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REVIEW

Antineutrophil cytoplasmic antibody associated vasculitides with renal involvement: Open challenges in the remission induction therapy

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Abstract

Renal involvement with rapidly progressive glomerulonephritis is a common manifestation of antineutrophil cytoplasmic antibody (ANCA) associated vasculitides, which is characterized by end-stage renal disease and high mortality rates in untreated and/or late referral patients. The long-term renal survival has improved dramatically since the addition of cyclophosphamide (CYC) and recently of rituximab (RTX) in association with corticosteroids in the remission induction therapeutic regimens. However, renal prognosis remains unfavorable for many patients and the mortality rate is still significantly high. In this review, we analyze the open challenges to be addressed to optimize the induction remission therapy, principally in patients with advanced kidney failure. This concern the first-line therapy (CYC or RTX) based on different parameters (estimated glomerular filtration rate at baseline, new or relapsed disease, ANCA specificity, tissue injury, safety), the role of plasma exchange and the role of new therapies. Indeed, we discuss future perspectives in induction remission therapy by reporting recent advances in new targeted therapies with particular reference to avacopan, an orally administered selective C5a receptor inhibitor.

Key words: Rapidly progressive glomerulonephritis; Remission induction therapy; Antineutrophil cytoplasmic antibody associated vasculitides; Cyclophosphamide; Rituximab; Corticosteroids; Plasma exchange; Avacopan

Core tip: Antineutrophil cytoplasmic antibody (ANCA) associated vasculitides with renal involvement, presents as Rapidly Progressive Glomerulonephritis are organ-threatening and potentially life-threatening diseases.

Although remission induction immunosuppressive regimens overall have been very successful in the treatment of these conditions, many questions remain unanswered. The still open challenges and questions concern: (1) The choice of the first-line therapy (cyclophosphamide versus rituximab) based on renal function at baseline, new versus relapsed disease, ANCA specificity, tissue injury and safety; (2) the role of plasma exchange in combination with steroid and non steroid agents; and (3) the advent of novel target therapies and strategies.

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INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) represent a heterogeneous group of autoimmune systemic necrotizing vasculitides that affect predominantly small vessels, with few or no immune deposits, and the appearance of circulating ANCA with specificity toward proteinase-3 (PR3) or myeloperoxidase (MPO). AAVs include granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA; previously known as Churg–Strauss syndrome) and organ-limited AAV, such as renal-limited vasculitis (RLV)[1].

These autoimmune disorders can potentially affect any organ, but the kidney is often involved. Renal involvement ranges between 71% and 88% among patients with GPA and MPA[2], whereas in EGPA it occurs only in up to 25% of cases[3]. EGPA belongs to the spectrum of AAV, but is treated as a separate entity in most clinical trials because it exhibits different pathogenetic mechanisms, genetic associations and clinical manifestations. In particular, severe renal involvement is an uncommon finding in EGPA, and ANCA positivity is observed with much lower frequency than in GPA and MPA[4]. Therefore, in this review, we will focus exclusively on GPA and MPA, the two clinical conditions with major renal involvement.

The pathologic term Pauci-immune Necrotizing Crescentic Glomerulonephritis (PiNCGN) is commonly used, along with the clinical term Rapidly Progressive Glomerulonephritis (RPGN), which refers to a condition characterized by a nephritic syndrome rapidly progressing to end-stage renal disease (ESRD). Therefore, all patients with proven active ANCA-associated glomerulonephritis require prompt immunosuppressive therapy.

Prior to the introduction of cyclophosphamide (CYC)-based regimens in the late 1970s, the 2-year survival rates were approximately 20%[5]. Standard immunosuppression with CYC and gradually tapered corticosteroids (CCS) for remission induction therapy have dramatically improved the prognosis of patients with generalized or severe AAV, with remission rates usually exceeding 90% and 5-year survival rates as high as 80%[5]. However, this treatment is associated with significant toxicity, including enhanced risk of infection, myelosuppression, infertility, malignancy and cardiovascular disease[6]. The possibility of partially reducing CYC toxicity by employing intravenous pulse regimens instead of daily oral CYC for remission induction therapy was assessed in the CYCLOPS trial[7] and recently in the CORTAGE trial[8]; the pulsed regimen minimized exposure and cumulative toxicity of the drug while maintaining a high efficacy of treatment (Table 1). However, long-term follow-up of patients in the CYCLOPS trial showed that a reduced dose of CYC was associated with a higher risk of relapse, primarily in patients with anti-PR3 ANCA[9].

Consequently, there has been a growing impetus to look for a new, less toxic and more specific treatment for patients with generalized and severe disease. Two randomized controlled trials (RAVE and RITUXVAS), found that Rituximab (RTX), a B cell-depleting agent, is as effective as CYC for induction of remission in patients with newly diagnosed GPA and MPA[10,11] (Table 1). The RAVE trial also demonstrated the superiority of RTX versus CYC in patients with relapsing disease[10]. Nevertheless, in both trials, the short-term adverse event rate after RTX treatment was not lower compared to CYC.

