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Efficacy of Rituximab and Plasma Exchange in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis with Severe Kidney Disease

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Significance Statement

Efficacy of rituximab (RTX) in ANCA-associated vasculitis (AAV) in patients with severe renal involvement (eGFR<30 ml/min per 1.73 m^2) has not been addressed in clinical trials. This observational study did not find statistically significant differences between RTX and cyclophosphamide (CYC) for remission-induction therapy or any apparent benefit from the addition of plasma exchange (PLEX) to standard remission-induction therapy for patients with AAV and severe renal in-

volvement. Although our analyses suggest that the benefits and risks of these therapeutic choices (RTX versus CYC with and without PLEX) are balanced, a randomized, controlled trial is needed to confirm these findings.

Keywords: ANCA, glomerulonephritis, rituximab, cyclophosphamide, Plasmapheresis

Visual Abstract

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Abstract

Background

Treatment of patients with ANCA-associated vasculitis (AAV) and severe renal involvement is not established. We describe outcomes in response to rituximab (RTX) versus cyclophosphamide (CYC) and plasma exchange (PLEX).

Methods

A retrospective cohort study of MPO- or PR3-ANCA–positive patients with AAV (MPA and GPA) and severe kidney disease (eGFR <30 ml/min per 1.73 m^2). Remission, relapse, ESKD and death after remission-induction with CYC or RTX, with or without the use of PLEX, were compared.

Results

Of 467 patients with active renal involvement, 251 had severe kidney disease. Patients received CYC (*n*=161) or RTX (*n*=64) for remission-induction, and 51 were also treated with PLEX. Predictors for ESKD and/or death at 18 months were eGFR <15 ml/min per 1.73 m^2 at diagnosis (IRR 3.09 [95% CI 1.49 to 6.40], *P*=0.002), renal recovery (IRR 0.27 [95% CI 0.12 to 0.64], *P*=0.003) and renal remission at 6 months (IRR 0.40 [95% CI 0.18 to 0.90], *P*=0.027). RTX was comparable to CYC in remission-induction (BVAS/WG=0) at 6 months (IRR 1.37 [95% CI 0.91 to 2.08], *P*=0.132). Addition of PLEX showed no benefit on remission-induction at 6 months (IRR 0.73 [95% CI 0.44 to 1.22], *P*=0.230), the rate of ESKD and/or death at 18 months (IRR 1.05 [95% CI 0.51 to 2.18], *P*=0.891), progression to ESKD (IRR 1.06 [95% CI 0.50 to 2.25], *P*=0.887), and survival at 24 months (IRR 0.54 [95% CI 0.16 to 1.85], *P*=0.330).

Conclusions

The apparent benefits and risks of using CYC or RTX for the treatment of patients with AAV and severe kidney disease are balanced. The addition of PLEX to standard remission-induction therapy showed no benefit in our cohort. A randomized controlled trial is the only satisfactory means to evaluate efficacy of remission-induction treatments in AAV with severe renal involvement.

Renal involvement is common in patients with ANCA-associated vasculitis (AAV) (64%–85%), often presenting as rapidly progressive GN with a pauci-immune necrotizing crescentic GN on renal biopsy sample histology,[1–4] and it is associated with increased morbidity and mortality.[5] Despite advances in therapy, a significant number of patients progress to ESKD.[6–8] In addition, outcome data derived from patients with severe kidney disease are scarce and are on the basis of data from small cohorts.[9,10]

Remission-induction regimens with rituximab (RTX) or cyclophosphamide (CYC) were shown to have similar efficacy and safety in patients with mild-to-moderate renal disease secondary to AAV in the RAVE (Rituximab in ANCA-Associated Vasculitis) trial.[11–13] However, treatment responses to RTX and outcomes in patients with more advanced degrees of renal dysfunction were only addressed in the RITUXVAS (rituximab versus cyclophosphamide in ANCA-associated vasculitis) trial, which included 33 patients randomized to a combined treatment of RTX and CYC, and 11 patients to CYC only independently of the severity of renal involvement.[14,15] In that study, the isolated efficacy of RTX was not evaluated as the patients treated with RTX also received two pulses of intravenous (iv) CYC.[14,15]

The use of plasma exchange (PLEX) therapy for remission-induction of AAV is controversial.[16–32] The scientific rationale for the use of PLEX is the suspected pathogenic role of ANCA.[33] An increase in renal recovery rates at 12 months in patients dependent on dialysis with the addition of PLEX to remission-induction therapy for patients with severe ANCA-associated GN was observed in the MEPEX (methylprednisolone versus plasma exchange) trial studying patients with baseline serum creatinine (SCr) >5.8 mg/dl.[16–18] However, other studies found no benefit of adding PLEX to standard remission-induction therapy,[27–29] or in patients with microscopic polyangiitis (MPA) or eosinophilic granulomatosis with polyangiitis.[30] Moreover, long-term follow-up of the MEPEX trial patients showed that the renal survival benefit disappeared after 12 months.[20] Furthermore, the recent report of the PEXIVAS (plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis) trial showed no benefit from adding PLEX to standard remission-induction therapy in patients with eGFR<50 ml/min per 1.73 m^2.[34]

This study was conducted to (*1*) describe the remission-induction outcomes in response to RTX compared with CYC and to (*2*) evaluate the benefits of adding PLEX to standard remission-induction therapy, in patients with AAV and severe kidney disease.

Methods

Study Design

After obtaining approval from the Institutional Review Board, we conducted a single-center retrospective cohort study of all consecutive patients with AAV-associated renal disease evaluated at Mayo Clinic from January 1, 1996 to December 31, 2015 with last follow-up on December 31, 2017. The “Mayo Clinic ANCA-associated vasculitis cohort” comprised a total of 1830 patients with

a diagnosis of AAV verified by vasculitis experts. Patients with renal involvement were identified by applying an internal search engine (Advanced Cohort Explorer) using the following keywords: "kidney disease," "renal failure," "pauci-immune GN," "hematuria," "proteinuria," and "renal biopsy."

Patient Characteristics

All data were abstracted retrospectively from electronic medical records and included demographic characteristics, comorbidities, laboratory findings, biopsy results, therapies, and outcomes. The date of diagnosis of severe renal involvement (index date) was registered for the calculation of outcome time-points. The Birmingham Vasculitis Activity Score for Wegener Granulomatosis (BVAS/WG) was used to quantify disease activity at presentation and during the follow-up.[35–37]

Myeloperoxidase (MPO)- or proteinase 3 (PR3)–ANCA–positive patients with newly diagnosed AAV or relapsing disease with active renal involvement and fulfilling the American College of Rheumatology criteria and Chapel Hill consensus definition for granulomatosis with polyangiitis and MPA were included (Figure 1).[38–40] Patients with positive anti-GBM antibodies, eosinophilic granulomatosis with polyangiitis, AAV without evidence of GN, or who were MPO- or PR3-ANCA negative were excluded. Patients with at least one follow-up visit after their index date were included. Active renal involvement was defined by the presence of (*1*) active, biopsy-proven, pauci-immune GN; (*2*) red blood cell casts on urine microscopy; or (*3*) rise in SCr >30% (or >25% decline in creatinine clearance) attributed to active vasculitis. Severe kidney disease was defined by eGFR<30 ml/min per 1.73 m^2 at diagnosis of renal disease secondary to AAV. Patients were grouped according to the interventions received for remission-induction (CYC or RTX and with or without PLEX). No patient received RTX in combination with CYC. For the purpose of this study, which was to evaluate different treatment options in patients with AAV and severe kidney disease, time of diagnosis of severe renal involvement coincides with the start of the remission-induction treatments.

Renal Function Assessment

eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation,[41,42] and was recorded at baseline and at 6, 12, 18, and 24 months. Further categorization of severity of renal impairment at baseline for the determination of predictors of outcomes included the eGFR cut-off (<15 and ≥15–30 ml/min per 1.73 m^2). Time-trend values of eGFR were determined for 5-year periods and compared between groups.

