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CLINICAL RESEARCH

Kidney Outcomes in ANCA-Glomerulonephritis According to Induction Immunosuppression and Histopathology

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Introduction: Cyclophosphamide (CYC) and rituximab (RTX), alone or combined, are the mainstays of induction therapy in antineutrophil cytoplasmic autoantibody (ANCA)-glomerulonephritis. It is unknown whether the response to induction is differentially affected by kidney histopathology.

Methods: This is a retrospective, multicenter study including patients with biopsy-proven ANCA-glomerulonephritis. Cases were grouped according to the Berden nephropathology classification. Estimated glomerular filtration rate (eGFR) recovery at 6 months was defined as eGFR increase $\geq$ 15 ml/min per 1.73 m^2 or discontinuation of kidney replacement therapy (KRT); kidney failure was defined as sustained eGFR $<$ 15 ml/min per 1.73 m^2 or long-term KRT. Multivariable regression models were used to explore independent predictors of kidney outcomes across Berden classes.

Results: The cohort included 304 patients; median baseline eGFR was 20 ml/min per 1.73 m^2 (interquartile range [IQR]: 11–35). Induction immunosuppression was with CYC in 59%, with RTX in 17%, and with RTX-CYC in 24%. Overall, 50% recovered kidney function and 19.4% had kidney failure over a median follow-up of 42 months (IQR: 18–72). In the crescentic class, the RTX group had lower chances of eGFR recovery than CYC (odds ratio [OR]: 0.23, 95% confidence interval [CI]: 0.05–0.98, $P = 0.047$); the trend was similar in comparison with RTX-CYC (OR: 0.20, 95% CI: 0.03–1.19, $P = 0.077$). In the crescentic class, RTX monotherapy was marginally associated with increased risk of kidney failure, compared with both CYC (hazard ratio [HR]: 3.42, 95% CI: 1.03–11.35, $P = 0.045$) and RTX-CYC (HR: 5.33, 95% CI: 0.91–31.18, $P = 0.063$). No significant differences were observed in the other Berden classes.

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Conclusion: Patients with crescentic class ANCA-glomerulonephritis receiving RTX monotherapy may have worse kidney outcomes than those treated with CYC-based regimens. Further studies are needed to validate these results and better understand how to personalize treatment.

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ANCA-associated vasculitides (AAV) are rare autoimmune diseases characterized by inflammation of small vessels.[1] Kidney involvement is one of the most severe manifestations, with a significant impact on long-term prognosis.[2] The prototypical kidney involvement consists of paucimmune crescentic glomerulonephritis presenting as rapidly progressive kidney failure; a slowly progressive form is a less common variant.[3,4] Although not mandatory in cases with a typical clinical picture, kidney biopsy plays an important role in confirming diagnosis and providing important prognostic information. In 2010, Berden and colleagues proposed a histopathological classification system defining 4 histological classes based on the predominant glomerular lesions: focal ($\geq$ 50% of normal glomeruli), crescentic ($\geq$ 50% glomeruli with cellular crescents), sclerotic ($\geq$ 50% glomeruli globally sclerotic) and mixed class ($<$ 50% normal, $<$ 50% crescents, $<$ 50% globally sclerotic glomeruli). As reported in the initial study and in several independent validation cohorts,[5,6] this classification consistently showed a robust association with kidney prognosis, with outcomes being most favorable in the focal class, worst in the sclerotic one and intermediate in the crescentic and mixed group. In 2022, the Mayo clinic group further demonstrated the prognostic relevance of chronic kidney histological changes at the glomerular, tubulointerstitial, and vascular level, as assessed by the Mayo Clinic chronicity score.[7] Importantly, histological features, when combined with clinical information, improved the predictive power of composite scores, as demonstrated by the ANCA kidney risk score[8] and its recently revised version.[9]

Current standard-of-care for induction therapy consists of a combination immunosuppressive therapy, namely CYC and/or RTX, and glucocorticoids (GCs, both i.v. and oral), with avacopan recently added to the therapeutic armamentarium as an alternative or additional agent to GCs.[10,11] Although RTX has become established as first line treatment for induction of remission in most scenarios, it remains unclear whether CYC may remain preferable in some specific contexts.

Data on the use of RTX in patients with the most severe forms of kidney involvement are scarce. In the RAVE trial that compared an RTX- to a CYC-based induction regimen, kidney outcomes appeared comparable across the 2 arms.[12,13] However, patients with the most severe kidney presentations (serum creatinine $>$ 4 mg/dl) were excluded from this study. The only randomized clinical trial testing RTX and including patients with severe kidney involvement was RITUXVAS.[14,15] In this context, outcomes with the combination of RTX and low-dose CYC (2, maximum 3 i.v. infusions) were similar to standard CYC induction. The question of the effectiveness of RTX monotherapy in severe ANCA-glomerulonephritis therefore remained open, whereas the RTX-CYC combination emerged as an option.

This gap of knowledge regarding RTX use in severe kidney impairment has been addressed in retrospective case series, where no significant differences in kidney outcomes between RTX and CYC emerged.[16–18]

Previous studies on kidney outcomes did not examine whether histopathologic lesions may influence the efficacy of different immunosuppression therapies. To close this gap, this multicentric, retrospective study aimed to assess how different induction therapy approaches affect kidney outcomes in ANCA-glomerulonephritis, focusing on groups of patients with homogeneous kidney histological features.