Despite this advancement and the enrichment of our therapeutic armamentarium, the management of remission induction in patients with AAV and renal involvement continues to challenge nephrologists, as renal prognosis is still unfavorable and a significant proportion of patients (20%-25%) develop ESRD within a few years after diagnosis[12].

In this review, we report and discuss the remaining open challenges and questions in the management of remission induction in AAVs with renal involvement. For this purpose, we have explicitly taken into consideration current randomized controlled trials as they represent the most potent scientific tool for evaluating medical treatments and the basis of current International guidelines for the treatment of AAVs.

The topics covered by the review are the following: (1) should all patients with AAV and renal involvement be primarily treated with RTX? (2) should there be differences in the therapeutic approach between patients with newly diagnosed AAV and those with relapsing disease? And if so, what is the relevance of the antigenic specificity of ANCA in guiding therapeutic choice? (3) should all patients with advanced renal involvement be treated with adjunctive plasma exchange (PLEX) sessions, as suggested by short-term results[13]? Additionally, we present recent advances in novel targeted therapies and treatment strategies which may further help to modify the disease course, thereby

Table 1 Randomized controlled trials for induction of remission in antineutrophil cytoplasmic antibody associated vasculitides with renal involvement and cyclophosphamide-sparing regimens

Name of the Trial (number of patients)	Inclusion criteria	Treatment groups (drug dose)	Primary end points	Outcome
CYCLOPS[7] (149)	New diagnosis of GPA, MPA, or relapse with renal involvement, creatinine 150–500 μmol/L (1.7- 5.66 mg/dL)	Intravenous pulse CYC (15 mg/kg) *vs* Daily oral CYC (2 mg/kg)	Remission, Time to relapse	Pulse CYC not inferior to oral CYC Less leucopenia and trend towards more relapses with pulse CYC
CORTAGE[8] (104)	New diagnosis of MPA, GPA, EGPA, PAN and age > 65 yr	Rapid CCS tapering and reduced-dose intravenous pulse CYC (500 mg) *vs* Standard intravenous pulse CYC (500 mg/m²)	Severe adverse events	Less severe adverse events with reduced immunosuppression, no difference in remission and relapse rates
RAVE[10] (197)	New or relapsing GPA or MPA creatinine ⩽ 353.6 μmol/L (4 mg/dL)	RTX (4 × 375 mg/m² infusions) *vs* Daily oral CYC	Complete remission and cessation of CCS at 6 mo	RTX not inferior to oral CYC, RTX better in patients with relapse than after first diagnosis
RITUXVAS[11] (44)	New diagnosis of AAV and severe renal involvement	RTX (4 × 375 mg/m² infusions) plus two intravenous pulses of CYC *vs* intravenous pulse CYC only	Sustained remission	RTX not inferior to pulse CYC

AAV: Antineutrophil cytoplasmic antibody associated vasculitides; CYC: Cyclophosphamide; RTX: Rituximab; CCS: Corticosteroids; GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; PAN: Polyarteritis nodosa.

leading to increased renal outcomes and patient survival.

SHOULD ALL PATIENTS WITH AAV AND RENAL INVOLVEMENT BE PRIMARILY TREATED WITH RTX?

Rituximab, a chimeric monoclonal anti-CD20 antibody that induces depletion of all B-lineage cells with the exception of plasma cells and pre-B cells, which do not express surface CD20, was initially used in open label-trials among patients with refractory or relapsing GPA and MPA[14-18]. The rationale for choosing RTX was based on the primary role performed by B cells in the pathogenesis of the disease and the pathogenicity of ANCA[19]. The results showed that clinical remission was achieved in approximately 90% of cases within 6 mo[14-18]. However, these preliminary studies did not include patients with severe renal involvement.

These data established the foundation for the design of two randomized controlled trials of RTX as first-line therapy in patients with severe GPA and MPA. In 2010, the results of RAVE and RITUXVAS heralded a new era in the management of the disease by demonstrating that RTX plus CCS is not inferior to CYC plus CCS for the induction of remission[11,12]. However, renal function outcomes remain unclear, especially in patients with advanced renal failure at diagnosis, posing an ongoing challenge to the nephrologists who have to decide on the choice of induction therapy.

What the results of current studies are tell us about renal outcomes?