Remission-Induction Therapies and PLEX

Indication for remission-induction and treatment used were not defined by a pre-established protocol but decided by the treating physicians. Patients who received CYC (oral, 2 mg/d for 6 months) followed a strict clinical practice protocol of laboratory monitoring, every 1–2 weeks, for early detection of leukopenia. Patients who received RTX (iv, 375 mg per m^2 of body surface area once weekly for 4 weeks) had absolute B-cell counts measured at intervals determined by the

treating physician. The tapering of glucocorticoids was not performed following a pre-established protocol. The decision to use PLEX was also determined by the treating physician. The replacement fluid used for PLEX at our institution was 5% albumin with 3 U of fresh frozen plasma as the final portion in the presence of bleeding in accordance with the American Society of Apheresis guidelines.[43] The apheresis devices used during the study period to perform the PLEX procedures were the TerumoBCT COBE Spectra, the TerumoBCT Spectra Optia, and the Fresenius KABI Fenwal Amicus. Anticoagulant consisted of acid citrate dextrose solution A with the addition of 10,000 U of heparin in patients without bleeding risk and acid citrate dextrose solution A only in those with bleeding risk. A 1-plasma-volume exchange was performed daily for 7–14 days with the apheresis devices calculating the volume to be exchanged on the basis of a hematocrit obtained within 24 hours of the procedure.[43] As per our practice, RTX was not given within the 48 hours before receiving a PLEX treatment.

Outcomes Assessment

Remission was defined by a BVAS/WG of 0 independent of the dose of prednisone, and complete remission was defined by a BVAS/WG of 0 with a complete discontinuation of prednisone. These events were assessed at 6 months and during follow-up. Renal remission was defined as improvement of hematuria (<10 red cells per high-power field), and improvement (eGFR increase >10%) or stabilization (stable eGFR or decrease <15%) of renal function. Relapse was defined by an increase of BVAS/WG >1 that resulted in therapy changes (increases in doses of maintenance-remission therapy or the start of a new remission-induction cycle). The number of relapses after achievement of remission, the type of relapse (major or minor), the organ involvement (renal versus nonrenal), and the BVAS/WG at the time of relapse were recorded.

Kidney disease progression was determined by the development of ESKD defined as eGFR<15 ml/min per 1.73 m^2 or the need to initiate RRT. Renal recovery was defined as independence of RRT for those in whom this therapy was initiated. Date of death was recorded to assess survival. Remission at 6 months and “combined events” end point of ESKD and/or death at 18 months were defined as the primary outcomes of the study. Survival, ESKD, and combined events at 24 months were secondary outcomes.

Statistical Analyses

Categoric variables were presented as count (percentage), whereas continuous variables were presented as mean (SD) if they were normally distributed as determined by Shapiro–Wilk test, or as median (interquartile range) if non-normal. For comparisons of categoric variables between groups, the Pearson’s chi-squared test was used if the number of elements in each cell was ≥5; Fisher’s exact test was used otherwise. For comparison of continuous variables between groups, an unpaired *t* test for independent samples was used for distributions consistent with normality, and the Mann–Whitney *U* test was used otherwise. We dichotomized age into <60 years and ≥60 years to include the variable in the logistic regression for the estimation of risk factors for severe renal involvement, as the same cut-off was used in the recent PEXIVAS trial.[34] We used the receiver operated curves to confirm whether this cut-off fit our data. eGFR was dichotomized according with pre-established classification cut-offs used in clinical practice.[44]

Logistic regression models were developed to examine the predictive role of the baseline clinical characteristics for the development of severe kidney disease. Variables were considered for the multivariate logistic regression models if they occurred before the development of the outcome of interest, had <10% of missing values, had *P* values <0.05 in the univariate analysis, and were clinically plausible. The final model was determined using both clinical and statistical criteria, taking into consideration collinearity, interaction, and the number of patients who experienced the outcome of interest. Some of the continuous variables were categorized with cut-offs determined according to pre-established guidelines or clinical practice.[44] The odds ratios (ORs) with 95% confidence intervals (95% CIs) were reported when appropriate.

The Kaplan–Meier method was used to assess cumulative incidence of remission, time to relapse, cumulative incidence of ESKD, time to death (survival), and cumulative incidence of combined events of ESKD and/or death at the more relevant time points. Cox proportional hazards regression models were used to determine predictive factors of the outcomes. We report the incidence rate ratio (IRR) with a 95% CI when appropriate.[45] We treated the patient's observation as right-censored: we included the observation in the survival analysis up to the last point at which the outcome was known to have not yet occurred. A multivariable Cox proportional hazards regression model was used to assess the effect of being treated in each decade on the probability of the outcome.

In addition, we also performed propensity score (PS) matching analysis with the objective to match patients by severity and to account for potential unequal distribution of important covariates between groups resulting from potential nonrandom assignment typical in observational studies like ours. The PS or the probability of receiving CYC versus RTX and that of receiving PLEX versus no PLEX were calculated separately for the two comparisons using logistic regression models. The number of covariates used in the PS models was conditioned by the number of patients assigned to RTX and PLEX. For the probability of being assigned to CYC versus RTX, the PS model included the following variables: eGFR<15 ml/min per 1.73 m^2 at renal involvement secondary to AAV diagnosis, alveolar hemorrhage, treatment with PLEX, and use of iv methylprednisolone as part of the remission-induction protocol. Similarly, the PS model for PLEX versus no PLEX included the following variables: eGFR<15 ml/min per 1.73 m^2, alveolar hemorrhage, treatment with CYC versus RTX, and use of iv methylprednisolone as part of the remission-induction protocol. We applied nearest-neighbor PS matching without replacement with a caliper of 0.001. After matching, effects on binary (yes/no) outcomes were assessed through ORs, and effects on time-to-event outcomes through IRRs. Model fit calibration was assessed by the Hosmer–Lemeshow goodness-of-fit test. We verified the performance of the PS matching by comparing the balance in the distribution of the variables between groups pre– and post–PS matching. *P* values <0.05 (two-sided) were considered significant. We did not adjust for the matched pairs arising from the PS matching.[46,47] Finally, after generating a dichotomous variable for the decade, we built a multivariable logistic regression model to assess the effect of being treated for each decade on the probability of the outcome after PS matching analysis.

IBM SPSS Statistics for MacOS, version 25 (IBM, Armonk, NY) was used for all data analysis with exception of the PS matching analysis that was calculated using Stata, StataCorp, version 13.1 (College Station, TX).

Results

Patient Characteristics and Clinical Outcomes

Of the 1830 patients with AAV evaluated during the study period, active renal disease was documented in 467 (25.5%) whereas 251 (13.7%) met the inclusion criteria of severe kidney disease (Figure 1). Baseline demographics and outcomes for the 251 patients with severe kidney disease are presented in Tables 1 and 2, respectively. Dialysis was required in 54 (21.5%) patients, 38 (72.2%) within 4 weeks of renal involvement diagnosis, and 12 (22.2%) of those were subsequently able to discontinue RRT: nine patients treated with CYC and three patients treated with RTX, and in seven patients PLEX was added to remission-induction immunosuppression. Remission (BVAS/WG=0) was achieved in 168 (66.9%) patients at 6 months and in a total of 198 (78.8%) patients during the follow-up. Renal remission was observed in 177 (70.5%) patients at 6 months and in a total of 199 (79.3%) patients during the follow-up. Relapses were documented in 81 (32.3%) patients, and in 46 (18.3%) patients these were renal relapses. PR3-ANCA–positive patients had a higher proportion of relapses in comparison with MPO-ANCA–positive patients (43.7% versus 34.1%, P=0.158). Nine patients died within 4 weeks of presentation, and a total of 13 patients died before 6 months (eight in the CYC group versus five in the RTX group, P=0.419). At the end of the follow-up (median of 5.6 years [interquartile range, 1.9–11.5]), a total of 62 patients (24.7%) had died, with death attributed to active AAV in 19 patients.

In patients who achieved remission, eGFR improved in the first 6 months, and continued to improve until 24 months (Figure 2), irrespective of the therapy used for remission-induction. At 6 months, the proportion of patients that were ANCA-negative was comparable for CYC (28.0%) and RTX (20.3%, P=0.231), and with or without the addition of PLEX (25.0% versus 23.5%, P=0.683).

