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Therapeutic plasma exchange (PLEX) is an adjunctive treatment for patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and kidney involvement. Little is known about the effect of PLEX on early changes in kidney function. This *post-hoc* analysis of the PEXIVAS trial investigated the effects of PLEX on changes in kidney function within 12 months. PEXIVAS was a randomized controlled trial recruiting 691 patients with ANCA-associated glomerulonephritis, of whom 349 underwent PLEX and 342 received no-PLEX. The primary outcomes of this *post hoc* study of PEXIVAS were change in estimated glomerular filtration rate (eGFR) from baseline and recovery of kidney function (defined as eGFR increase of 15ml/min/1.73m^2 or more). Baseline eGFR was 21.7 ± 20.3 and 20.6 ± 18.7 ml/min/1.73m^2 in the PLEX and no-PLEX groups, respectively. Mean improvements in eGFR at weeks two, four, and eight after initiation of therapy were greater for the PLEX vs. the no-PLEX groups. The greatest significant difference in recovery of kidney function in the PLEX compared to the no-PLEX groups was at week four (relative risk (RR): 1.41; 95% confidence interval:1.09-1.82). Increased eGFR or recovery of kidney function at week four were significantly associated with lower risk for end-stage kidney disease at week 52 (RR: 0.96: 0.95-0.97, and RR: 0.29: 0.16-0.52; respectively). Neither changes in eGFR nor recovery of kidney function differed by reduced- compared to standard-dose glucocorticoid group. Overall, our study indicates that PLEX improves early kidney function in patients with ANCA-associated glomerulonephritis.

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KEYWORDS: ANCA; end-stage kidney disease; glomerulonephritis; kidney function; plasma exchange; vasculitis

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Patients with anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) face a variable disease course, ranging from moderate disease to severe, life-threatening manifestations, including pulmonary hemorrhage and glomerulonephritis (GN), potentially leading to end-stage kidney disease (ESKD). ANCA may be pathogenic, and rapid reductions in ANCA levels may reduce organ damage and improve recovery of kidney function.[1] Therapeutic plasma exchange (PLEX), a method of reducing antibodies, was evaluated in AAV in several randomized controlled trials.

Lay Summary

Therapeutic plasma exchange (PLEX), a method of reducing antibodies, and different glucocorticoid (GC) dosing strategies were evaluated in anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) in several randomized controlled trials. However, little is known about the effect of PLEX and different GC doses on early changes in kidney function. We performed a *post hoc* analysis of an international, randomized, controlled trial (PEXIVAS [Plasma exchange and glucocorticoid dosing in the treatment of ANCA)-associated vasculitis: a multicentre randomized controlled trial]) studying the effects of PLEX and 2 GC dosing regimens on kidney outcomes in patients with ANCA-associated glomerulonephritis. In this analysis, we found that the addition of PLEX to standard immunosuppressive therapy increased early recovery of kidney function. At the same time, the use of a reduced-dose regimen of glucocorticoids resulted in similar kidney function outcomes to those observed with a standard-dose regimen. These findings might help to individualize treatment decisions when treating patients with AAV with kidney involvement and might improve longer-term kidney outcomes.

The effects of PLEX on important outcomes for patients with AAV varied across trials performed over the past 40 years. A meta-analysis of 9 randomized controlled trials found that the risk of kidney failure at 12 months was lower when PLEX was added to other immunosuppressive measures used in the induction of remission, but increased the risk of serious infections.[2] However, the outcome of kidney failure may be insensitive to the effects of PLEX on kidney function, and how the effects of PLEX on kidney function over time change remains uncertain.

This *post hoc* analysis of data from the PEXIVAS (Plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis: a multicentre randomized controlled trial) trial analyzed the effects of PLEX on changes in kidney function within the first year of initiating therapy, and the association between baseline patient characteristics and the recovery of kidney function. Moreover, further analyses were performed to investigate the effects of 2 glucocorticoid (GC) dosing regimens and ANCA serotype on kidney outcomes during this time period.

METHODS

Study design

The PEXIVAS trial was a multicenter, international, open-label, factorial design, randomized controlled trial to investigate the efficacy of adjunctive PLEX in addition to standard-of-care immunosuppressive therapy and the efficacy of 2 GC regimens (standard vs. reduced dose) in patients with AAV and estimated glomerular filtration rate (eGFR) <50 ml/min per 1.73 m^2 or lung hemorrhage (trial registration: NCT00987387).[3] Participants were randomized in a 2-by-2 factorial design, allowing a 1:1:1:1 ratio to receive PLEX followed by a standard-dose oral GC regimen, PLEX followed by a reduced-dose oral GC regimen, no-PLEX followed by a standard-dose oral GC regimen, or no-PLEX followed by a reduced-dose oral GC regimen. The full PEXIVAS study protocol is available at https://clinicaltrials.gov/study/NCT00987389.