The RAVE trial enrolled 197 patients, of whose approximately half had significant renal disease defined by the presence of at least one of the following findings at baseline: (1) Active, biopsy-proven, pauci-immune glomerulonephritis; (2) red blood cell casts on urine microscopy; and (3) increase in serum creatinine > 30% or decrease in creatinine clearance > 25%. Although in patients with significant renal disease, the baseline mean estimated glomerular filtration rate (e-GFR) was worse in the RTX group, a post hoc analysis of the trial showed that RTX was as effective as oral CYC in this subgroup[20]. The proportion of patients who reached clinical remission at 6 mo were not significantly different between the two treatment groups and there was no difference in the proportion of patients with sustained remission at 18 mo[20]. The latter finding is significant because in order to achieve remission at 3-6 mo, a maintenance regimen with azathioprine (AZA) was administered only to patients in the CYC group, whereas those in the RTX group received no further therapy[10,20]. Mean e-GFR also increased similarly in both groups when patients were stratified by baseline e-GFR, even among those with e-GFR < 30 mL/min per 1.73 m^2[20]. These data supported the use of RTX in patients with major renal involvement. However, patients with advanced renal failure (serum creatinine > 4 mg/dL) were excluded from RAVE because the clinical evidence was not sufficient to suggest their inclusion in an investigational treatment study at the launch of the trial[10]. Therefore, the authors concluded that additional studies were required to fully understand the applicability of RTX among this subset of patients since its effectiveness in advanced renal failure had not been investigated in the RAVE trial[20].

In contrast with the RAVE trial, RITUXVAS enrolled 44 patients newly diagnosed with GPA and MPA with severe renal disease (median e-GFR of 20 mL/min per 1.73 m^2), including also patients requiring dialysis at trial entry. The participants were randomized, in a 3:1 ratio to receive either RTX plus CCS without further maintenance treatment or intravenous CYC for 3-6 mo plus CCS followed by AZA in the maintenance phase. Patients in the RTX group also received two concomitant pulses of intravenous CYC and, for those

with progressive disease within the first 6 mo, a third dose of intravenous CYC was allowed. Furthermore, about a quarter of the patients in both groups received plasma exchange therapy before enrolment[11]. At 12 and 24 mo, there was no difference in the proportion of sustained remission and ESRD between the RTX and CYC groups[11,21].

Mansfield *et al*[22] investigated in a single centre prospective cohort study (CycLow-Vas) the long-term efficacy of another RTX-based CYC-sparing regimen for renal AAV. The protocol involved the use of RTX as a CYC sparing agent, enabling a cumulative dose of no > 3.5 g of CYC per patient. Twenty-three patients with severe renal involvement (median e-GFR of 24 mL/min per 1.73 m^2) were treated. At 6 mo, all patients had achieved complete clinical remission and significant improvement in their renal function[22]. Median e-GFR increased from 24 mL/min at presentation to 33 mL/min at 1 mo and 42 mL/min at 6 mo. However, in this study, as well as in the RITUXVAS trial it is very difficult to discern the specific contribution of CYC in the RTX-treated patients.

Basing on these data, and in the absence of knowledge regarding RTX as a sole remission induction agent in patients with severe renal involvement, two years after the publication of the RAVE and RITUXVAS trials the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommended the use of RTX plus CCS as an alternative initial treatment only in patients without severe renal disease or in whom CYC is contraindicated[23] (Table 2).

Recently, two retrospective multi-center studies evaluated the efficacy of RTX plus CCS without concomitant CYC in patients with severe renal involvement (e-GFR < 20 mL/min per 1.73 m^2)[24,25]. Shah *et al*[24] evaluated 14 patients with a median e-GFR at diagnosis of 12 mL/min per 1.73 m^2 with 7 of them requiring dialysis at presentation. All patients achieved remission with a median time to remission of 55 d, and 5 of the 7 patients requiring dialysis recovered renal function and discontinued dialysis by 6-mo follow-up. Geetha *et al*[25] evaluated 37 patients with a median e-GFR at diagnosis of 13 mL/min per 1.73m^2 and 15 were dialysis dependent at presentation. Twelve patients received RTX and CCS and twenty five patients received CYC, RTX and CCS. Thirty two of 33 patients with a minimum follow up of 6 mo achieved disease remission at 6 mo and 10 of 15 patients requiring dialysis recovered renal function. There were no differences in outcome when groups were stratified according to use of concomitant CYC and no significant difference in the percentage of dialysis-dependent patients who achieved renal recovery between the two groups. However, these studies have limitations due to their retrospective design and small sample size. Further prospective randomized trials are needed to confirm these findings in this subset of patients.

In 2016, the 2009 EULAR recommendations for the management of ANCA-associated vasculitis were updated by the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA)[26]. For remission induction of new-onset or major relapse of organ-threatening or life-threatening GPA and MPA, treatment with a combination of CCS and either CYC or RTX is now recommended. The grade of recommendation was A for both CYC and RTX, but with a different level of evidence 1A for CYC and 1B for RTX, confirming the need for further evidence in this field (Table 2).

The decision of which immunosuppressive regimen is most appropriate in paediatric patients with AAV and renal involvement is also controversial as current treatment regimens are extrapolated from adult studies and at present, there are very little data to allow the development of a paediatric-specific AAV guideline[27]. A phase IIa study of intravenous RTX in paediatric participants with severe GPA or MPA is currently ongoing (NCT01750697)[28] and will provide valuable information in this regard.

What is the impact of tubular lesions on therapeutic choice?