Predictors of Severe Kidney Disease

Compared with patients with active nonsevere renal involvement (n=216) (for demographic characteristics please refer to Supplemental Table 1), patients with severe kidney disease at diagnosis (n=251) were more likely to be older than 60 years of age (OR 2.27; 95% CI, 1.60 to 3.29; P<0.001) and to have arterial hypertension (OR 2.13; 95% CI, 1.44 to 3.15; P<0.001), diabetes mellitus (OR 2.67; 95% CI, 1.56 to 4.57; P<0.001), dyslipidemia (OR 1.79; 95% CI, 1.20 to 2.69; P=0.005), body mass index (BMI) ≥30 kg/m^2 (OR 1.52; 95% CI, 1.01 to 2.28; P=0.046), renal limited disease (OR 3.68; 95% CI, 2.26 to 5.98; P<0.001), MPA (OR 1.84; 95% CI, 1.27 to 2.65; P=0.001), MPO-ANCA (OR 2.09; 95% CI, 1.44 to 3.03; P<0.001), and lower levels of hemoglobin (OR 1.53; 95% CI, 1.38 to 1.75; P<0.001). Multivariable logistic regression analysis showed that older age, arterial hypertension, diabetes mellitus, BMI≥30 kg/m^2, renal limited disease, and lower levels of hemoglobin, but not MPO-ANCA, were independently associated with the severity of renal disease at diagnosis (Supplemental Table 2).

RTX versus CYC for Remission-Induction

Of the 251 patients with severe renal involvement, CYC was the remission-induction immunosuppressant of choice in 161 (64.1%) patients and RTX in 64 (25.5%) patients, whereas 26 patients were treated with other therapies (Figure 1). All patients received glucocorticoids at the time of remission-induction. The combination of iv methylprednisolone boluses with either CYC or RTX (59.0% versus 81.3%) followed by oral glucocorticoids was the main strategy (Table 3). Patients treated with CYC had lower mean eGFR at diagnosis in comparison with patients treated with RTX (15.6 versus 17.7 ml/min per 1.73 m^2, *P*=0.050) (Figure 2A). This was also observed in patients who received PLEX and CYC in comparison with those who received PLEX and RTX (12.5 versus 18.5 ml/min per 1.73 m^2, *P*=0.026) (Figure 2C).

There were no statistically significant differences between CYC and RTX in the frequency of remission (BVAS/WG = 0) at 6 months (76.6% versus 83.3%, *P*=0.291), combined events of ESKD and/or death at 18 months (29.8% versus 23.4%, *P*=0.336), death at 24 months (8.1% versus 12.5%, *P*=0.303), ESKD at 24 months (28.0% versus 15.6%, *P*=0.052), and combined events of ESKD and/or death at 24 months (31.1% versus 23.4%, *P*=0.255) (Table 4). In contrast, in comparison with CYC, complete remission (BVAS/WG=0 without prednisone) at 6 months was more frequently achieved in the RTX group (17.7% versus 31.7%, *P*=0.031). In comparison with CYC, remission-induction treatment with RTX allowed faster prednisone tapering and subsequent discontinuation (median prednisone dose at 6 months, 10.0 versus 2.5 mg, *P*=0.002; 12 months, 5.0 versus 0.0 mg, *P*=0.001; 18 months, 3.0 versus 0.0 mg, *P*=0.036) (Table 3). Renal recovery occurred at the same pace in both treatment groups over 6 months despite the baseline differences in eGFR (Figure 2A).

Using the unadjusted Kaplan–Meier method, we determined that time to remission at 6 months was different between CYC and RTX (4.2 versus 3.5 months, *P*=0.002), but the time to combined events at 18 months was not statistically significantly different between CYC and RTX groups (Supplemental Figure 1).

To adjust for observed imbalances in the distribution of disease features including the severity of renal impairment and treatments, we performed PS analysis for matching the patients according to the presence of eGFR<15 ml/min per 1.73 m^2 versus ≥15–30 ml/min per 1.73 m^2 at diagnosis, alveolar hemorrhage, administration of iv methylprednisolone as part of the remission-induction treatment, and receiving PLEX or no PLEX (Supplemental Table 3). The incidences of the outcomes in the matched sample indicate no statistically significant differences between groups (Supplemental Table 4). Patients treated with RTX showed a statistically nonsignificantly shorter time to achieve remission (BVAS/WG=0) (time to event estimated by post-PS Kaplan–Meier analysis, 3.5 versus 4.1 months, *P*=0.069) at 6 months (Figure 3A) and a statistically nonsignificantly higher probability of achieving remission (BVAS/WG=0) by 6 months (IRR 1.37; 95% CI, 0.91 to 2.08; *P*=0.132) (Table 5) compared with patients treated with CYC. There were no statistically significant differences in the probability or time to relapse at 12 months after remission, combined events of ESKD and/or death at 18 months (Figure 3B), survival at 24 months, progression to ESKD at 24 months, and combined events of ESKD and/or death at 24 months (Table 5). In addition, in order to demonstrate our rationale on the renal involvement severity cut-off choice, we

also provide the comparison of clinical characteristics and outcomes between the two groups with eGFR<15 ml/min per 1.73 m^2 versus ≥15–30 ml/min per 1.73 m^2 at diagnosis in Supplemental Table 5.

PLEX as an Adjunct to Remission-Induction Therapy

PLEX was added to standard immunosuppressive remission-induction therapy in 51 (20.3%) patients. The underlying remission-induction immunosuppressant was CYC in 37 (72.5%) and RTX in 14 (27.5%). Patients who received PLEX also received concomitant iv methylprednisolone more frequently (90.2% versus 55.5%, *P*<0.001) (Table 6). Indications for PLEX were severe renal involvement in 48 (94.1%) patients and renal involvement with alveolar hemorrhage in 19 (37.3%) patients (Table 1). The median number of PLEX sessions was 7. Patients who received PLEX presented more frequently with eGFR<15 ml/min per 1.73 m^2 (56.9% versus 37.5%, *P*=0.012), had lower mean eGFR at diagnosis (14.1 versus 16.8 ml/min per 1.73 m^2, *P*=0.035), required renal function replacement therapy more frequently (39.3% versus 17.0%, *P*<0.001) (Figure 2B), and had higher BVAS/WG at diagnosis (9 versus 7 points, *P*=0.007). From the 222 patients with biopsy-proven diagnosis of AAV with severe renal involvement, we were able to review 199 biopsy samples (90% of the cases). The histologic pattern was focal in 39 (19.6%), crescentic in 49 (24.6%), mixed in 73 (36.7%), and sclerotic in 38 (19.1%) patients. There were no statistically significant differences in the distribution of the histologic categories between patients that received PLEX in comparison with the patients who did not receive PLEX (*P*=0.375).

In the unadjusted analysis, there were no statistically significant differences between patients who did not receive PLEX in comparison with those who did in the achievement of remission (BVAS/WG=0) at 6 months (78.1% versus 73.5%, *P*=0.497), complete remission (BVAS/WG=0 without prednisone) at 6 months (21.7% versus 23.9%, *P*=0.754), or renal remission at 6 months (79.4% versus 77.6%, *P*=0.775); or in the combined events of ESKD and/or death at 18 months (24.5% versus 35.3%, *P*=0.120), or death at 24 months (9.0% versus 7.8%, *P*=0.794) (Table 7). However, among patients treated with PLEX, a statistically nonsignificantly higher incidence of ESKD was observed at 24 months compared with patients not treated with PLEX (33.3% versus 21.0%, *P*=0.064). The pace of prednisone tapering was not statistically significantly different between patients treated with or without PLEX (median prednisone dose at 6 months, 7.5 versus 5.0 mg, *P*=0.386; 12 months, 5.0 versus 5.0 mg, *P*=0.927; 18 months, 0.0 versus 0.0 mg, *P*=0.289). The frequency of relapses by 12 months after remission (14.9% versus 13.1%, *P*=0.745) was not statistically significantly different between groups. Renal recovery occurred at similar rates in both groups over 6 months despite the baseline difference in eGFR observed (Figure 2B), and this was independent of the choice of remission-induction therapy (Figure 2C).