Study participants

The PEXIVAS trial recruited 704 patients with AAV (myeloperoxidase [MPO]–ANCA or proteinase 3 [PR3]–ANCA positive) from 95 centers in 16 countries between June 2010 and September 2016. This analysis includes 691 participants from the original study who had kidney involvement, defined as a kidney biopsy demonstrating focal necrotizing GN or active urine sediment characterized by glomerular hematuria and proteinuria, and eGFR <50 ml/min per 1.73 m^2 (of note, patients with previously documented eGFR <60 ml/min per 1.73 m^2 required a decline of at least 25% of previous eGFR). Patients with pulmonary hemorrhage without kidney involvement were excluded from this analysis.

Outcomes

eGFR was calculated by using the “2021 Chronic Kidney Disease Epidemiology Collaboration creatinine” equation without race.[4] Primary end points were as follows: (i) the fixed point Δ change in eGFR from baseline at weeks 2, 4, 8, 12, 26, 39, and 52; and (ii) recovery of kidney function (as defined by an increase in eGFR of ≥15 ml/min per 1.73 m^2) at weeks 4, 26, and 52. Changes at week 4 were defined as early renal response and used to investigate the association with occurrence of ESKD at 52 weeks, that was defined as the requirement of kidney replacement therapy (hemodialysis or peritoneal dialysis) for at least 12 consecutive weeks or the receipt of a kidney transplant.

Secondary end points were as follows: (i) sustained low eGFR (defined as a persistent low eGFR [<15 ml/min per 1.73 m^2] at baseline sustained over at least 4 weeks, evidenced by 2 consecutive measurements); and (ii) frequency of participants with a decline in eGFR of at least 5 ml/min per 1.73 m^2 from baseline within 4 weeks after randomization.

Statistical analysis

Descriptive statistics are presented as mean (SD) or median (25th–75th percentile) for continuous variables, and as absolute and relative frequencies for categorical variables, unless otherwise noted.

The continuous outcome, absolute difference in eGFR (follow-up minus baseline value), was compared between the treatment groups PLEX versus no-PLEX and reduced versus standard GC by using a generalized estimation equation, with identity link function and normal distribution. Least square mean group differences (PLEX vs. no-PLEX and reduced GC vs. standard GC) and their corresponding 95% confidence intervals (CIs) at each of weeks 2, 4, 8, 12, 26, 39, and 52 were calculated.

For categorical outcomes, including renal recovery (yes/no), sustained low eGFR (yes/no), and decline in eGFR (yes/no), the treatment groups PLEX versus no-PLEX and reduced versus standard GC were compared using generalized estimation equations. Relative risks (RRs) and their 95% corresponding CIs were obtained using a log-binomial regression model. In case of multiple time points, the model terms treatment group, time, and PLEX group–time and GC group–time interactions were included. An unstuctured working correlation structure was used unless the model did not converge, in which case exchangeable correlation structures were used. The models were adjusted for the PLEX group, reduced- versus standard-dose GC, and the 5 minimization parameters used in randomization (age: <60 vs. ≥60 years; kidney function: serum creatinine level <5.66 mg/dl [500 μmol/l] vs. ≥5.66 mg/dl or use of dialysis; ANCA subtype: PR3 vs. MPO; severity of pulmonary hemorrhage: no hemorrhage vs. nonsevere hemorrhage vs. severe hemorrhage [defined as an oxygen saturation of ≤85% while the patient was breathing ambient air or the use of mechanical ventilation]; and planned type of induction immunosuppressive therapy: i.v. cyclophosphamide vs. oral cyclophosphamide vs. rituximab), consistent with the PEXIVAS trial's main protocol and Statistical Analysis Plan.[3]

For the primary end points, subgroup analyses according to baseline eGFR (0–15, 15–30, and >30 ml/min per 1.73 m^2), ANCA subtype (PR3-ANCA or MPO-ANCA), and dialysis dependency at baseline (yes vs. no, only for change in eGFR) were performed with the models described above but without adjustment for the minimization parameters because of failure of the models to converge.

Associations of occurrence of ESKD by 52 weeks with change in eGFR, recovery of kidney function, sustained low eGFR, and decline in eGFR at week 4 as covariates were each investigated with log binomial regression or log Poisson regression model, separately.

For the primary analysis, documented eGFR measurements were censored after development of ESKD, and no missing data imputation was done. As sensitivity analysis, measurements after ESKD were imputed with eGFR = 0, and last observation carried forward was applied for missing values (excluding missing values due to lost to follow-up, withdrawal, or death).

$P < 0.05$ was considered statistically significant. The results are exploratory, and no correction for multiple testing was performed. All analyses were performed by using SAS version 9.4 (SAS Institute).