The evaluation of histological parameters along with clinical parameters could also be relevant in understanding the effects of treatment on histopathological processes and outcomes and in determining the choice of treatment. Among patients in the RITUXVAS trial, both B cell and T cell-mediated tubulointerstitial lesions were present in renal biopsies before treatment with RTX. However, only tubular intraepithelial T cells were predictive of impaired renal function during follow-up. However, the analysis of the immunostained sections from patients in the control arm who were treated with CYC, an immunosuppressive agent also directed towards T-cells, did not show any evidence that T cell tubulitis was related to renal outcome[29]. The latter analysis was likely underpowered due to the small size of the control arm, which included only 10 biopsies, but it raised the question of whether T cell tubulitis represents a negative predictor for all treatments or whether its predictive significance is limited to RTX as a result of under- treatment of T cell-mediated lesions by B cell-depleting agents. Unfortunately, for practical and ethical reasons, it was not possible to perform repeat protocol renal biopsies and assess this question in patients who participated in the RITUXVAS trial[29]. Recently, Geetha *et al*[30] conducted a similar study using renal biopsies from patients who participated in the RAVE trial. In contrast to the results of the RITUXVAS study, this study showed that interstitial B- and T-cell infiltrates had no significant impact on long-term prognosis, regardless of the immunosuppression regimen used (RTX or CYC)[30].

Interestingly, a study of repeat protocol renal biopsies in patients treated with CYC showed a significant decrease in the number of B cells, whereas the number of T cells did not decrease to the same extent[31]. There are currently no data on repeat renal biopsies after treatment with RTX; thus, the impact of this agent in the

Table 2 Current guidelines in the remission induction therapy for antineutrophil cytoplasmic antibody associated vasculitides with severe renal involvement

KDIGO recommendations[23]
Initial treatment of pauci-immune focal and segmental necrotizing GN with or without systemic vasculitis, and with or without circulating ANCA:
We recommend that CYC and CCS be used as initial treatment (1A)
We recommend that RTX and CCS be used as an alternative initial treatment in patients without severe disease or in whom CYC is contraindicated (1B)
We recommend the addition of PLEX for patients requiring dialysis or with rapidly increasing sCr (1C)
Treatment of relapse
We recommend treating patients with severe relapse of ANCA vasculitis (life- or organ threatening) according to the same guidelines as for the initial therapy (1C)
EULAR/ERA-EDTA recommendations[26]
For remission-induction of new-onset organ-threatening or life threatening AAV we recommend treatment with a combination of CCS and either CYC or RTX
CYC: Level of evidence 1A for GPA and MPA; grade of recommendation A; strength of vote 100%
RTX: Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 82%
For a major relapse of organ-threatening or life-threatening disease in AAV we recommend treatment as per new disease with a combination of CCS and either CYC or RTX
CYC: Level of evidence 1A for GPA and MPA; grade of recommendation A; strength of vote 88%
RTX: Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 94%
PLEX should be considered for patients with AAV and a serum creatinine level of > 500 mmol/L (5.7 mg/dL) due to rapidly progressive glomerulonephritis in the setting of new or relapsing disease. Level of evidence 1B; grade of recommendation B; strength of vote 77%

AAV: Antineutrophil cytoplasmic antibody associated vasculitides; KDIGO: Kidney disease improving global outcomes; EULAR: European league against rheumatism; ERA-EDTA: European renal association-european dialysis and transplant association; GN: Glomerulonephritis; GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; CYC: Cyclophosphamide; RTX: Rituximab; CCS: Corticosteroids; PLEX: Plasma exchange.

presence of B and T cell tubulointerstitial lesions remains uncertain. Repeat renal biopsies in future trials would help to clarify the contradictory results of the current studies and identify the extent of B and T cell infiltration that could potentially be a significant clinical factor in determining adequate therapy for individual patients in order to ensure that active lesions are adequately treated.

What is the impact of safety and adverse events on therapeutic choice?

Given that safety is a key concern in the evaluation of immunosuppressive agents, there may be individual clinical situation in which RTX is more appropriate than CYC; these may include patients with a high cumulative dose of CYC due to previous exposure, patients with a history of malignancy, and those who are of childbearing age but do not yet have any offspring. However, RAVE and RITUXVAS did not show any benefit of RTX in terms of the incidence of adverse events, regardless of severity[10,11,32].