Using the unadjusted Kaplan–Meier method, we observed that there was no statistically significant difference of adding PLEX on the achievement of remission (BVAS/WG=0) at 6 months, relapse at 12 months, and combined events of ESKD and/or death at 24 months. However, combined events of ESKD and/or death at 18 months tended to occur earlier in patients who received PLEX (13.6 versus 14.4 months, *P*=0.099) (Supplemental Figure 2). When the same analysis was performed

only in patients that received PLEX, and stratified by immunosuppression therapy received for remission-induction, we observed no statistically significant differences in the time to the outcomes between the combination of PLEX with CYC or RTX (Supplemental Figure 3).

To adjust for the confounding introduced by differences in disease severity in patients who received PLEX compared with those who did not, PS analysis was performed using the previously mentioned variables. In this case, the matching accounted also for the probability of receiving CYC or RTX (Supplemental Table 6). The outcome incidence after PS matching is displayed in Supplemental Table 7, which showed no statistically significant difference between the two groups. There were no statistically significant differences in the probability and time to remission (BVAS/WG=0) at 6 months (Figure 4A), relapse at 12 months after remission, combined events of ESKD and/or death at 18 months (Figure 4B), survival at 24 months, progression to ESKD at 24 months, and combined events of ESKD and/or death at 24 months (Table 5). After PS matching, we confirmed that adding PLEX had no benefit in the rate of improvement of eGFR (Supplemental Figure 4).

Predictors of Combined Events of ESKD and/or Death at 18 Months

Patients who incurred the combined end point of ESKD and/or death by 18 months more often remained ANCA-positive at 12 months after remission-induction treatment than those who did not (IRR 3.30; 95% CI, 1.05 to 10.37; P=0.041), had an eGFR<15 ml/min per 1.73 m^2 at diagnosis (IRR 3.00; 95% CI, 1.82 to 4.95; P<0.001), and had lower eGFR at 6 and 12 months (respectively, IRR 1.10; 95% CI, 1.07 to 1.14; P<0.001; IRR 1.07; 95% CI, 1.04 to 1.11; P<0.001). Renal function recovery for an eGFR>30 ml/min per 1.73 m^2 at 6 months and renal remission at 6 months were protective factors for the achievement of the end point (respectively, IRR 0.25; 95% CI, 0.11 to 0.57; P=0.001; and IRR 0.25; 95% CI, 0.15 to 0.42; P<0.001). Multivariable Cox regression showed that patients with eGFR<15 ml/min per 1.73 m^2 at diagnosis were at higher risk to evolve to ESKD and/or death at 18 months and that renal recovery and achieving renal remission at 6 months were protective factors for this outcome (Supplemental Table 8).

Outcome Comparison per Decade

In order to assess any potential time-trend bias, we adjusted for decades while evaluating outcomes in the propensity-matched sample. There were no statistically significant differences in the risks for the outcomes between decades (Supplemental Table 9).

Discussion

Our study showed that after using PS matching analysis for adjustment for confounding introduced by different disease severity, remission (BVAS/WG=0) at 6 months was not statistically significantly different, whether CYC or RTX was used for induction of remission, or whether PLEX was added as an adjunct therapy in patients with severe kidney disease. In accordance with previous studies, renal function at presentation was the main determinant of ESKD-free survival or death in patients with renal involvement of AAV.[48,49] In our cohort, patients presented with a mean

eGFR value of 16.3 ml/min per 1.73 m^2, similar to the values reported in other smaller cohorts.[9,10] The presence of MPO-ANCA (versus PR3-ANCA) has previously been reported as a determinant of renal outcome,[5,50,51] but multivariable modeling did not identify it as a risk factor for the development of severe kidney disease in our cohort. Moreover, we showed that the presence of classic cardiovascular risk factors and increased age appear to aggravate the susceptibility of the kidney for severe kidney disease in ANCA-associated GN.

The RAVE and RITUXVAS trials provided robust data about the efficacy of RTX for remission-induction in comparison with CYC.[11,14] In the RAVE trial, patients with an SCr>4 mg/dl at baseline were excluded. Nevertheless, eGFR was lower than 30.0 ml/min per 1.73 m^2 in 35% of patients randomized to the RTX group and in 27% of those randomized to the CYC group.[11,13] Similarly, in the RITUXVAS trial, the median eGFR was 20.0 ml/min per 1.73 m^2 in the RTX arm and 12.0 ml/min per 1.73 m^2 in the CYC arm.[14] A *post-hoc* analysis of the RAVE trial found that patients enrolled with an eGFR<30.0 ml/min per 1.73 m^2 at baseline responded similarly to RTX and CYC, and there was no statistically significant difference in the mean eGFR increase over the 18 months of follow-up.[13] In this study, which includes the largest number of patients with severe kidney disease treated with RTX (n=64), remission (BVAS/WG=0) at 6 months was achieved at similar rates in patients in the group treated with CYC compared with patients in the group treated with RTX, which is in line with the results reported in the RAVE trial.[11,13]

After PS matching analysis, RTX remained, at a minimum, not statistically significantly different from CYC as remission-induction therapy in patients that presented with severe kidney disease in AAV. Furthermore, the group treated with RTX achieved remission earlier, which might have contributed to the improvement of renal outcomes and renal recovery and be related to the lower incidences of overall ESKD and combined events in this group.

PLEX has been advocated as an adjunct therapy in AAV with renal involvement but without a clear consensus.[16–32] The MEPEX trial included patients with severe kidney disease (median SCr of 8.31 mg/dl) and, on the basis of the results, it was concluded that PLEX was of initial benefit for patients with severe renal failure,[18] but the effect was lost over longer term follow up.[20] However, results of the PEXIVAS trial in patients with newly diagnosed or relapsing severe AAV, including those with alveolar hemorrhage and/or GN (eGFR<50 ml/min per 1.73 m^2), who were randomized to receive or not receive PLEX for up to seven sessions during the span of 14 days as an adjunct to standard remission-induction therapy, indicate that PLEX does not reduce the risk of ESKD or death in patients with AAV.[34] This was even true when the combined outcome of ESKD or death was evaluated at 12 months and it is consistent with our observations where the addition of PLEX to standard remission-induction therapy did not improve the achievement of remission or reduce the progression to ESKD and/or death in patients with AAV with severe kidney disease. Furthermore, a prior study from our group showed that in patients with AAV and diffuse alveolar hemorrhage addition of PLEX did not add benefit to their treatment.[52] Consequently, we found no evidence to support the use of PLEX as an adjunct to standard remission-induction therapy in AAV.

This study has limitations inherent to its retrospective design. First, our cohort consists of a Midwestern United States white population with predominantly Scandinavian and Northern European ethnic backgrounds; therefore, the results may not be generalizable. Second, the stan-

dard of care between 1996 and 2010 was to use CYC, with RTX use becoming widespread only after the publication of the RAVE[11] and RITUXVAS trials in 2010,[14] and therefore a time-trend bias regarding the prescription of RTX versus CYC was considered. However, the differences in the standard of care between decades did not translate into differences in the risk for the outcome estimation after PS matching analysis. Third, treatment assignments were not protocol-driven and thus prone to selection biases on the basis of the disease severity and degree of renal impairment. For this reason, we adjusted our analyses for confounding variables using PS matching analysis as previously reported by our group.[52] Fourth, the dosing and tapering of glucocorticoids was not protocolized, and complete discontinuation of prednisone by 6 months was not a primary intent in the majority of cases. Therefore, it is no surprise that the primary outcome of the RAVE trial (complete remission at 6 months) was met by fewer patients in our study. For similar reasons, our outcome of remission at 6 months cannot directly be compared with the secondary end point of the RAVE trial of BVAS/WG of 0 and prednisone dose of <10 mg at 6 months, even though it comes close as the median prednisone dose at 6 months was 10 mg.[11,12,53] Lastly, we cannot completely exclude the possibility that different maintenance therapy choices may have had minor variable effects on the various outcomes evaluated in our study.

Despite these limitations, this is the largest cohort of patients with active severe renal involvement of AAV providing a detailed analysis of clinical characteristics and outcomes in response to different treatments in real clinical practice. Even though the treatment of these patients does not follow a strictly standardized protocol, there is homogeneity in the care of these patients by a group of experts in AAV, who followed consistent patterns and decisions. In addition, the high frequency of biopsy-proven severe kidney disease makes this large patient population the best-characterized cohort of patients with AAV with severe renal involvement reported to date.