METHODS

Patient Cohort

Patients with a diagnosis of granulomatosis with polyangiitis or microscopic polyangiitis with kidney involvement and available kidney biopsy information were identified at 11 European expert centers within the European Vasculitis Society (EUVAS) network. Cases were classified as granulomatosis with polyangiitis or microscopic polyangiitis according to the European Medicines Agency algorithm.[19] The inclusion criteria were as follows: (i) biopsy-proven ANCA-associated glomerulonephritis (biopsy performed within 6 months from the onset of active kidney involvement), (ii) induction treatment for active disease with RTX, CYC, or a combination of both RTX and CYC, defined as administration of the 2 drugs within a period of $\leq$ 6 months, and (iii) follow-up of $\geq$ 6 months (or shorter in case of death). Patients with

eosinophilic granulomatosis with polyangiitis, secondary forms of AAV, concomitant cancer, infections, or other systemic autoimmune disorders were excluded. The study was conducted in accordance with the Declaration of Helsinki and in compliance with local ethics requirements.

Data Collection and Outcomes

Clinical data and histopathological reports were collected using retrospective chart review. Sex was recorded from health records as female or male (sex assigned at birth). Kidney biopsy reports were assessed and categorized according to the Berden classification.[6]

Kidney remission was defined as a Birmingham Vasculitis Activity Score (version 3)[20] of 0 for kidney items and confirmation of achievement of kidney remission by the treating physician. Remission was assessed 6 months after induction therapy. If remission data at 6 months was unavailable, the closest available data point between 6 and 12 months was used.

eGFR was calculated using the 2009 Chronic Kidney Disease-Epidemiology Collaboration formula.[21] In case of patients on KRT, a conventional eGFR value of 5 ml/min per 1.73 m^2 was assigned.

The composite outcome of eGFR recovery at 6 months was defined as an absolute increase in eGFR at 6 months $\geq$ 15 ml/min per 1.73 m^2 compared to baseline, or for patients requiring KRT at baseline, as the ability to discontinue KRT.

The composite outcome of kidney failure was defined as either sustained eGFR $<$ 15 ml/min per 1.73 m^2 (confirmed during 2 consecutive encounters $\geq$ 3 months apart from each other and occurring $>$ 6 months after induction therapy), or long-term KRT (start of chronic dialysis or kidney transplantation).

Statistical Analysis

Results were presented as percentages for categorical variables and median with IQR or mean $\pm$ SD for continuous variables, as appropriate. Differences between groups were tested using Fisher exact tests for categorical variables and the Kruskal-Wallis rank sum test or analysis of variance for continuous variables. *P*-values $<$ 0.05, 2 sided, were considered significant. In case of significant results in the initial test comparing multiple groups, *post hoc* pairwise comparisons were performed using Fisher exact, Mann-Whitney U, or *t* tests, with Hommel's method to correct for multiple testing. Statistical analysis and plots were generated using R version 4.4.1[22] and the packages, tidyr, tableone, ggplot2 , ggsci, and ggpubr.

Survival curves were generated using the Kaplan-Meier estimator and outcomes were compared between groups with the log-rank test, using the R packages survival[23] and survminer.[24]

Multivariable logistic regression and Cox proportional hazard regression models were used to test independent predictors of eGFR recovery at 6 months and kidney failure, respectively. The models were adjusted for baseline clinical features and other treatment-related variables. In case of limited number of events per predictors, Firth's penalized logistic regression models or Cox models with Firth's penalized partial likelihood were used to mitigate small-sample bias, as implemented in the R packages logistf[25] and coxphf.[26] Variables with a proportion of missing values exceeding 10% were not included in the models. For variables with $<$ 10% missing values, multiple imputation by chained equations was performed using the R package, mice.[27] Outcome variables were included as predictors in the imputation model but were not imputed. For the kidney failure outcome, the Nelson-Aalen cumulative hazard was calculated and used as an auxiliary variable in the imputation model, following the approach described by White and Royston.[28] Five imputed datasets were generated; modelling was performed separately in each imputed dataset, and resulting estimates were pooled according to Rubin's rules[29] with the Barnard-Rubin small-sample correction.[30]

RESULTS

Clinical Characteristics

Overall Study Cohort

A total of 304 patients with active biopsy-proven ANCA-glomerulonephritis, diagnosed between 1997 and 2019 in 11 centers were included. Most patients were classified as microscopic polyangiitis (n = 182, 61.1%) and had new onset disease (293/304, 96.4%). The median follow-up was 42 months (IQR: 18–72). In Table 1, we show clinical, laboratory, and histopathological characteristics at the time of diagnosis in the overall cohort. Mean age was 61 $\pm$ 13 years and 59.5% of patients were male. Of the patients, 54.3% were myeloperoxidase -ANCA positive, 43.4% were proteinase 3–ANCA positive, 2% were dual-positive, and 4.5% were ANCA-negative. Baseline median eGFR and proteinuria were 20 ml/min per 1.73 m^2 (IQR: 11–35) and 1600 mg/d (IQR: 790–3524), respectively, with 54 patients (17.8%) being dialysis dependent. CYC was the most used induction regimen (58.6%), followed by the combination of CYC and RTX in 24.3% and RTX alone in 17.1%. CYC was administered orally in a minority of cases (23.6% in the CYC and 2.7% in the CYC-RTX group) and as i.v. pulses in most instances. As part of induction therapy, 65.6% of patients