Although efficacious remission induction treatment using RTX in patients with severe infection has been reported[33], this is not recommended as moderate to severe hypogammaglobulinemia occurs in > 50% of AAV patients treated with RTX, resulting in increased risk of infections that could be even higher in patients with reduced renal function[34-36]. As highlighted in two small cohorts of patients with AAV, the negative impact of RTX on IgG levels can be exacerbated by higher previous CYC exposure[37,38]. Late-onset neutropenia following RTX has also been described in both GPA and MPA and is associated with a high incidence of infections[39]. Uncommon but serious adverse events after RTX treatment include hepatitis B (HBV) reactivation, which is largely preventable with antiviral prophylaxis, and progressive multifocal leukoencephalopathy (PML) caused by reactivation of the human JC polyomavirus[40-42]. Nevertheless, we must emphasize that PML occurs in the context of a severe cellular immunosuppression and is not specifically associated with any immunosuppressive agent[43]. In fact, PML has also been reported in patients with GPA treated with CYC[44]. Moreover, beyond the infectious risk after RTX treatment, RAVE and RITUXVAS raised concerns about a possible higher incidence of malignancy in patients treated with RTX[10,11,20]. A retrospective study of 323 patients with AAV recently compared the incidence of malignancy between RTX and CYC[45]. During a mean follow-up of 5.6 years, patients treated with RTX did not show an increased risk compared with the general population. In contrast, patients treated with CYC had a 4.61-fold higher risk of developing malignancies than those treated with RTX. Longer follow-up studies are now required to validate these data.

SHOULD THERE BE DIFFERENCES IN THE THERAPEUTIC APPROACH BETWEEN PATIENTS WITH NEWLY DIAGNOSED AAV AND THOSE WITH DISEASE RELAPSE? IF SO, WHAT IS THE IMPORTANCE OF THE ANTIGENIC SPECIFICITY OF ANCA IN GUIDING THERAPEUTIC CHOICE?

The therapeutic approach to relapses in patients with GPA or MPA and renal involvement remains a challenge and depends on the degree of severity and whether

or not the patient is still undergoing treatment with a maintenance immunosuppressive regimen at the time of relapse.

Treatment of mild renal relapse

Patients with mild, non-organ-threatening relapse (*e.g.*, recurrent red blood cell casts on urine microscopy without concomitant increase in serum creatinine) who are still undergoing maintenance therapy can initially be treated by increasing the dose of CCS and of the immunosuppressive agent used for maintenance therapy, especially if the relapse occurs during a reduction in the dose of maintenance therapy[26,46]. Mild, non-organ-threatening relapses that arise after discontinuation of maintenance therapy can be treated with the resumption of the prior maintenance therapy. In the latter case, the maintenance therapy should be continued for a more extended period than planned before the relapse[26]. If the nephrologist is uncertain that the relapse is mild, a kidney biopsy should be performed to clarify whether repeat-induction therapy is warranted. In patients with multiple mild relapses, B cell depletion with RTX must be considered as an alternative approach[46].

Treatment of severe renal relapse

Severe relapses should be treated with the resumption of induction therapy using a CYC-based or RTX-based regimen as for a new case[26]. In patients who relapse after a successfully achieving remission with a CYC-based regimen, RTX is preferred because the cumulative dose of CYC is associated with significant toxicity, particularly in patients with frequent relapses[26,47]. RTX is also the therapy of choice for patients who relapse after previously achieving remission with RTX-based therapy, patients who had difficulty tolerating CYC or those who had a contraindication to CYC during initial induction therapy[26,47]. The best data in patients with relapsing GPA and MPA come from the RAVE trial. The rate of remission induction in patients with relapse was higher with RTX at 6 and 12 mo, but not at 18 mo[10,32]. RTX and CYC followed by AZA achieved similar remission rates at 18 mo, although patients in the RTX group who achieved a complete remission by 6 mo received no additional immunosuppression for more than one year[32]. However, CYC-based therapy should be considered for patients whose relapse is characterized by advanced renal failure, as it is for patients with newly diagnosed AAV, for the abovementioned reasons (Table 2).

What is the impact of the antigenic specificity of ANCA on therapeutic choice?

To date, there is growing evidence that ANCA specificity is superior to clinical diagnosis in defining homogeneous groups of patients, as PR3-ANCA and MPO-ANCA are associated with different genetic backgrounds and epidemiologic patterns[48]. MPO-ANCAs are present in > 80% of patients with isolated PiNCGN, whereas patients with PR3-ANCAs have more extra-renal organ manifestations[49,50]. In the RAVE trial, renal involvement was more common in patients with MPO-ANCAs than in those with PR3-ANCAs (79% *vs* 59%). Additionally, based on the international working group of renal pathologists (IWGRP) classification system for ANCA-associated glomerulonephritis[51,52], patients with MPO-ANCAs have a more severe histological phenotype[53,54]. For instance, in the study by Quintana *et al*[53], MPO-ANCAs were associated with a higher frequency of mixed and sclerotic pathology, characterized by more advanced fibrotic changes in the interstitium and worse renal function at 1 and 2 years. These data are in agreement with those observed in most cohorts, which show that patients with MPO-ANCAs have poorer renal outcomes than those with PR3-ANCAs[49,55-58]. However, numerous studies have shown that relapses are much more frequent in patients with PR3-ANCA seropositivity[2,49,59-62].