Our observational study fills important gaps left by various clinical trials. The population included in our cohort comprises a spectrum of patients ranging from patients similar to those enrolled in the MEPEX and RITUXVAS trials to the patients with severe kidney disease (eGFR<30 ml/min per m^2) enrolled in the RAVE and PEXIVAS trials. This is the only study that compares the outcomes of RTX versus CYC for remission-induction in such a large number of patients with this spectrum of renal disease, while at the same time evaluating the effects of PLEX.[11,14,18,34] Moreover, our study adds to the PEXIVAS trial results in three important ways: (*1*) by adding a large population of patients with eGFR<30 ml/min per 1.73 m^2 (*n*=251); (*2*) we used a more aggressive approach to PLEX because, as per our practice, PLEX was generally given for a minimum of seven sessions and up to 14 session, versus PEXIVAS where maximum session were 7[34]; (*3*) in addition, not all patients seen at the individual PEXIVAS trial sites that qualified for enrollment in PEXIVAS were enrolled in the trial, whereas all patients that were seen at our institution, and that we could ascertain an outcome for, were included. As such, our study represents a more faithful picture of real practice in patients with AAV and severe renal and pulmonary disease.

In conclusion, our results do not support the preferential use of CYC over RTX or the addition of PLEX to standard remission-induction therapy in patients with AAV and severe kidney disease. However, a randomized trial is the only satisfactory means to evaluate efficacy of remission-induction treatments in patients with AAV and severe renal involvement. The degree of renal dysfunction at diagnosis is the best predictor of ESKD and/or death in patients with severe kidney disease

in AAV and the achievement of renal remission was the best predictive factor for favorable outcomes. Early diagnosis of renal involvement is crucial in order to prevent irreversible renal damage.

Disclosures

All authors have nothing to disclose.

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Supplementary Material

Supplemental Data:

Acknowledgments

Dr. Marta Casal Moura, Dr. Ulrich Specks, and Dr. Fernando C. Fervenza designed the study. Dr. Marta Casal Moura, Dr. Maria V. Irazabal, and Dr. Alfonso Eirin abstracted the data. Dr. Marta Casal Moura, Dr. Sanjeev Sethi, Dr. Ulrich Specks, and Dr. Fernando C. Fervenza analyzed the data. Dr. Marta Casal Moura, Dr. Bijan J. Borah, Mr. James P. Moriarty, and Miss Viengneesee Thao performed the statistical analysis. Dr. Marta Casal Moura, Dr. Ladan Zand, Dr. Ulrich Specks, and Dr. Fernando C. Fervenza drafted and revised the paper. All authors provided input for the final version of the manuscript. Dr. Fernando C. Fervenza received unrestricted grants from Genentech Inc., South San Francisco, CA, outside the submitted work. Dr. Ulrich Specks reports grants from Genentech, grants from Bristol Myer Squibb, grants and personal fees from ChemoCentryx, grants from GSK, grants and other from AstraZeneca, and other from InsMed, outside the submitted work. Dr. Kenneth Warrington reports grants from Eli Lilly, grants from Roche/Genentech, grants from GlaxoSmithKline, grants from Kiniksa, personal fees from Roche/Genentech, and personal fees from Sanofi, outside the submitted work.

Footnotes

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Supplemental Material

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2019111197/-/DCSupplemental.

Supplemental Table 1. Demographic and clinical characteristics description of patients with Anti-Neutrophil Cytoplasmic Antibodies (ANCA) associated vasculitis (AAV) and non-severe kidney disease.

Supplemental Table 2. Multivariable analysis of predictive factors for severe kidney disease in patients with Anti-Neutrophil Cytoplasmic Antibodies (ANCA) associated vasculitis (AAV).

Supplemental Table 3. Analysis of the distribution of the variables included in the propensity score matching analysis in patients with AAV and active severe kidney disease treated with cyclophosphamide (CYC) or rituximab (RTX) for remission induction.

Supplemental Table 4. Post propensity score matching outcomes comparison of patients with AAV and active severe kidney disease treated with cyclophosphamide (CYC) or rituximab (RTX) for remission induction.

Supplemental Table 5. Clinical characteristics, and outcomes of patients with AAV and active severe kidney disease treated stratified according to eGFR at admission: <15 mL/min/1.73m^2 vs. ≥ 15 to 30 mL/min/1.73m^2.

Supplemental Table 6. Analysis of the distribution of the variables included in the propensity score matching analysis in patients with AAV and active severe kidney disease according with the status of treatment with plasma exchange (PLEX).

Supplemental Table 7. Post propensity score matching outcomes comparison of patients with AAV and active severe kidney disease according with the status of treatment with plasma exchange (PLEX).

Supplemental Table 8. Multivariable analysis of predictive factors for combined events of ESKD and/or Death at 18 months in patients with Anti-Neutrophil Cytoplasmic Antibodies (ANCA) associated vasculitis (AAV) with active severe Kidney disease.

Supplemental Table 9. Risk for the outcome stratified by treatment after propensity score matching analysis and adjusted per decade (1996–2005 vs. 2006–2015).

Supplemental Figure 1. Remission and combined events before PS matching analysis. Before propensity score matching Kaplan Meier plots of remission achieved over 6 months after initiating remission-induction therapy (1A), and combined events (ESRD and/or death) at 18 months (1B), according with the remission-induction immunosuppression-CYC vs. RTX and before propensity score matching analysis.

Supplemental Figure 2. Remission and combined events before PS matching analysis. Before propensity score matching Kaplan Meier plots of remission achieved over 6 months after initiating remission-induction therapy (2A), and combined events (ESRD and/or death) at 18 months (2B), according with the status of treatment or no treatment with PLEX and before propensity score matching analysis

Supplemental Figure 3. Remission and combined events before PS matching analysis. Before propensity score matching Kaplan Meier plots of remission achieved over 6 months after initiating remission-induction therapy (3A), and combined events (ESRD and/or death) at 18 months (3B), for patients treated with PLEX stratified by remission-induction immunosuppression-CYC vs. RTX.

Supplemental Figure 4. Changes in mean eGFR with follow up after PS matching analysis. eGFR at baseline, and 6, 12, 18, and 24 months post-diagnosis for severe renal involvement in after PS matching.