Table 1. Clinical features of the study overall cohort, and stratified by Berden histopathological class

Characteristics	All ($N = 304$)	Focal ($n = 71$)	Mixed ($n = 101$)	Crescentic ($n = 96$)	Sclerotic ($n = 36$)	missing	*P*-value
Age at baseline (yrs)	61.1 ± 13.4	62.2 ± 12.7	63.2 ± 12.3	58.4 ± 13.7	60.2 ± 16.4	1 (0.3%)	0.073
Male sex	181 (59.5%)	45 (63.4%)	60 (59.4%)	56 (58.3%)	20 (55.6%)	-	0.865
ANCA specificity						-	
PR3	132 (43.4%)	37 (52.1%)	35 (34.7%)	50 (52.1%)	10 (27.8%)		0.008
MPO	165 (54.3%)	34 (47.9%)	67 (66.3%)[a]	40 (41.7%)[a,b]	24 (66.7%)[b]		0.001
PR3 and MPO	6 (2.0%)	1 (1.4%)	4 (4.0%)	1 (1.0%)	0 (0.0%)		0.560
Negative	13 (4.5%)	1 (1.5%)	3 (3.3%)	7 (7.6%)	2 (5.6%)		0.269
Clinical diagnosis						6 (2.0%)	
GPA	116 (38.9%)	30 (42.3%)	32 (32.7%)	46 (48.4%)	8 (23.5%)		0.030
MPA	182 (61.1%)	41 (57.7%)	66 (67.3%)	49 (51.6%)	26 (76.5%)		0.030
eGFR (ml/min per 1,73 m^2)	20.0 (11.0–35.2)	41.0 (19.5–77.0)[c,d,e]	19.0 (12.0–28.0)[d]	14.0 (5.0-28.5)[c]	19.0 (12.8–24.2)[e]	-	< 0.001
Dialysis dependence	54 (17.8%)	5 (7.0%)[c]	14 (13.9%)[a]	28 (29.2%)[a,c]	7 (19.4%)	-	0.001
Proteinuria (g/d)	2.1 ± 2.0	1.4 ± 1.4[c,d]	2.4 ± 1.9[d]	2.3 ± 2.4[c]	1.9 ± 1.6	51 (16.8%)	0.010
Hypertension	125 (47.0%)	19 (31.1%)[d]	45 (54.2%)[d]	44 (51.2%)	17 (47.2%)	38 (12.5%)	0.036
BVAS v3	17.9 ± 6.0	18.2 ± 5.6	18.0 ± 5.4	18.6 ± 6.8[b]	15.2 ± 4.9[b]	20 (6.6%)	0.043
Extrarenal involvement							
Lung	143 (47.0%)	39 (54.9%)[e]	47 (46.5%)	48 (50.0%)	9 (25.0%)[e]	-	0.026
Peripheral nervous system	26 (8.6%)	7 (9.9%)	8 (7.9%)	8 (8.3%)	3 (8.3%)	-	0.981
Central nervous system	5 (1.6%)	3 (4.2%)	0 (0.0%)	2 (2.1%)	0 (0.0%)	-	0.133
Ocular	14 (4.6%)	7 (9.9%)	4 (4.0%)	2 (2.1%)	1 (2.8%)	-	0.143
Musculoskeletal	59 (19.4%)	13 (18.3%)	17 (16.8%)	22 (22.9%)	7 (19.4%)	-	0.751
Gastrointestinal	14 (4.6%)	4 (5.6%)	4 (4.0%)	4 (4.2%)	2 (5.6%)	-	0.887
Cardiovascular	3 (1.0%)	1 (1.4%)	0 (0.0%)	2 (2.1%)	0 (0.0%)	-	0.495
ENT	77 (25.3%)	23 (32.4%)[e]	22 (21.8%)	29 (30.2%)	3 (8.3%)[e]	-	0.019
Skin	43 (14.1%)	15 (21.1%)	12 (11.9%)	13 (13.5%)	3 (8.3%)	-	0.268
Induction regimen						-	
CYC	178 (58.6%)	39 (54.9%)	56 (55.4%)	61 (63.5%)	22 (61.1%)		0.599
RTX	52 (17.1%)	14 (19.7%)	14 (13.9%)	12 (12.5%)[b]	12 (33.3%)[b]		0.036
RTX-CYC	74 (24.3%)	18 (25.4%)	31 (30.7%)[f]	23 (24.0%)	2 (5.6%)[f]		0.015
RTX cumulative dose (g)[g]	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.0 (2.0-2.0)	2.0 (1.0-2.5)	9 (7.1%)	0.899
CYC cumulative dose (g)[h]	3.0 (2.2–6.0)	4.0 (2.2–6.0)	3.0 (2.2–6.0)	3.0 (2.2–4.9)	3.0 (3.0–4.5)	20 (7.9%)	0.156
PLEX	56 (28.0%)	12 (28.6%)	11 (15.7%)[a]	31 (44.9%)[a,b]	2 (10.5%)[b]	104 (34.2%)	<0.001
i.v. glucocorticoids	197 (66.8%)	43 (61.4%)	59 (60.2%)	72 (76.6%)	23 (69.7%)	9 (3%)	0.067
Dose (g)	1.5 (0.5–2.0)	1.5 (1.5–2.0)	1.5 (1.0–2.2)	1.5 (0.4–2.1)	1.0 (0.4–1.5)		0.144
Oral glucocorticoids	295 (98.3%)	70 (98.6%)	99 (98.0%)	92 (98.9%)	34 (97.1%)	4 (1.3%)	0.922
Starting dose (mg/d)	60 (32–60)	60 (40–60)	60 (32–60)	60 (32–60)	40 (32–60)	38 (12.5%)	0.387
Maintenance therapy at 6 mos						45 (14.8%)	
Azathioprine	134 (51.7%)	26 (43.3%)	50 (54.9%)	45 (55.6%)	13 (48.1%)		0.443
RTX	21 (8.1%)	8 (13.3%)	3 (3.3%)	9 (11.1%)	1 (3.7%)		0.082
CYC	13 (5.0%)	2 (3.3%)	4 (4.4%)	6 (7.4%)	1 (3.7%)		0.683
MMF	14 (5.4%)	3 (5.0%)	5 (5.5%)	6 (7.4%)	0 (0.0%)		0.532
Glucocorticoids only	61 (23.6%)	17 (28.3%)	23 (25.3%)	11 (13.6%)	10 (37.0%)		0.044
Combination/other	16 (6.2%)	4 (6.7%)	6 (6.6%)	4 (4.9%)	2 (7.4%)		0.953