In the RAVE trial, at the 6 mo time point, significantly more patients became PR3-ANCA-negative after RTX therapy than after CYC/AZA therapy (50% *vs* 17%), whereas comparable proportions of patients receiving either therapy became MPO-ANCA-negative[10]. Most importantly, a post hoc analysis of the RAVE trial showed similar rates of complete remission at 6 mo in both treatment groups among the subgroup of patients with MPO-ANCA seropositivity, whereas RTX was significantly more effective than CYC/AZA in the subgroup of patients with PR3-ANCAs (65% *vs* 48%)[63]. Moreover, among patients with PR3-ANCAs who had relapsing disease at baseline, the risk of disease relapse in RTX-treated patients was inferior not only at 6 mo, but also at 12 and 18 mo, despite the fact that patients randomized to RTX had not received a maintenance regimen[63]. However, in another post hoc analysis of patients with renal involvement enrolled in the RAVE trial, no variations in remission rates or improvements in eGFR at 18 mo were observed when the analysis was stratified by ANCA type, AAV diagnosis (GPA *vs* MPA), or new diagnosis versus relapsing disease at entry[20].

In conclusion, the demonstrated superiority of RTX compared to CYC in patients with PR3-ANCAs and in patients with relapsing disease has not yet been confirmed in long-term follow-up in patients with renal involvement[20]. Further clinical trials are needed to evaluate this question in well-defined homogenous patient populations according to ANCA specificity.

SHOULD ALL PATIENTS WITH ADVANCED RENAL INVOLVEMENT BE TREATED WITH ADJUNCTIVE PLASMA EXCHANGE SESSIONS, AS SUGGESTED BY SHORT-TERM RESULTS?

The rationale for PLEX in AAV is that removal of ANCAs and other plasma constituents involved in the

pathogenesis of the disease, such as protein produced by activated lymphocytes and macrophages, cytokines, complement components, clotting factors, and adhesion molecules, could reduce further tissue damage and promote reversal of the pathologic process[64,65].

The effect of PLEX in addition to standard immunosuppressive therapy in patients with AAV and renal involvement, was evaluated in an initial randomized trial that demonstrated the efficacy of PLEX in the subgroup of patients with serum creatinine of at least 500 mmol/L (5.8 mg/dL) or on dialysis at diagnosis, but not in the group with a creatinine lower than 500 mmol/L[66]. In 2007, the methylprednisolone *vs* plasma Exchange (MEPEX) trial, the largest randomized trial in patients with a severe renal disease (serum creatinine > 500 mmol/L) was published[13]. All 137 enrolled patients were treated with CYC plus oral CCS and were randomly assigned to receive either seven PLEX sessions or three pulses of 1000 mg of methylprednisolone. At 3 mo, the proportion of patients who were alive and independent of dialysis was significantly higher in the PLEX group compared to the methylprednisolone group (69% *vs* 49%). Additionally, PLEX was associated with a 24% reduction in the risk of progression to ESRD at 12 mo, although the overall rates of survival and adverse events were similar between both groups after 1 year of follow-up[13].

A subsequent meta-analysis of 387 patients from nine trials, including the MEPEX trial, showed a 20% relative risk (RR) reduction in the composite outcome of death or ESRD requiring dialysis after the addition of PLEX to standard immunosuppressive therapy[67]. However, the authors of the meta-analysis concluded that, although this result was statistically significant, too few patients had been randomly assigned and sensitivity analyses were not sufficiently robust to reliably conclude that PLEX results in at least a moderate decrease in the composite end point of ESRD or death[67].

Moreover, although these short-term results obtained with PLEX are encouraging, the long-term benefits remain unclear. In fact, long-term follow up of the MEPEX trial showed an attenuated benefit of PLEX with no significant reduction of progression to ESRD at four years, and equivalent mortality in both groups (51%)[68]. Currently, the most recent EULAR/ERA-EDTA recommendations for the management of AAV suggest that PLEX should be considered for patients with AAV and a serum creatinine level of > 500 μmol/L in the setting of new or relapsing disease. The level of evidence is 1B and the grade of recommendation is B[26] (Table 2).

In conclusion, PLEX continues to be a promising therapy, but further trials are required before widespread use for patients with renal vasculitis can be implemented. The ongoing PEXIVAS trial [Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody (ANCA) - Associated Vasculitis; ClinicalTrials.gov Identifier: NCT00987389] should help to further clarify the value of PLEX in these patients[69].

NOVEL TARGETED AGENTS AND FUTURE PERSPECTIVES IN THE INDUCTION REMISSION THERAPY FOR AAV WITH RENAL INVOLVEMENT

The greatest challenge in the management of AAV is the development of new agents and innovative strategies, which are urgently needed to improve patients' prognosis and reduce the co-morbidities associated with current regimens. Future potential therapies, including molecules that block signaling pathways crucial in the pathogenesis of AAV and the development of PiNCGN, are currently being investigated in preclinical studies and early clinical trials, with promising results.

As previously mentioned, to date, high-dose CCS remain an integral part of induction remission therapy for AAV, in combination with an immunosuppressive agent (CYC) or a biological agent (RTX). Even though CCS rapidly control inflammation and prevent further renal damage, the increased susceptibility to infections and other potential co-morbidities such as diabetes mellitus, cardiovascular events, osteoporosis, cataracts and gastrointestinal complications[70], have prompted researchers to reduce or replace their use.

