treatment with both, RTX or AZA over a period of 36–48 months results in lower rates of relapse.[3 7] Biomarker-driven retreatment of RTX is feasible but may result in a greater relapse risk.[14] The optimal duration, intensity and personalisation of treatment remains to be further defined.

Data guiding the management of refractory disease remain scarce and this complex situation warrants detailed clinical workup and expert consultation.

The strength of our approach includes comprehensive literature search based on PICO questions by a group of expert clinicians and patient research partners, critical review of the literature and formal quality assessment. Some limitations need to be considered: first, our results are limited to the articles in English; moreover, most available studies have at least some remaining RoB: several investigator-initiated RCTs are unblinded (even though end points like ESKD or death are solid even in case of unblinded treatment). Second, the majority of meta-analyses has flaws in two or more critical domains of the AMSTAR 2 quality assessment instrument, lowering the overall confidence in the results. Third, the complexity and heterogeneity of AAV and the applied treatment protocols makes unbiased comparisons in retrospective study designs difficult. However, despite the rarity and complexity of AAV, major progress has been made in the last years by several well-performed landmark trials that provide high-quality evidence that refined and further developed treatment approaches.

The findings of this SLRs provide an up-to-date summary of available studies covering treatment strategies in GPA and MPA and highlight open questions and unmet needs in their management. The provided data supported the development of the 2022 EULAR recommendations for the management of AAV.[17]

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