ANCA, antineutrophil cytoplasmic antibody; BVAS v3, Birmingham Vasculitis Activity Score version 3; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; ENT, Ear, Nose, and Throat; GPA, granulomatosis with polyangiitis; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PLEX, plasma exchange; PR3, proteinase 3; RTX, rituximab; RTX-CYC, rituximab plus cyclophosphamide.

[a] *P*-value < 0.05 crescentic vs. mixed.
[b] *P*-value < 0.05 crescentic vs. sclerotic.
[c] *P*-value < 0.05 crescentic vs. focal.
[d] *P*-value < 0.05 focal vs. mixed.
[e] *P*-value < 0.05 focal vs. sclerotic.
[f] *P*-value < 0.05 mixed vs. sclerotic.
[g] Refers only to patients treated with RTX or CYC-RTX.
[h] Refers only to patients treated with CYC or CYC-RTX.

Values are reported as mean ± SD, median (interquartile range) or count (percentage). *P*-values refer to analysis of variance, Kruskal-Wallis rank sum test, or Fisher exact tests, as appropriate, to compare the 3 groups. When these tests reached statistical significance ($P < 0.05$), *post hoc* pairwise comparisons were performed. The superscript symbols indicate pairwise comparisons with $P < 0.05$ (with Hommel correction for multiple testing). Absolute numbers (percentages) of missing data are reported in the "missing" column.

received both i.v. and oral GCs, 32.7% received oral GCs only, and few cases ($n = 3$) received i.v. GCs only or no GCs at all ($n = 2$). The median cumulative dose of i.v. methylprednisolone in the overall cohort was 1500 (IQR: 500–2000) mg and the median starting oral prednisone equivalent dose was 60 (32–60) mg/d. Plasma exchange was employed in 28% of cases (56/200).

Immunosuppressive therapy at 6 months was as follows: out of 259 patients with available data, 134 (51.7%) were on azathioprine, 61 (23.6%) on GCs alone, 21 (8.1%) on RTX, 14 (5.4%) on mycophenolate mofetil, 13 (5.0%) on CYC, and 16 (6.2%) received either a combination of therapies or other treatments. GCs were withdrawn in 12% of patients (31/258) within 6 months from start of treatment.

Kidney biopsies contained a mean of 21.21 ± 13.24 glomeruli per sample. According to the Berden classification, 23.4% biopsies were classified as focal, 31.6% as crescentic, 33.2% as mixed, and 11.8% as sclerotic.

Study Cohort Stratified by Histological Class

In Table 1, we summarize clinical features of the cohort stratified by kidney histology class. Most patients with the sclerotic and mixed class were myeloperoxidase–ANCA positive (67% and 66% respectively), whereas PR3-ANCA prevailed in focal and crescentic classes (52% each). Patients with the sclerotic class more often exhibited a microscopic polyangiitis phenotype, with less frequent lung involvement as well as ear, nose, and throat manifestations; and displayed lower average Birmingham Vasculitis Activity Score than the other groups. Kidney function at baseline was best preserved in the focal class, with higher eGFR (41 [IQR: 19–77] ml/min per 1.73 m^2) than in the other classes (mixed: 19 [IQR: 12–28]; crescentic: 14 [IQR: 5–28]; sclerotic: 19 [IQR: 13–24] ml/min per 1.73 m^2) and the lowest proportion of patients on dialysis (7% vs. 14% in mixed, 29% in crescentic and 19% in sclerotic). CYC was used in > 50% of patients across all histological classes. Patients with the sclerotic class were treated with RTX alone more often than the other groups (33% vs. 20% in focal, 14% in mixed, and 12% in crescentic), whereas they rarely received RTX-CYC (6%, opposed to 25%, 31% and 24% in the focal, mixed and crescentic group, respectively). GC use was comparable across Berden classes, whereas plasma exchange was used most frequently in the crescentic class (45%), followed by the focal (29%), mixed (16%), and sclerotic (10%) classes.