Currently, several ongoing trials are assessing different strategies to minimize the use of CCS for remission induction. The above-mentioned multinational PEXIVAS trial (NCT00987389)[69] and the LoVAS (Low-dose Glucocorticoid Vasculitis Induction) trial (NCT02198248)[71] could provide valuable information on this crucial question (Table 3).

However, the most promising advancement for remission induction therapy is avacopan (CCX168), an orally administered selective C5a receptor inhibitor (Table 4). The efficacy of avacopan was first tested in an ANCA-associated glomerulonephritis mouse model induced by injection of MPO IgG[72]. The recently completed CLEAR study, a phase 2, randomized, double-blind, placebo-controlled trial, met its primary endpoint, indicating that avacopan can replace high-dose CCS efficiently and safely in patients with newly diagnosed or relapsing AAV[73] (Table 3). The 67 enrolled patients were randomized to receive placebo plus prednisone starting at 60 mg daily (control group), avacopan (30 mg, twice daily) plus reduced-dose prednisone (20 mg daily), or avacopan (30 mg, twice daily) without prednisone. The early efficacy of avacopan was substantiated by a rapid improvement in albuminuria, which was statistically significantly superior to that of the control group. Moreover, renal inflammation improved rapidly and to a higher degree in the avacopan groups compared with the control group, as demonstrated by the greater reduction of urinary MCP-1 (Monocyte Chemoattractant Protein-1) levels,

Table 3 Trials for induction of remission in antineutrophil cytoplasmic antibody associated vasculitides with renal involvement and corticosteroids-sparing regimens

Name of the Trial (number of patients)	Inclusion criteria	Treatment groups (drug dose)	Primary end points	Outcome
LoVAS[71] (140)	New clinical diagnosis of MPA or GPA, Age > 20 yr, eGFR > 15 mL/min	Low-dose CCS (0.5 mg/kg per day tapered and off within 6 mo) plus RTX *vs* High-dose CCS (1.0 mg/kg per day tapered to 10 mg/d within 6 mo) plus RTX	Proportion of the patients achieving remission at 6 mo (BVAS = 0 and CCS < 10 mg)	Ongoing trial (NCT02198248)
PEXIVAS[69] (704)	New or previous clinical diagnosis of MPA or GPA, Age > 15 yr, eGFR < 50 mL/min	without PLEX: normal versus reduced CCS *vs* with PLEX: normal versus reduced CCS (reduced dose regimen provides approximately 55% of the standard dose regimen over the first 6 mo)	All-cause mortality and ESRD at 2 yr	Ongoing trial (NCT00987389)
CLEAR[73] (67)	New or previous clinical diagnosis of MPA or GPA, Age > 18 yr, eGFR > 20 mL/min	Placebo plus 60 mg prednisone *vs* Avacopan (30 mg x 2/d) plus 20 mg prednisone *vs* Avacopan (30 mg x 2/d) without prednisone	Safety of Avacopan in subjects with AAV over the 12-wk treatment period	Avacopan can replace high-dose CCS efficiently and safely in patients with newly diagnosed or relapsing AAV
ADVOCATE[75] (300)		Avacopan in combination with RTX or CYC/AZA *vs* Prednisone in combination with RTX or CYC/AZA	The proportion of patients achieving disease remission at 26 wk	Ongoing trial (NCT02994927)

AAV: Antineutrophil cytoplasmic antibody associated vasculitides; GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; CYC: Cyclophosphamide; AZA: Azathioprine; RTX: Rituximab; CCS: Corticosteroids; PLEX: Plasma exchange; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; BVAS: Birmingham vasculitis activity score.

a renal inflammation marker, in the avacopan groups. The most important finding from the CLEAR trial with regard to renal outcomes is that e-GFR and hematuria improved similarly in all three groups over the 12-wk treatment period, indicating that improvement in renal function in patients receiving avacopan did not require high-dose CCS. Another phase 2 trial, the CLASSIC trial (NCT02222155) investigated the addition of two different doses of avacopan or placebo to standard-dose CCS with CYC or RTX. No safety concerns were described in the avacopan treatment groups, and a trend towards a dose-dependent improvement in clinical response was shown[74]. ADVOCATE (NCT02994927), a phase 3 trial, is now enrolling patients and will assess the safety and effectiveness of avacopan as an alternative to prednisone in inducing and maintaining remission in patients with AAV[75] (Table 3).

Other new potential therapeutic agents in the induction remission therapy for AAV with major renal involvement include the following (Table 4).