RESULTS

Baseline characteristics

Of 704 randomized participants, 691 (98.2%) had kidney involvement and 342 were assigned to PLEX, 349 to no-PLEX, 346 to reduced-dose GC, and 345 to standard-dose GC. Baseline characteristics were similar for patients receiving PLEX and no-PLEX and reduced or standard dose of GC. When categorized by ANCA serotype, 279 patients had PR3-AAV and 412 had MPO-AAV, of whom 138 (49.4%) and 204 (49.5%) received PLEX, respectively. Detailed characteristics of patients receiving or not receiving PLEX in the whole study cohort, in those with different GC dosing regimen, and PR3-AAV and MPO-AAV are shown in Table 1 and Supplementary Tables S1 and S2, respectively.

Outcomes related to treatment by PLEX

Change in eGFR from baseline. Baseline eGFR was 21.7 ± 20.3 and 20.6 ± 18.7 ml/min per 1.73 m^2 in the PLEX and no-PLEX groups, respectively. The mean eGFR change from baseline was higher in the PLEX group compared with the no-PLEX group at weeks 2, 4, and 8, but did not differ at any later predefined time points, as shown in Figure 1 and Supplementary Table S3. The mean difference in eGFR change from baseline for the PLEX compared with the no-PLEX group was 4.8 (95% CI, 2.9–6.9) ml/min per 1.73 m^2 at 2 weeks, 4.2 (95% CI, 2.0–6.4) ml/min per 1.73 m^2 at 4 weeks, and 4.3 (95% CI, 1.5–7.0) ml/min per 1.73 m^2 at 8 weeks.

Subgroup analyses for different eGFR thresholds and for ANCA subtypes revealed no treatment-subgroup-time interactions ($P = 0.487$ and $P = 0.602$, respectively). Descriptive results stratified by subgroups are presented in Supplementary Figures S1 and S2. Similarly, no interaction was observed, when patients on dialysis at baseline were analyzed ($P = 0.339$). In the subgroup of patients with a baseline eGFR of <15 ml/min per 1.73 m^2, 118 (34.7%) required kidney replacement therapy at baseline. Data on ESKD and mortality rates according to the eGFR thresholds are summarized in Supplementary Table S4.

Recovery of kidney function. The number of participants with recovery of kidney function was 103 (32.7%) at 4 weeks, 159 (56.8%) at 26 weeks, and 170 (64.9%) at 52 weeks in the PLEX group compared with 73 (23.0%) at 4 weeks, 144 (54.8%) at 26 weeks, and 146 (58.2%) at 52 weeks in the no-PLEX group. The RR of recovery of kidney function in the PLEX group compared with the no-PLEX group was 1.41 at week 4 (95% CI, 1.09–1.82; $P = 0.008$), 1.09 at week 26 (95% CI, 0.94–1.26; $P = 0.268$), and 1.16 at week 52 (95% CI, 1.02–1.33; $P = 0.028$), as summarized in Table 2. Subgroup analyses by the baseline eGFR thresholds and by ANCA subtypes revealed no treatment-subgroup-time interactions ($P = 0.367$ and $P = 0.682$, respectively). Descriptive results stratified by subgroups are presented in Supplementary Tables S5 and S6.

Sustained low eGFR and eGFR decline. In total, 115 patients (18.5%) had a sustained low eGFR over at least 4 weeks after randomization, of whom 49 (15.7%) received PLEX and 66 (21.3%) were not treated with PLEX (RR, 0.76; 95% CI, 0.57–1.01; $P = 0.058$; Table 2).

At week 4, 11 (3.5%) of PLEX and 21 (6.6%) of no-PLEX treated patients had a decline in eGFR of at least 5 ml/min per 1.73 m^2 from baseline. The risk for decline in eGFR did not differ in the PLEX group compared with the group without PLEX (RR, 0.53; 95% CI, 0.26–1.06; $P = 0.081$; Table 2).