In Supplementary Table S1, we report on comparisons between subgroups of patients treated with different induction immunosuppression, stratified by Berden classes. Overall, we did not find major differences in clinical features among subgroups. There was a trend for better GFR preservation in patients receiving RTX-CYC, most evident in the crescentic class (*P*-values for overall and pairwise comparisons in Supplementary Table S1). Moreover, patients treated with RTX-CYC received i.v. GCs less often than the other groups and had lower CYC cumulative dose than those treated with CYC alone.

Kidney Outcomes

Kidney Remission

Kidney remission at 6 months was achieved by 91.1% of patients (236/259) overall, with no significant differences across Berden classes. Specifically, the remission rate was 95.1% (58/61) in the focal class, 92.1% (82/89) in the mixed one, 87.8% (72/82) in the crescentic one, and 88.9% (24/27) in the sclerotic one (Fisher exact test $P = 0.457$).

Next, we stratified patients by Berden classes and examined remission rates across the 3 induction treatments. Remission rates were comparable among treatments in patients with focal, crescentic, and sclerotic classes. In the mixed class, however, kidney remission rate was lower in patients treated with RTX-CYC (23/29, 79.3%), compared with CYC (46/47, 97.9%) and RTX (13/13, 100%; Fisher exact test $P = 0.011$). (Supplementary Figure S1). Given the overall limited number of patients not achieving remission, multivariate modelling was not performed.

Trends in eGFR After Induction Treatment

Longitudinal eGFR data at 6 and 12 months were available for 85.8% (261/304) and 82.6% (251/304) of the study cohort, respectively. Overall, median eGFR increased from 20 ml/min per 1.73 m^2 (IQR: 11–35) at baseline to 39 (IQR: 23–55) at 6 months and 40 (IQR: 24–58) at 12 months.

eGFR trends across histological classes are shown in Supplementary Figure S2 and Supplementary Table S2. During follow-up, eGFR increased in the focal and mixed classes (absolute median difference from baseline to 6 months by + 11.0 [IQR: −5.2 to 23.0] and + 11.0 [IQR: 1.0–21.0] ml/min per 1.73 m^2, respectively) and even more in the crescentic class (+ 21.0 [IQR: 7.0–36.0] ml/min per 1.73 m^2), whereas little change was observed in the sclerotic class (+ 0.5 [IQR: −1.2 to 9.0]). At 6 months, median eGFR was highest in the focal class (53.0 ml/min per 1.73 m^2 [IQR: 40.2–82.5]), followed by the crescentic (41.5 ml/min per 1.73 m^2 [IQR: 23.8–57.2]), mixed (34.0 ml/min per 1.73 m^2 [IQR: 21.0–48.0]) and sclerotic class (18.5 ml/min per 1.73 m^2 [IQR: 11.8–28.0]) (pairwise comparisons in Supplementary Table S2). Results at 12 months were substantially comparable to the 6-month time point and are reported in Supplementary Table S2.

After stratification of patients by Berden classes, we investigated longitudinal eGFR trends according to treatment. Data are summarized in Figure 1 and Supplementary Table S3. At baseline, there was a trend for higher eGFR in patients receiving the RTX-CYC combination in all histological classes, except the sclerotic one, with the difference being most marked in the crescentic group (statistical testing