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Figures and Tables

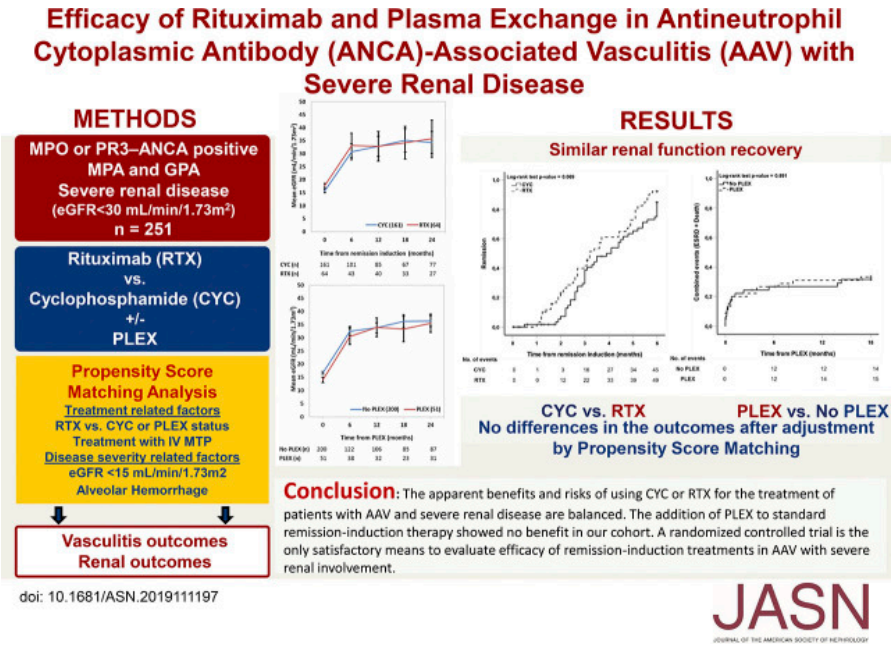
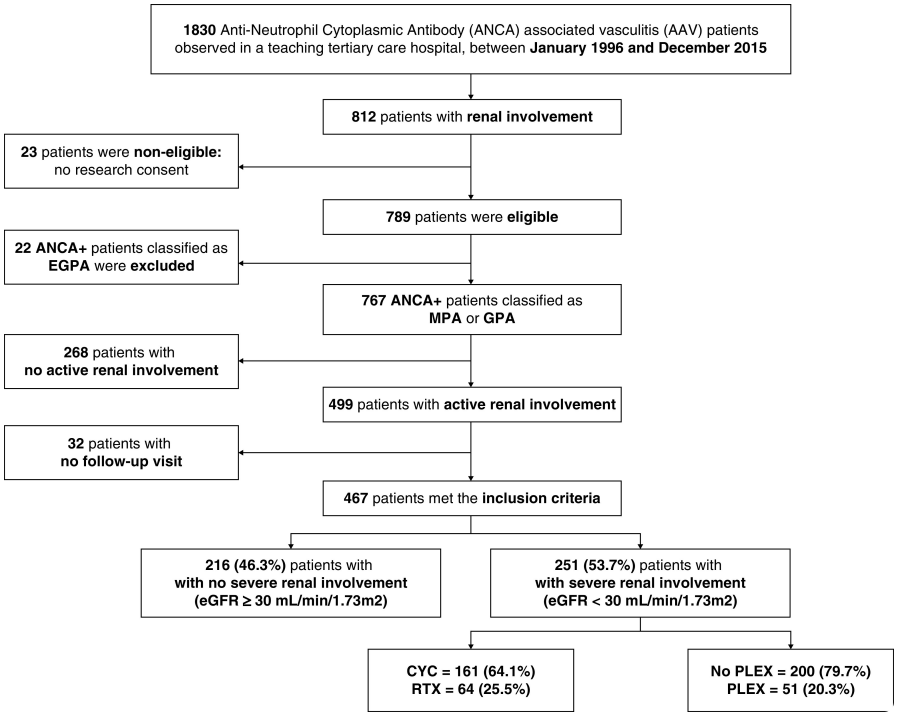


Figure 1.



Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) flowchart for the selection of patients with severe renal involvement in AAV. Active renal involvement was defined by the presence of (*1*) active, biopsy-proven, pauci-immune GN; (*2*) red blood cell casts on urine microscopy; or (*3*) rise in SCr >30% (or >25% decline in creatinine clearance) attributed to active vasculitis. Severe kidney disease was defined by eGFR<30 ml/min per 1.73 m^2 at diagnosis of renal disease secondary to AAV. Patients were grouped according to the interventions received for remission-induction (CYC or RTX and with or without PLEX). To assess the efficacy of CYC (*n*=161) in comparison with RTX (*n*=64) for remission-induction in patients with AAV and severe renal involvement, we excluded 26 patients treated with other immunosuppressants. In the group of patients that received PLEX (*n*=51), 37 (72.5%) were treated with CYC and 14 (27.5%) were treated with RTX for remission-induction. EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis.

Table 1.

Demographic and clinical characteristics of patients with AAV with active severe kidney disease

Characteristic	Active Severe Kidney Disease in AAV *n*=251
Age at diagnosis of severe renal involvement, median (IQR) yr[a]	66 (55–74)
Male, *n* (%)	128 (51.0)
Disease presentation, *n* (%)	
AAV new diagnosis	194 (77.3)
AAV relapse	57 (22.7)
AAV, *n* (%)	
MPA	140 (55.8)
GPA	111 (44.2)
ANCA specificity (ELISA), *n* (%)	
MPO	156 (62.2)
PR3	95 (37.8)
BVAS/WG at renal involvement diagnosis, median (IQR)	8 (7–10)
Renal limited disease, *n* (%)	84 (33.5)
Alveolar hemorrhage, *n* (%)	40 (15.9)
Pulmonary-renal syndrome, *n* (%)	33 (13.1)
Cardiovascular risk factors, *n* (%)	
Arterial hypertension	187 (74.5)
Diabetes mellitus	56 (22.3)
Dyslipidemia	91 (36.3)
BMI>30 kg/m^2	87 (34.7)
Laboratory findings	
Hemoglobin, mean (SD) g/dl	9.7 (8.7–11.0)
ESR>22 mm/h, *n* (%)	145 (57.8)
SCr at diagnosis, median (IQR) mg/dl	3.1 (2.5–4.2)
eGFR at diagnosis, mean (SD) ml/min per 1.73 m^2	16.3 (10.2–21.9)
Biopsy proven, *n* (%)	222 (88.4)
Intervention	
Remission-induction treatment, *n* (%)	
CYC	161 (64.1)

EGFR is estimated using the Chronic Kidney Disease Epidemiology collaboration method. IQR, interquartile range; GPA, granulomatosis with polyangiitis; ESR, erythrocyte sedimentation rate.

[a]Treatment was started on average within 16 h of the diagnosis of severe renal involvement.

Table 2.

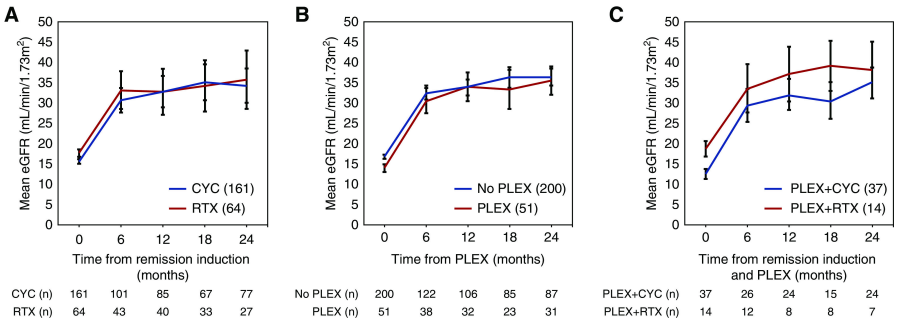
Outcomes of patients with AAV with active severe kidney disease

Variable	Active Severe Kidney Disease in AAV *n*=251
Outcomes	
Vasculitis, *n* (%)	
Remission	
6 mo	168 (66.9)
Total[a]	198 (78.8)
Time to remission, median (IQR) mo	3.7 (2.5–5.5)
Complete remission	
At 6 mo	46 (18.3)
Total[a]	119 (47.4)
Time to complete remission, median (IQR) mo	11.9 (3.2–17.6)
Renal remission	
At 6 mo	177 (70.5)
Total[a]	199 (79.3)
Relapse	
At 12 mo	32 (12.7)
Total[a]	81 (32.3)
Time to relapse, median (IQR) mo	16.0 (8.5–50.0)
Renal relapse	46 (18.3)
Death	
At 24 mo	22 (8.8)
Total[a]	62 (24.7)
Time to death, median (IQR) mo	44.8 (11.5–87.8)
Death AAV related, *n* (%)	34 (13.5)
Renal, *n* (%)	
ESKD	
At 24 mo	59 (23.5)
Total[a]	78 (31.1)
Time to ESKD, median (IQR) mo	3.0 (0.1–29.5)

IQR, interquartile range; FU, follow-up.

[a]"Total" refers to the number of occurrences during all follow-up time.

Figure 2.



Changes in mean eGFR with follow up. Estimates for the mean and SEM of eGFR (ml/min per 1.73 m^2) at baseline and at 6, 12, 18, and 24 months after beginning remission-induction therapy for each treatment group are displayed: (A) CYC versus RTX (mean eGFR at baseline, 15.6 versus 17.7 ml/min per 1.73 m^2; P=0.050); (B) PLEX versus no PLEX (mean eGFR at baseline, 14.1 versus 16.8 ml/min per 1.73 m^2; P=0.035); (C) CYC + PLEX versus RTX + PLEX (mean eGFR at baseline, 12.5 versus 18.5 ml/min per 1.73 m^2; P=0.026). GFR was estimated using the Chronic Kidney Disease Epidemiology collaboration formula.

Table 3.