Table 1 | Baseline characteristics of patients without and with PLEX

	Patients no-PLEX (N = 349)	Patients with PLEX (N = 342)
Age, yr Median (25th–75th percentile)	65 (57–73)	65 (55–72)
Female gender, n (%)	156 (44.7)	144 (42.1)
BMI, kg/m^2 Median (25th–75th percentile)	25.7 (23.6–30.1)	26.5 (23.4–30.3)
Baseline BVAS/GPA Median (25th–75th percentile)	8 (6–10)	8 (6–11)
History of vasculitis, n (%)	27 (7.7)	31 (9.7)
ANCA serotype, n (%)		
Anti-PR3	141 (40.4)	138 (40.4)
Anti-MPO	208 (59.6)	204 (59.6)
Pulmonary hemorrhage, n (%)		
Not severe	65 (18.6)	61 (17.8)
Severe	30 (8.6)	28 (8.2)
Dialysis, n (%)	74 (21.2)	64 (18.7)
Organ involvement, n (%)		
Lung	148 (42.4)	140 (40.9)
Heart	4 (1.1)	6 (1.8)
Ear, nose, and throat	103 (29.5)	94 (27.5)
Mucous membranes/eyes	16 (4.6)	20 (5.8)
Cutaneous	39 (11.2)	36 (10.5)
Nervous system	25 (7.2)	37 (10.8)
Glucocorticoid dose regimen, n (%)		
Standard	174 (49.9)	171 (50.0)
Reduced	175 (50.1)	171 (50.0)
Planned immunosuppressive therapy, n (%)		
i.v. cyclophosphamide	176 (50.4)	172 (50.3)
Oral cyclophosphamide	120 (34.4)	117 (34.2)
Rituximab	53 (15.2)	53 (15.5)
Laboratory results		
Creatinine, μmol/l[a] Median (25th–75th percentile)	336 (209–491)	327 (212–491)
Creatinine <500 μmol/l n (%)	245 (70.2)	243 (71.1)
Creatinine ≥500 μmol/l n (%)[b]	104 (29.8)	99 (28.9)
eGFR, ml/min per 1.73 m^2 Mean (±SD)	21.7 (20.3)	20.6 (18.7)
Hemoglobin, g/l Median (25th–75th percentile)	95 (85–106)	94 (83–105)

ANCA, anti-neutrophil cytoplasmic antibody; BMI, body mass index; BVAS, Birmingham Vasculitis Activity Score; eGFR, estimated glomerular filtration rate; GPA, granulomatosis with polyangiitis; MPO, myeloperoxidase; PLEX, plasma exchange; PR3, proteinase 3.
[a]Creatinine: <500 μmol/l = <5.66 mg/dl.
[b]Or on dialysis.

End-stage kidney disease. At week 52, ESKD rates were 14.0% (48/342) and 16.9% (59/349) in the PLEX and no-PLEX groups, respectively. To assess the consequence of immediate effects of PLEX on renal outcome at week 52, the association between predefined end points at week 4 and ESKD rate was analyzed. Patients with greater eGFR improvement at week 4 had a lower risk of ESKD at week 52. In addition, patients with sustained low eGFR were at increased risk to develop ESKD at week 52. Detailed results are summarized in Table 3.

Outcomes related to treatment by different GC regimen

Change in eGFR from baseline. Baseline eGFR was 22.2 ± 20.7 and 20.1 ± 18.3 ml/min per 1.73 m^2 in the reduced-dose GC and standard-dose GC groups, respectively. The mean change from baseline eGFR did not differ between the reduced-dose and standard-dose GC groups at any predefined time points (Figure 2), whereas mean differences in eGFR change from baseline for the reduced-dose GC compared with the standard-dose GC group are summarized in Supplementary Table S3.

Subgroup analyses for different eGFR thresholds and for ANCA subtypes revealed no significant treatment-subgroup-time interactions ($P = 0.602$ and $P = 0.773$, respectively). Descriptive results stratified by subroups are presented in Supplementary Figures S3 and S4. Similarly, no interaction was observed for the subgroup of patients on dialysis versus not on dialysis at baseline ($P = 0.467$).

Recovery of kidney function. The number of participants with recovery of kidney function were 88 (27.8%) at 4 weeks, 150 (53.2%) at 26 weeks, and 158 (59.2%) at 52 weeks in the reduced-dose GC group compared with 88 (27.9%) at 4 weeks, 153 (58.6%) at 26 weeks, and 158 (64.2%) at 52 weeks in the standard-dose GC group. The RR of recovery of kidney function in the reduced-dose GC group compared with the standard-dose GC group was 0.98 at week 4 (95% CI, 0.77–1.26; $P = 0.884$), 0.92 at week 26 (95% CI, 0.80–1.07; $P = 0.286$), and 0.89 at week 52 (95% CI, 0.78–1.02; $P = 0.083$), as summarized in Table 4. Subgroup analyses for different eGFR thresholds or for ANCA subtypes revealed no treatment-subgroup-time interactions ($P = 0.299$ and $P = 0.950$, respectively). Descriptive results stratified by subroups are presented in Supplementary Tables S5 and S6.

Sustained low eGFR and eGFR decline. The number of participants with sustained low eGFR over at least 4 weeks after randomization was 54 (17.4%) in the reduced-dose GC and 61 (19.6%) in the standard-dose groups (RR, 0.89; 95% CI, 0.68–1.17; $P = 0.411$; Table 4).

At week 4, 18 (5.7%) of patients receiving reduced-dose GC and 14 (4.4%) receiving standard-dose GC had a decline in eGFR of at least 5 ml/min per 1.73 m^2 from baseline (RR, 1.26; 95% CI, 0.64–2.48; $P = 0.508$; Table 4).