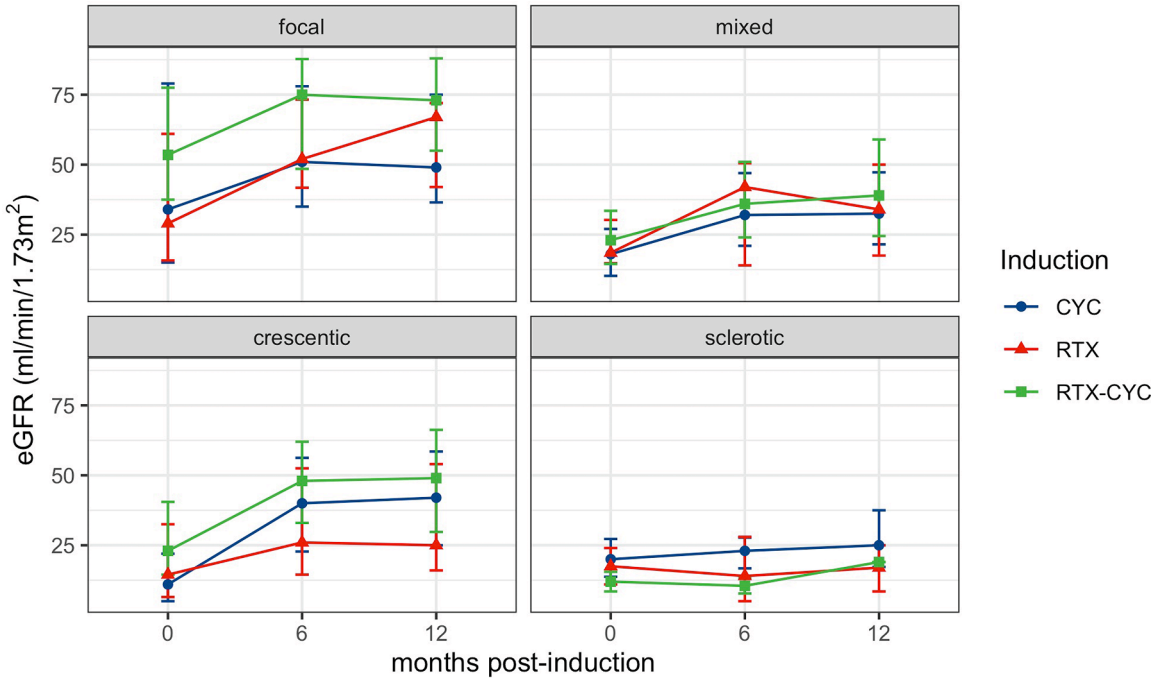

Figure 1. eGFR at baseline, 6 and 12 months after induction according to induction treatment, in subgroups by Berden histopathological classes. Dots indicate medians and lines refer to IQR of eGFR values (ml/min per 1.73 m^2). CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; RTX, rituximab; RTX-CYC, rituximab plus cyclophosphamide.

reported in Supplementary Table S3). Changes in eGFR at 6 and 12 months, relative to baseline, were comparable across treatments in all the histological classes (Supplementary Table S3).

eGFR Recovery at 6 Months

Overall, 50% of patients (131/262) reached the eGFR recovery end point at 6 months. Rates of eGFR recovery were highest in the crescentic class (70.2%, 59/84), intermediate in the focal (45%, 27/60) and mixed (42.7%, 38/89), and lowest in the sclerotic one (24.1%, 7/29, Fisher exact test $P < 0.001$).

A multivariate logistic regression was performed to identify clinical features predictive of eGFR recovery in the overall cohort. As summarized in Supplementary Table S4, older age (OR: 0.48 [95% CI: 0.37–0.64] per 10-year increase in age, $P < 0.001$) and higher eGFR at baseline (OR: 0.55 [95% CI: 0.45–0.67] per 10 ml/min per 1.73 m^2 increase in eGFR, $P < 0.001$), were independently associated with lower chances of eGFR recovery. Berden class was an independent predictor of eGFR recovery, with chances of recovery being highest in the focal and crescentic classes, intermediate in the mixed one and lowest in the sclerotic class (ORs for pairwise comparisons are reported in Supplementary Table S4).

eGFR Recovery at 6 Months by Induction Treatment Across Berden Classes

Multivariate modelling for the eGFR recovery outcome was performed in groups stratified by Berden class. Given the small sample size, Firth's penalized logistic regression was used with a limited set of predictors, namely age, baseline eGFR, induction immunosuppression, and use of i.v. steroids. Variable selection was based on results from the full cohort analysis and on their relevance to the research question. Results are summarized in the Forest plot of Figure 2 and full details are reported in Supplementary Table S5.

Overall, the significant associations between age and baseline eGFR and eGFR recovery that were observed in the overall cohort were replicated in the subgroups by Berden class. The only exception was in the sclerotic class, where baseline eGFR was not significantly associated with chances of eGFR recovery (OR: 1.21, 95% CI: 0.61–2.39 per 10 ml/min per 1.73 m^2 increases in baseline eGFR, $P = 0.574$).

The different induction regimens were not associated with eGFR recovery in the focal, mixed, and sclerotic classes. In contrast, in the crescentic class, RTX was associated with reduced chances of eGFR recovery compared with CYC (OR: 0.23 [95% CI: 0.05–0.98], $P = 0.047$). In this setting, a trend for reduced odds of eGFR recovery with RTX, compared with RTX-CYC, was found (OR: 0.20 [95% CI: 0.03–1.19], $P = 0.077$).

Kidney Failure Outcome

The median follow-up time was 42 (IQR: 18–72) months. During the observation period, 11 patients died (time-to-death: range: 6–42 months, median: 24

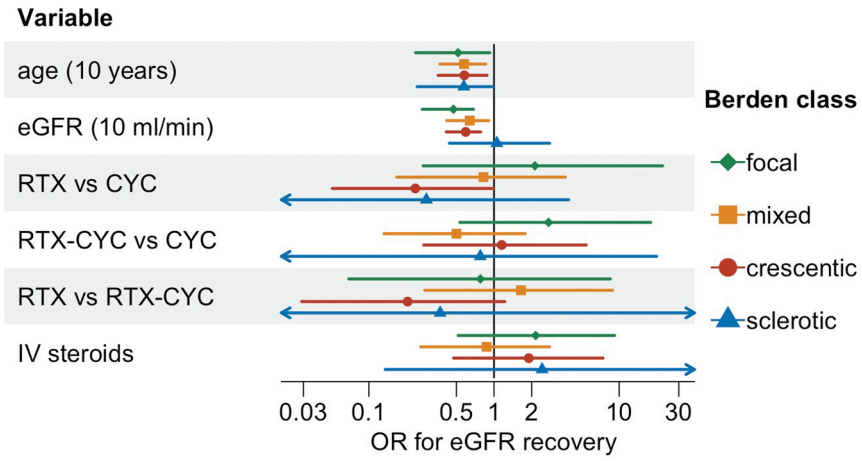

Figure 2. Forest plot summarizing multivariable Firth's penalized logistic regression models to predict eGFR recovery in subgroups by Berden class. Separate models were developed for each subgroup by Berden class, using the same set of predictors. Symbols represent ORs for eGFR recovery and lines indicate 95% confidence intervals. CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; OR, odds ratio; RTX, rituximab; RTX-CYC, rituximab plus cyclophosphamide.

months), and 59 patients (19.4%) reached the kidney failure outcome. Kidney survival differed significantly across Berden histological classes, with the best survival in the focal class, the worst in the sclerotic one, and intermediate outcomes for the mixed and crescentic class (log-rank test $P < 0.001$, Supplementary Figure S3).