Clinical characteristics of patients with AAV and active severe kidney disease treated with CYC or RTX for remission-induction (*n*=225)

Characteristic	CYC *n*=161 (64.1%)	RTX *n*=64 (25.5%)	Std. Diff. (%)[a]
Age at diagnosis of severe renal involvement, median (IQR) yr[b]	65 (55–74)	69 (59–75)	11.0
Male, *n* (%)	86 (53.4)	32 (50.0)	−6.0
AAV, *n* (%)			
MPA	83 (51.6)	35 (54.7)	6.2
GPA	78 (48.4)	29 (45.3)	−6.2
ANCA specificity (ELISA), *n* (%)			
MPO	95 (59.0)	38 (59.4)	0.8
PR3	66 (41.0)	26 (40.6)	−0.8
BVAS/WG at diagnosis, median (IQR)	8 (7–10)	8 (7–10)	0.0
Renal limited disease at diagnosis, *n* (%)	50 (31.1)	21 (32.8)	3.6
Rapidly progressive GN, *n* (%)	69 (42.8)	21 (26.6)	−34.5
Alveolar hemorrhage BVAS/WG at diagnosis, *n* (%)	27 (16.8)	10 (15.6)	3.3[c]
Biopsy proven, *n* (%)	145 (90.1)	52 (81.3)	−25.3
Cardiovascular risk factors, *n* (%)			
Arterial hypertension	119 (73.9)	48 (75.0)	2.5
Diabetes mellitus	38 (23.6)	13 (20.3)	−8.0
Dyslipidemia	59 (36.6)	26 (40.6)	8.2
BMI>30 kg/m^2	51 (33.6)	27 (49.1)	31.8
Laboratory findings			
Hemoglobin, mean (SD) g/dl	9.6 (8.6–10.7)	9.9 (8.9–11.1)	18.4
ESR>22 mm/1st h, *n* (%)	88 (83.0)	39 (76.5)	−16.2
eGFR at diagnosis of renal involvement, mean (SD) ml/min per 1.7 3m^2	15.6 (7.2)	17.7 (6.9)	29.7
eGFR at diagnosis of renal involvement <15 ml/min per 1.73 m^2, *n* (%)	71 (44.1)	24 (37.5)	−13.5[c]
eGFR at 6 mo, median (IQR)	28.8 (16.3–37.6)	30.5 (22.2–45.3)	13.4
eGFR at 12 mo, median (IQR)	29.9 (20.5–41.5)	31.5 (19.2–44.7)	0.0

eGFR is estimated using the Chronic Kidney Disease Epidemiology collaboration method. IQR, interquartile range; GPA, granulomatosis with polyangiitis; ESR, erythrocyte sedimentation rate.

[a]Standardized mean differences.

[b]Treatment was started on average within 16 h of the diagnosis of severe renal involvement.

[c]Variables used in the propensity score.

Table 4.

Outcomes of patients with AAV and active severe kidney disease treated with CYC or RTX for remission-induction (*n*=225)

Variable	Prematching			Postmatching[a]		
	CYC *n*=161 (64.1%)	RTX *n*=64 (25.5%)	*P* Value[b]	CYC *n*=60 (37.3%)	RTX *n*=60 (93.8%)	*P* Value[b]
Outcomes						
Vasculitis activity, *n* (%)						
Remission						
6 mo	105 (76.6)	50 (83.3)	0.291	45 (75.0)	49 (81.7)	0.375
Total	124 (87.9)	54 (87.1)	0.866	53 (93.0)	54 (91.5)	0.769
Complete remission						
6 mo	23 (17.7)	19 (31.7)	0.031	12 (25.0)	18 (31.6)	0.457
Total	72 (54.5)	38 (66.7)	0.178	31 (54.4)	37 (62.7)	0.096
Renal remission						
6 mo	110 (78.0)	52 (83.9)	0.338			
Total	125 (88.7)	54 (87.1)	0.752			
Relapse						
Total	52 (38.5)	23 (40.4)	0.812			
Renal relapse	26 (16.1)	16 (25.0)	0.135			
Death						
24 mo	13 (8.1)	8 (12.5)	0.303			
Total	47 (29.2)	12 (18.8)	0.108			
Renal recovery, *n* (%)						
ESKD						
24 mo	45 (28.0)	10 (15.6)	0.052			
Total	58 (36.0)	11 (17.2)	0.006			
Dialysis (total)	41 (25.5)	4 (6.3)	0.002			
Renal function recovery after 6 mo to an eGFR>30 ml/min per 1.73 m^2	47 (46.5)	22 (51.2)	0.611			
Combined events of ESKD and/or death, *n* (%)						

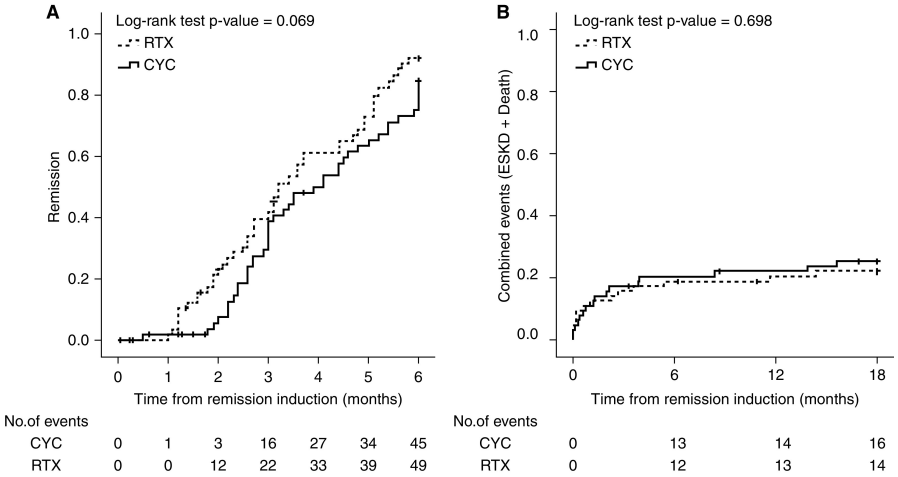
Population follow-up: 6 mo, CYC: *n*=137 versus RTX: *n*=57; 18 mo, CYC: *n*=120 versus RTX: *n*=51; 24 mo, CYC: *n*=112 versus RTX: *n*=49. IQR, interquartile range; FU, follow-up.

[a]The pairs used for the variables comparison after matching were obtained by analyzing the outcome of remission at 6 mo. Therefore, the comparisons pertaining to other outcomes are not shown.

[b]*P* value <0.05 is considered significant (Pearson chi-squared test for categoric variables, *t* test for continuous variables with normal distribution, and Mann–Whitney *U* test for continuous variables with skewed distribution).

[c]"Total" refers to the number of occurrences during all follow-up time.

Figure 3.



Remission and combined events after PS matching analysis. Kaplan–Meier plots of remission achieved over 6 months after initiating remission-induction therapy ([A] 60 CYC versus 60 RTX patients, 45 versus 49 events, time to event 4.1 versus 3.5 months, *P*=0.069), and combined events (ESKD and/or death) at 18 months ([B] 64 CYC versus 64 RTX patients, 16 versus 14 events, time to event 14.3 versus 14.7 months, *P*=0.698), according to the remission-induction immunosuppression, CYC versus RTX.

Table 5.

Risk for the outcome stratified by treatment after PS matching analysis

Variable	Post–PS Matching Analysis			
	Logistic Regression		Cox Regression	
	OR (95% CI)	*P* Value	IRR (95% CI)	*P* Value[a]
Remission at 6 mo				
RTX versus CYC	1.49 (0.62 to 3.57)	0.377	1.37 (0.91 to 2.08)	0.132
PLEX versus no PLEX	0.61 (0.23 to 1.63)	0.323	0.73 (0.44 to 1.22)	0.230
Relapse at 12 mo				
RTX versus CYC	1.81 (0.69 to 4.80)	0.230	1.61 (0.67 to 3.89)	0.289
PLEX versus no PLEX	1.90 (0.51 to 7.09)	0.337	0.53 (0.16 to 1.82)	0.315
Combined events of ESKD and/or death at 18 mo				
RTX versus CYC	0.84 (0.37 to 1.91)	0.677	0.87 (0.42 to 1.78)	0.699
PLEX versus no PLEX	1.11 (0.46 to 2.68)	0.822	1.05 (0.51 to 2.18)	0.891
Survival at 24 mo				
RTX versus CYC	1.69 (0.52 to 5.46)	0.384	1.57 (0.51 to 4.80)	0.429
PLEX versus no PLEX	0.53 (0.14 to 1.95)	0.340	0.54 (0.16 to 1.85)	0.329
ESKD at 24 mo				
RTX versus CYC	0.56 (0.23 to 1.34)	0.191	0.61 (0.28 to 1.35)	0.224
PLEX versus no PLEX	1.11 (0.45 to 2.74)	0.818	1.06 (0.50 to 2.25)	0.887
Combined events of ESKD and/or death at 24 mo				
RTX versus CYC	0.72 (0.32 to 1.60)	0.415	0.77 (0.38 to 1.54)	0.452
PLEX versus no PLEX	1.00 (0.42 to 2.40)	1.000	0.99 (0.48 to 2.02)	0.971

[a]*P* value <0.05 is considered significant.