Outcomes in patients with PR3-AAV and MPO-AAV

Change in eGFR from baseline. Improvement in eGFR was higher in patients with PR3-AAV compared with those with MPO-AAV from week 4 throughout all further predefined time points, as shown in Figure 3.

Recovery of kidney function. The number of participants with recovery of kidney function was 85 (33.2%) at 4 weeks, 140 (60.3%) at 26 weeks, and 145 (66.2%) at 52 weeks in the PR3-AAV group compared with 91 (24.2%) at 4 weeks, 163

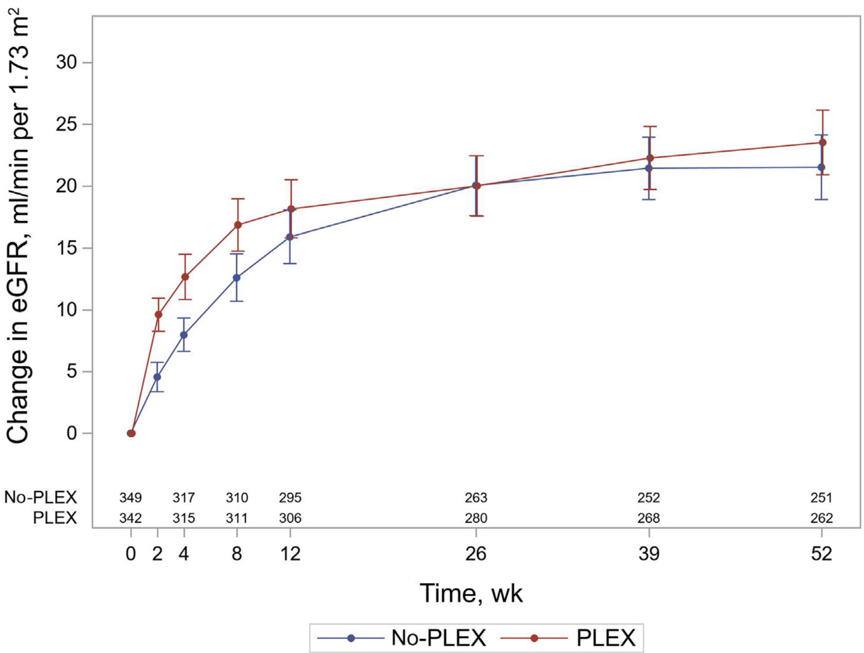

Figure 1 | Change in estimated glomerular filtration rate (eGFR) from baseline over the course of the 52-week observational period in patients receiving plasma exchange (PLEX) (red line) and no-PLEX (blue line). Data are presented as means and 95% confidence intervals. The mean change from baseline eGFR was higher in the PLEX group compared with the no-PLEX group at weeks 2, 4, and 8 ($P < 0.01$).

(52.4%) at 26 weeks, and 171 (58.2%) at 52 weeks in the MPO-AAV group. The RR of recovery of kidney function in the PR3-AAV group compared with the MPO-AAV group was 1.39 at week 4 (95% CI, 1.08–1.78; $P = 0.011$), 1.19 at week 26 (95% CI, 1.03–1.38; $P = 0.021$), and 1.19 at week 52 (95% CI, 1.04–1.37; $P = 0.012$).

Sustained low eGFR and eGFR decline. Patients with PR3-AAV had a lower risk for sustained low eGFR compared with patients with MPO-AAV (RR, 0.54; 95% CI, 0.37–0.79; $P = 0.002$). Nevertheless, no difference in risks for decline in eGFR were found at week 4.

DISCUSSION

This *post hoc* analysis of the PEXIVAS trial investigated the effects of PLEX, 2 GC dosing regimens, and ANCA serotype on kidney outcomes within the first 52 weeks of enrollment in patients with ANCA-associated GN. The addition of PLEX to standard immunosuppressive therapy increased early recovery of kidney function. Importantly, the use of a reduced-dose regimen of GC resulted in similar kidney function outcomes to those observed with a standard-dose regimen. Patients with PR3-AAV had better recovery of kidney function during the first year, but ANCA serotype did not modify the response to PLEX.

In this analysis, the use of PLEX resulted in greater absolute improvement in eGFR within the first 8 weeks after therapy initiation and recovery of kidney function at week 4. A recent meta-analysis of PLEX randomized clinical trials using data from a total of 999 patients with AAV, of whom 704 were from the PEXIVAS trial, showed a 42% RR reduction of ESKD at 12 months in patients treated with PLEX.[2] Similarly, in the MEPEX (Methylprednisolone Versus Plasma Exchange for Renal Vasculitis) trial, PLEX led to a greater improvement of kidney function at 3 months, which was associated with better ESKD outcomes at 1 year.[5] Why the effect of PLEX on kidney function attenuates on the longer-term in the PEXIVAS trial is unclear. It might reflect that standard therapy, comprising higher doses of GCs and

Table 2 | Effects of plasma exchange on measures of kidney function in patients with ANCA-associated GN in the PEXIVAS trial

Outcome	Week 4	*P* value	Week 26	*P* value	Week 52	*P* value
Recovery of kidney function	1.41 (1.09–1.82)	0.008	1.09 (0.94–1.26)	0.268	1.16 (1.02–1.33)	0.028
Sustained low kidney function	0.76 (0.57–1.01)	0.058	–	–	–	–
Decline in eGFR	0.53 (0.26–1.08)	0.081	–	–	–	–

–, analysis not performed; ANCA, anti-neutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; PEXIVAS, Plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis: a multicentre randomized controlled trial.