A Cox regression model with Firth's penalized partial likelihood was developed to explore clinical features associated with kidney failure (Supplementary Table S6). After adjustment for baseline characteristics and treatment, Berden class remained significantly associated with the risk of kidney failure. More specifically, the risk of kidney failure was significantly higher in the sclerotic class, compared with all the other ones (pairwise comparisons reported in Supplementary Table S6). Baseline eGFR emerged as an independent predictor of kidney failure (HR: 0.52 [95% CI: 0.39–0.70] per 10 ml/min per 1.73 m^2 increase in eGFR, $P < 0.001$), whereas no significant associations with age, sex, ANCA specificity, clinical syndrome, induction immunosuppression and use of IV steroids were found.

Kidney Failure Outcome by Induction Treatment Across Berden Classes

Patients were stratified by Berden class and time-to–kidney failure was compared across treatment groups using the Kaplan Meier method (Figure 3). Significant between-treatment differences were found only in the crescentic class (overall log-rank test $P = 0.035$). Specifically, in the crescentic subgroup, patients receiving RTX had a significantly higher risk of kidney failure than those treated with CYC (pairwise log-rank test $P = 0.039$) and a trend for worse outcome than those receiving RTX-CYC (log-rank test $P = 0.058$), with no significant differences between CYC and the RTX-CYC combination (log-rank test $P = 0.186$).

Next, multivariable Cox models with Firth's penalized partial likelihood were used to model the risk of kidney failure in subgroups stratified by Berden class. Based on the results of modelling in the whole cohort and the research question, the selected covariates were baseline eGFR, induction treatment, and i.v. steroids. Full results of the modelling are reported in Supplementary Table S7 and summarized in the Forest plot in Figure 4.

In patients with crescentic histology, there was an association between RTX monotherapy and an increased risk of kidney failure, compared with CYC (HR: 3.42 [95% CI: 1.03–11.35], $P = 0.045$). There was nonsignificant trend toward increased risk of kidney failure with RTX monotherapy, compared with the RTX-CYC combination (HR: 5.33 [95% CI: 0.91–31.18], $P = 0.063$). No significant between-treatment differences emerged in the mixed and sclerotic class. Modelling was not performed in the subgroup with focal histology, given the paucity of events (only 3 instances of kidney failure).

DISCUSSION

Kidney involvement is a key determinant of overall prognosis in patients with AAV.[2] In this work, we collected and reported kidney outcomes of induction treatment in > 300 patients with biopsy-proven ANCA-glomerulonephritis, with the aim of delving into the role of the kidney biopsy as a tool to inform management in these patients.

First, our results strongly reinforce the value of the kidney biopsy in predicting kidney prognosis in AAV. In line with the initial report from Berden and