Table 6.

Clinical characteristics of patients with AAV and active severe kidney disease according with the status of treatment with PLEX (*n*=251)

Characteristic	No PLEX *n*=200 (79.7%)	PLEX *n*=51 (20.3%)	Std. Diff. (%)[a]
Age at diagnosis of severe renal involvement, median (IQR) yr[b]	67 (55–75)	65 (56–74)	−3.5
Male, *n* (%)	97 (48.5)	31 (60.8)	24.9
AAV, *n* (%)			
MPA	120 (60.0)	20 (39.2)	−42.5
GPA	80 (40.0)	31 (60.8)	42.5
ANCA specificity (ELISA), *n* (%)			
MPO	134 (67.0)	22 (43.1)	−49.5
PR3	66 (33.0)	29 (56.9)	49.5
BVAS/WG at diagnosis, median (IQR)	7 (7–10)	9 (7–12)	39.7
Renal limited disease at diagnosis, *n* (%)	74 (37.0)	10 (19.6)	−39.3
Rapidly progressive GN, *n* (%)	74 (37.0)	23 (45.1)	16.5
Alveolar hemorrhage BVAS/WG at diagnosis, *n* (%)	25 (12.5)	15 (29.4)	42.4[c]
Biopsy proven, *n* (%)	178 (89.0)	44 (86.3)	−8.2
Cardiovascular risk factors, *n* (%)			
Arterial hypertension	151 (75.5)	36 (70.6)	−11.1
Diabetes mellitus	43 (21.5)	13 (25.5)	9.4
Dyslipidemia	71 (35.5)	20 (39.2)	7.7
BMI>30 kg/m^2	67 (36.0)	20 (44.4)	17.2
Laboratory findings			
Hemoglobin, mean (SD) g/dl	9.9 (9.0–11.3)	9.2 (7.9–10.0)	−64.6
ESR>22 mm/1st h, *n* (%)	122 (81.9)	23 (79.3)	−6.6
eGFR at diagnosis of renal involvement, mean (SD) ml/min per 1.73 m^2	16.8 (7.0)	14.1 (8.0)	−36.0
eGFR at diagnosis of renal involvement <15 ml/min per 1.73 m^2, *n* (%)	75 (37.5)	29 (56.9)	39.6[c]
eGFR at 6 mo, median (IQR)	29.9 (20.1–40.5)	27.7 (14.2–43.0)	−10.1
eGFR at 12 mo, median (IQR)	31.8 (21.2–42.0)	30.6 (22.1–49.2)	0.5

eGFR is estimated using the Chronic Kidney Disease Epidemiology collaboration method. IQR, interquartile range; GPA, granulomatosis with polyangiitis; ESR, erythrocyte sedimentation rate.

[a]Standardized mean differences.

[b]Treatment was started on average within 16 h of the diagnosis of severe renal involvement.

[c]Variables used in the propensity score.

Table 7.

Outcomes of patients with AAV and active severe kidney disease according with the status of treatment with PLEX (*n*=251)

Variable	Prematching			Postmatching[a]		
	No PLEX *n*=200 (79.7%)	PLEX *n*=51 (20.3%)	*P* Value[b]	No PLEX *n*=45 (22.5%)	PLEX *n*=45 (88.2%)	*P* Value[b]
Outcomes						
Vasculitis activity, *n* (%)						
Remission						
6 mo	132 (78.1)	36 (73.5)	0.497			
Total[c]	155 (88.6)	43 (87.8)	0.875			
Complete remission						
6 mo	35 (21.7)	11 (23.9)	0.754			
Total[c]	91 (52.0)	28 (57.1)	0.516			
Renal remission						
6 mo	139 (79.4)	38 (77.6)	0.775			
Total[c]	155 (88.6)	44 (89.8)	0.810			
Relapse						
12 mo	25 (13.1)	7 (14.9)	0.745			
Total[c]	62 (37.8)	19 (38.8)	0.902			
Renal relapse	36 (59.0)	10 (52.6)	0.623			
Death						
24 mo	18 (9.0)	4 (7.8)	0.794			
Total[c]	45 (22.5)	17 (33.3)	0.109			
Renal recovery, *n* (%)						
ESKD						
24 mo	42 (21.0)	17 (33.3)	0.064			
Total[c]	57 (28.5)	21 (41.2)	0.081			
Dialysis (total)	34 (17.0)	20 (39.3)	<0.0001	7 (15.5)	16 (35.5)	0.087
Renal function recovery after 6 mo to an eGFR>30 ml/min per 1.73 m^2	61 (50.0)	17 (44.7)	0.571			

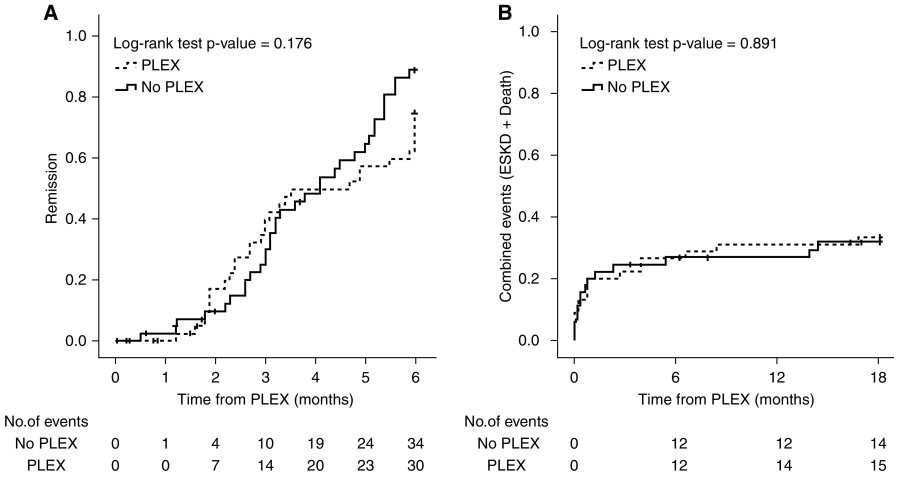
Population follow-up: 6 mo, no PLEX: *n*=172 versus PLEX: *n*=45; 12 mo, no PLEX: *n*=157 versus PLEX: *n*=45; 18 mo, no PLEX: *n*=147 versus PLEX: *n*=43; 24 mo, no PLEX: *n*=142 versus PLEX: *n*=39. IQR, interquartile range; FU, follow-up.

[a]The pairs resultant from the PS matching were obtained by the analysis of the outcome of combined events of ESKD and/or death at 18 mo. Therefore, the comparisons pertaining to other outcomes are not shown.

[b]*P* value <0.05 is considered significant (Pearson chi-squared test for categoric variables, *t* test for continuous variables with normal distribution, and Mann–Whitney *U* test for continuous variables with skewed distribution).

[c]"Total" refers to the number of occurrences during all follow-up time.

Figure 4.



Remission and combined events after PS matching analysis. Kaplan–Meier plots of remission achieved over 6 months after initiating remission-induction therapy ([A] 45 no PLEX versus 45 PLEX patients, 34 versus 30 events, time to event 4.0 versus 4.1 months, *P*=0.176), and combined events (ESKD and/or death) at 18 months ([B] 45 no PLEX versus 45 PLEX patients, 14 versus 15 events, time to event 13.3 versus 13.0 months, *P*=0.891), according to the status of treatment or no treatment with PLEX.