Data are expressed as relative risk (95% confidence interval). Definitions: recovery of kidney function: an increase in eGFR of ≥15 ml/min per 1.73 m^2; sustained low eGFR: persistent low eGFR (<15 ml/min per 1.73 m^2) at baseline sustained over at least 4 weeks, evidenced by 2 consecutive measurements; decline in eGFR: a decline in eGFR of at least 5 ml/min per 1.73 m^2 from baseline within 4 weeks after randomization.

Table 3 | Relative risk estimates of primary and secondary end points at week 4 on rate of end-stage kidney disease at week 52 in the PEXIVAS trial

Change in eGFR	Mean (±SD)		HR (95% CI)	*P* value
Patients without ESKD	11.7 (15.0)		0.95 (0.94–0.94)	<0.001
Patients with ESKD	2.2 (8.7)			
Recovery of kidney function	**Yes**	**No (reference)**		
Patients with ESKD	4 (2.3)	86 (18.9)	0.12 (0.04–0.32)	<0.001
Sustained low eGFR	**Yes**	**No (reference)**		
Patients with ESKD	54 (47.0)	33 (6.5)	7.21 (4.92–10.58)	<0.001
Decline in eGFR	**Yes**	**No (reference)**		
Patients with ESKD	6 (18.8)	84 (14.0)	1.34 (0.63–2.83)	0.444

CI, confidence interval; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; PEXIVAS, Plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis: a multicentre randomized controlled trial.
Data are expressed as number of patients (percentage). Definitions: recovery of kidney function: an increase in eGFR of ≥15 ml/min per 1.73 m^2; sustained low eGFR: persistent low eGFR (<15 ml/min per 1.73 m^2) at baseline sustained over at least 4 weeks, evidenced by 2 consecutive measurements; decline in eGFR: a decline in eGFR of at least 5 ml/min per 1.73 m^2 from baseline within 4 weeks after randomization.

cyclophosphamide or rituximab used to induce remission, is already an effective measure to control disease. In addition, trial-related visits might also allow for optimized surveillance of patients and initiation of nonimmunosuppressive therapies with the potential to reduce progression of chronic kidney disease.

The association between better early kidney function and a lower risk of kidney failure at 52 weeks may suggest that rapidly effective therapies beyond early and prompt diagnosis may improve long-term outcomes, which could, in turn, mean that kidney function is a reliable longitudinal predictor of the effect of other immunosuppressive or adjunctive therapies. It remains unclear why the absolute differences in eGFR between the PLEX and no-PLEX group are not seen beyond week 8, but we speculate that mechanisms contributing to kidney inflammation contribute to the immediate effects of PLEX, leading to reduction of pathogenic factors, such as constituents of the complement cascade and ANCA, which, in turn, lead to early improvement in kidney function. Direct and indirect effects of PLEX on endothelial dysfunction or limiting transition of acute lesions to chronic damage might play a critical role.[6] In line, the number of PLEX