Bortezomib: A proteasome inhibitor, was found to be more efficacious than CYC + CCS in decreasing the number of MPO-specific plasma cells and anti-MPO titers, thereby preventing the development of necrotizing crescentic glomerulonephritis in a mouse model of MPO AAV[76]. Currently, there is only a single case report of a patient with AAV refractory to conventional treatment who achieved a prolonged remission of kidney disease after a single cycle of Bortezomib (four subcutaneous injections of 1.3 mg/m^2 at weekly intervals). At four years of follow-up, kidney function remained stable without any maintenance treatment[77]. More studies are now required to determine the efficacy and safety of this agent in the treatment of AAV patients.

Fostamatinib: A selective spleen tyrosine kinase (SYK) inhibitor that blocks B cell activation has been shown to attenuate autoantibody production and reverse autoimmune crescentic glomerulonephritis in a rodent model of anti-glomerular basement membrane disease[78]. Additionally, in a rodent model of MPO AAV, SYK inhibition with fostamatinib has been an effective treatment for crescentic glomerulonephritis and lung hemorrhage[79]. Immunohistochemical analysis confirmed SYK expression in human ANCA-associated glomerulonephritis, and SYK expression correlated with histological disease severity.

Given these encouraging results, clinical studies investigating the effect of SYK –targeted treatment in ANCA-associated glomerulonephritis are now warranted.

Anakinra: A recombinant nonglycosylated human interleukin-1 receptor antagonist (IL-1Ra) used in the treatment of rheumatoid arthritis, reduced the severity of necrotizing crescentic glomerulonephritis in a mouse model of MPO AAV[80] and could be a potential therapeutic agent.

Gusperimus: An analogue of spergualin that inhibits the proliferation and activation of T cells, B cells, monocytes and dendritic cells and reduces the production of IFN-γ, IL-6 and IL-10[81] has been shown to improve mortality and reduce proteinuria in a murine model of ANCA-

Table 4 New agents investigated in preclinical models and clinical trials in humans for antineutrophil cytoplasmic antibody associated vasculitides with renal involvement

Agent	Therapeutic target	Preclinical models	Human trials
Avacopan	Complement C5a receptor inhibitor	Mice[72]	CLEAR, a phase Ⅱ trial, Status: Completed[73] CLASSIC, a phase Ⅱ trial, Status: Completed[74] ADVOCATE, a phase Ⅲ trial, Status: Recruiting (NCT02994927)[75]
Bortezomib	Proteasome inhibitor	Mice[76]	Not available
Fostamatinib	Spleen tyrosine kinase (Syk) inhibitor	Mice[79]	Not available
Anakinra	Interleukin-1 receptor antagonist (IL-1Ra)	Mice[80]	Not available
Gusperimus	NF-κB translocalization inhibition in leucocytes IFNγ, IL-6, IL-10 production reduction	Mice[82]	Phase Ⅱ trials[83-85] Status: Completed
Alemtuzumab	Anti-CD52 humanized antibody inducing T-cell and macrophages depletion	Not available	Phase Ⅱ trial[86] Status: Completed

associated crescentic nephritis[82]. Three multicenter open-label studies have demonstrated the effectiveness of this agent in the treatment of refractory GPA and relapsing GPA[83-85]. However, gusperimus should not be used in AAV due to serious adverse events and frequent neutropenia.

Alemtuzumab: An anti-CD52 monoclonal antibody that induces profound macrophages and T-cell depletion has also been shown to be effective in inducing remission in patients with relapsing or refractory AAV, but the increased frequency of relapse and severe adverse events limit its use[86].

CONCLUSION

In recent years RTX has enriched our armamentarium for remission induction treatment for severe organ- or life-threatening AAV. However, data from randomized controlled trials on the efficacy of RTX in patients with advanced kidney failure without concomitant CYC are lacking. Additionally, despite the reported superiority of RTX in patients with relapsing disease and those with PR3-ANCA seropositivity, no differences in remission rates or increases in e-GFR are evident when the analysis is stratified by ANCA type or by new diagnosis versus relapsing disease in patients with major renal involvement[20]. These data are contradictory and could create confusion for nephrologists who must decide on which immunosuppressive therapy is most appropriate for their patients. For that reason, new clinical trials in well-defined homogeneous patient populations, selected according to their ANCA specificity and renal function, are needed. Until then, CYC should remain the first-line treatment in the induction of remission for patients with severe renal involvement. Nevertheless, RTX may be considered as first-line treatment rather than CYC in young patients without offspring, patients with a history of malignancy and those who have received a high cumulative dose of CYC due to previous exposure as a result of relapsing disease.

Similarly, more data are needed to clearly define the utility of PLEX in the treatment of AAV with severe renal involvement. The results of the PEXIVAS study are expected to elucidate this question[69].

Finally, the continuous enrichment of our knowledge on the pathogenetic mechanisms of this disease may be translated into new therapeutic strategies based on novel biological drugs. Soon there may be therapeutic regimens with low doses of CCS or without CCS, thanks to the use of avacopan, a selective C5a receptor inhibitor that has proven to be an excellent glucocorticoid-sparing agent.

Other agents still under evaluation, with promising preclinical studies, are also expected to contribute to further improvement of renal outcomes and patient survival.

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