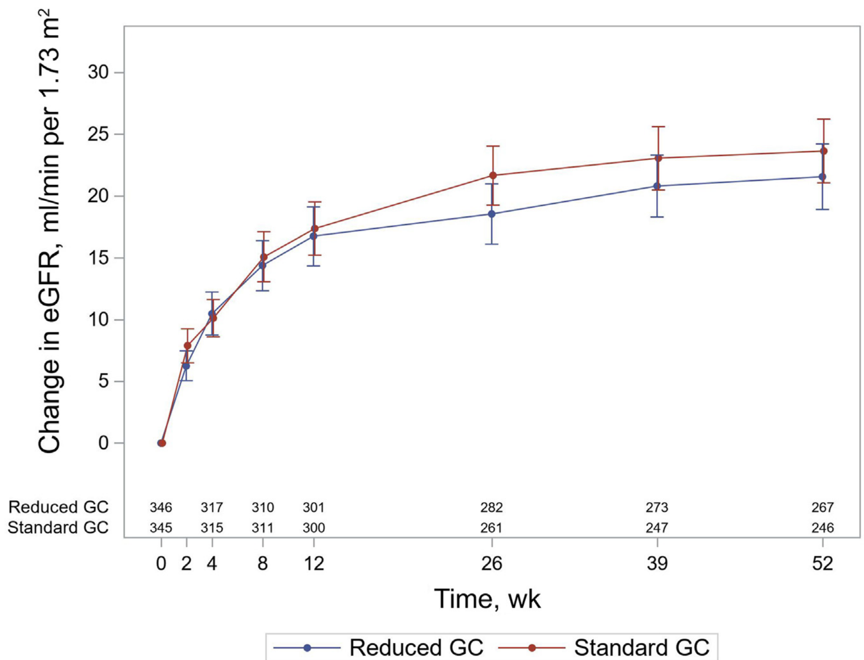

Figure 2 | Change in estimated glomerular filtration rate (eGFR) from baseline over the course of the 52-week observational period in patients receiving reduced (blue line) and standard (red line) glucocorticoid (GC) regimen. Data are presented as means and 95% confidence intervals. The mean change from baseline eGFR did not differ between the groups throughout the observational period ($P >$ 0.05).

Table 4 | Effects of reduced glucocorticoids compared with standard glucocorticoids on measures of kidney function in patients with ANCA-associated GN in the PEXIVAS trial

Outcome	Week 4	*P* value	Week 26	*P* value	Week 52	*P* value
Recovery of kidney function	0.98 (0.77–1.26)	0.884	0.92 (0.80–1.07)	0.286	0.89 (0.78–1.02)	0.083
Sustained low kidney function	0.89 (0.68–1.17)	0.411	–	–	–	–
Decline in eGFR	1.26 (0.64–2.48)	0.508	–	–	–	–

–, analysis not performed; ANCA, anti-neutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; PEXIVAS, Plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis: a multicentre randomized controlled trial.
Data are expressed as relative risk (95% confidence interval). Definitions: recovery of kidney function: an increase in eGFR of ≥15 ml/min per 1.73 m^2; sustained low eGFR: persistent low eGFR (<15 ml/min per 1.73 m^2) at baseline sustained over at least 4 weeks, evidenced by 2 consecutive measurements; decline in eGFR: a decline in eGFR of at least 5 ml/min per 1.73 m^2 from baseline within 4 weeks after randomization.

sessions might be an important factor to reach sufficiently suppressed antibody levels, that, in turn, contributes to the positive effects of PLEX on the long-term. However, a recent French prospective study indicated that 7 sessions of PLEX reduced ANCA by >90%, arguing that more sessions might not be of further help to reduce ANCA titers.[7] Nevertheless, the use of a higher dose of GC did not result in a greater kidney function recovery in this analysis. Similarly, the results of the ADVOCATE (Avacopan for the Treatment of ANCA-Associated Vasculitis) trial showed better kidney function outcomes with the use of avacopan after 3 months but not before,[8] suggesting a longer period of disease activity in the kidney. Further research is needed to understand the determinants of kidney outcomes in ANCA-associated GN and how different therapies and timing of their use might be best leveraged.

Patients with PR3-AAV showed greater improvement in eGFR and recovery of kidney function, whereas fewer patients had sustained low eGFR in comparison to those with MPO-AAV. Distinct genetic backgrounds and differences in kidney involvement due to antigen specificity are well known in AAV.[9–11] Recent data from a retrospective analysis revealed that slowly progressive kidney disease is more frequent in patients with MPO-AAV compared with PR3-AAV,[12,13] with such patients having more sclerosis on kidney biopsies, which reflect chronic irreversible damage and is associated with worse kidney outcomes.[13–15] In contrast, kidney lesions in PR3-AAV are more active with potential reversibility and associated with better kidney outcomes.[16] Despite this disparity, the stratified analysis by ANCA serotype found no differences in the effects of PLEX or GC regimens on changes in kidney function. This observation indicates that considering ANCA serology does not add extra value to personalized risk assessment for the use of PLEX, as has been propsed by a large retrospective study.[17] In this analysis, MPO-AAV was more frequent in the patient group having a benefit from the addition of PLEX.

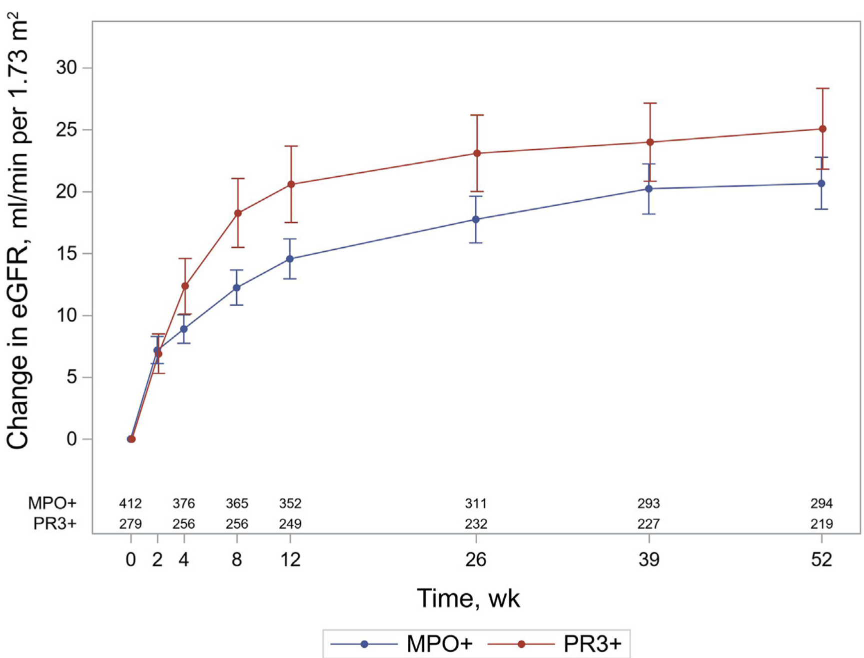

Figure 3 | Change in estimated glomerular filtration rate (eGFR) from baseline over the course of the 52-week observational period in patients with proteinase 3 (PR3)–anti-neutrophil cytoplasmic antibody (ANCA) (red line) and myeloperoxidase (MPO)–ANCA (blue line). Data are presented as means and 95% confidence intervals. Statistically significant differences ($P < 0.01$) were observed from 2 up to 52 weeks.

This study has several limitations. First, data on proteinuria and histopathologic review of the kidney specimens were not available for this analysis. In the MEPEX trial, patients treated with PLEX had higher rates of recovery of kidney function when presenting with predominantly (>50%) crescentic changes in the kidney histology, which is known to be associated with better outcomes.[18] Therefore, an unbalanced proportion of distinct histopathologic classes might result in different outcomes in this study population; however, given the size of the study population, randomization should have mitigated such a bias. Furthermore, eGFR-based surrogates of kidney outcomes need to be better established because there are no established methods for assessing recovery of kidney function in the population with AAV. The use of eGFR is limited in the setting of acute kidney injury and might limit the interpretation of differences in kidney function when it is rapidly changing. However, this analysis used 2 methods: increase in eGFR from baseline and an increase in eGFR of $\geq$15 ml/min per 1.73 m^2, and an impact of PLEX was demonstrated with both methods. Moreover, epidemiologic studies revealed a strong association between categorial changes in eGFR and all-cause mortality in patients with chronic kidney disease, whereas sustained low eGFR is an established surrogate for representing substantial loss of kidney function.[19,20] Furthermore, this analysis did not report the effect of nonrandomized immunosuppressive agents (namely, cyclophosphamide [either i.v. or per oral] and rituximab) on early renal response. However, prior data from RAVE (Rituximab Therapy for the Induction of Remission and Tolerance in ANCA-Associated Vasculitis) and RITUXVAS (An international, randomised, open label trial comparing a rituximab-based regimen with a standard cyclophosphamide/azathioprine based regimen in the treatment of active, generalised anti-neutrophilic cytoplasmic antibodies associated vasculitis) did not reveal differences in renal response between patients receiving rituximab and cyclophosphamide as part of their induction therapy.[21,22] PLEX also lowers serum creatinine because of short-term dilution by fluid loading that might bias its true effect on kidney function. Nevertheless, this diluting effect only lasts for a few hours after treatment, accounting for <5% of intravascular volume, and should not influence later eGFR evaluation. Finally, the question of whether successful removal of ANCA antibodies mediates the effects of PLEX on early kidney outcomes remains unclear from our research.

In conclusion, the addition of PLEX to standard immunosuppressive treatments leads to improvement in early kidney function, which may explain its benefits on kidney outcome at 52 weeks. The use of reduced-dose GC does not negatively impact kidney function at any time point in the first year. Rapid treatment effects may improve longer-term kidney outcomes and help differentiate treatment effects in patients with ANCA-associated GN. Finally, ANCA serology is an important tool in subclassifying patients with AAV; however, these results do not provide evidence for its role as a reliable biomarker in individualized therapy.

APPENDIX

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DATA STATEMENT

Following publication of all protocol-listed tertiary outcomes of the PEXIVAS trial, anonymized data can be requested by investigators whose proposed use of the data has been approved by the PEXIVAS Publications Committee for substudies and ancillary analyses with scientific merit that can be validly addressed with PEXIVAS data. Investigators may propose a substudy or analysis requiring PEXIVAS data by submitting a proposal to the PEXIVAS Publications Committee through 1 of the principal investigators. Approved substudies/analyses will provide a list of specific data items required, an analysis plan, evidence of sufficient capacity to conduct the proposed study, and enter into a data sharing agreement before the release of PEXIVAS data.

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