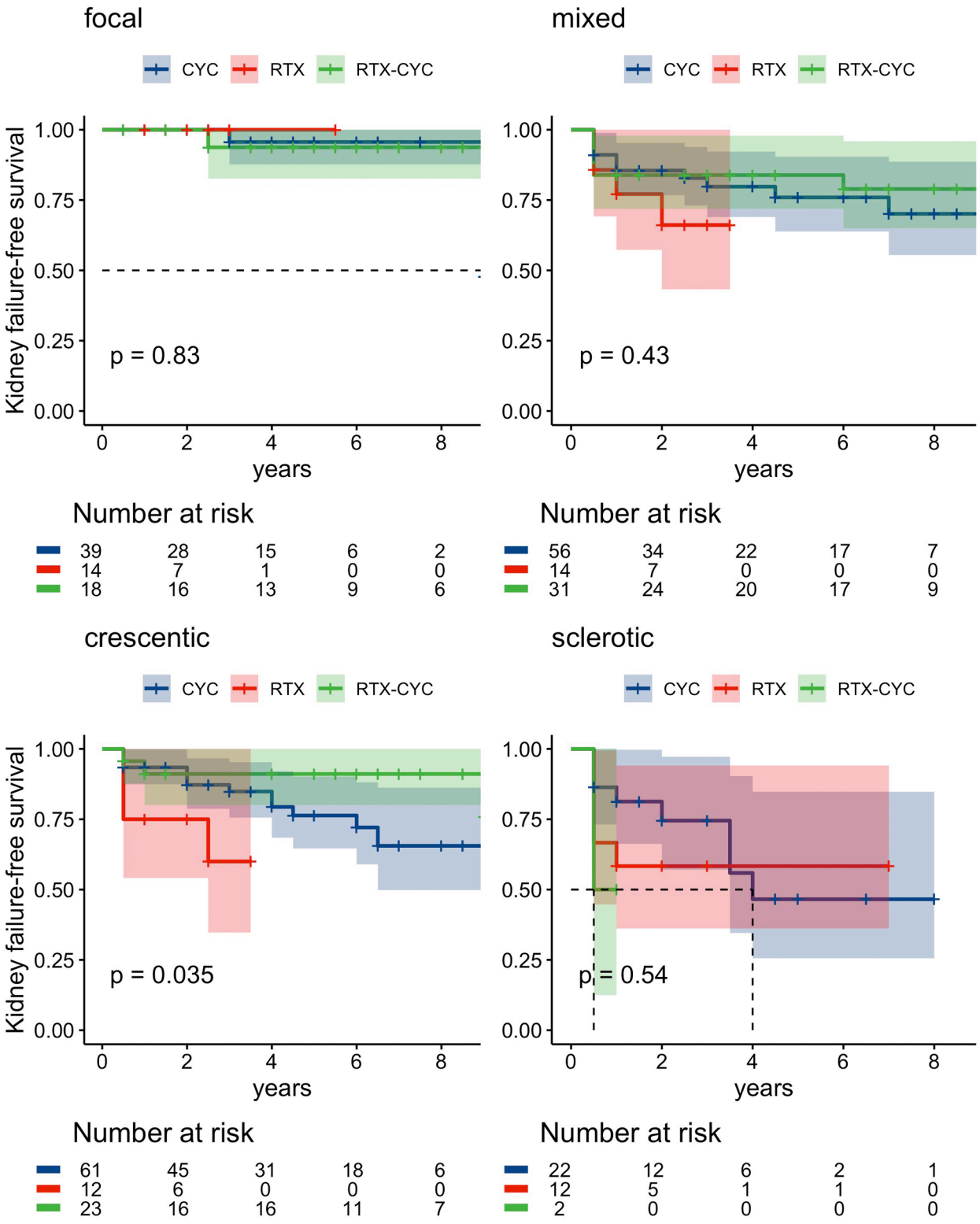

Figure 3. Kaplan Meier curves showing time to the kidney failure outcome according to induction immunosuppression in subgroups stratified by Berden histopathological classes. *P* values refer to results of log-rank tests. CYC, cyclophosphamide; RTX, rituximab; RTX-CYC, rituximab plus cyclophosphamide.

colleagues and subsequent studies,[5,6] cases with a predominance of sclerotic lesions were at the highest risk of kidney failure and showed only marginal eGFR recovery following induction immunosuppression. At the other end of the spectrum, patients with a focal class had the most favorable long-term kidney prognosis, with better preservation of kidney function at presentation, which further improved with treatment.

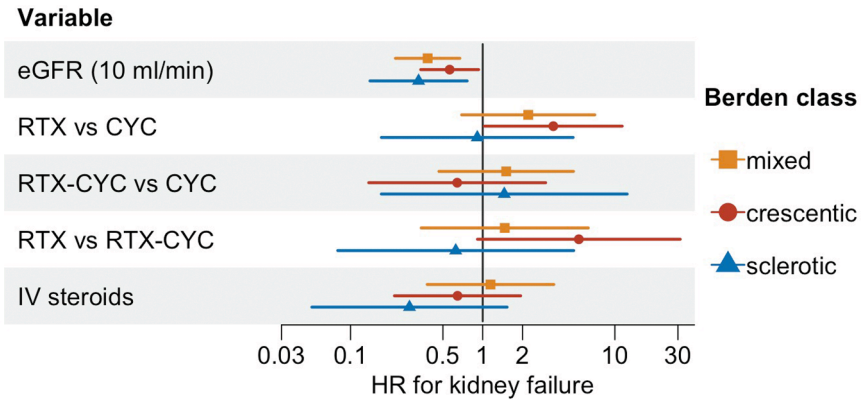

Figure 4. Forest plot summarizing multivariable Cox models with Firth's penalized partial likelihood to predict the kidney failure outcome in subgroups by Berden class. Separate models were developed for each subgroup by Berden class, using the same set of predictors. Symbols represent HRs for kidney failure and lines indicate 95% confidence intervals. CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; HR, hazard ratio; RTX, rituximab; RTX-CYC, rituximab plus cyclophosphamide.

The crescentic class, despite severe kidney impairment at the outset, showed the best functional recovery, likely reflecting the efficacy of immunosuppression in resolving active inflammatory lesions. For the mixed class, the risk of kidney failure was intermediate between the focal and sclerotic ones and overall similar to the crescentic, as previously reported.[5]

Our core research question was to explore whether kidney histopathological features can identify groups of patients with differential responses to immunosuppression. Although data from randomized controlled trials[12–15] and other observational cohorts[16,17] support that the most commonly used induction schemes, namely RTX, CYC, or their combination, have overall similar efficacy in terms of kidney outcomes, these reports did not take into account potential heterogeneity in responses linked to histopathological features. Similarly, when examining kidney outcomes in the overall cohort, we did not find significant differences between induction treatments. However, when analyzing kidney outcomes in subgroups of patients stratified by Berden classes, intriguing signals emerged. We found a trend for worse kidney responses in patients with crescentic histology treated with RTX monotherapy, compared with those treated with CYC or RTX-CYC combination. Such signals emerged exclusively in the crescentic class, both for the eGFR recovery and kidney failure outcomes. These findings suggest that RTX monotherapy may be less effective than CYC to quickly dampen the intense glomerular inflammation underlying crescentic lesions, resulting in potentially suboptimal functional recovery. This hypothesis appears biologically plausible: compared with RTX, CYC is a broader spectrum immunosuppressant and can directly target not only B lymphocytes, but also other immune cells, like neutrophils and T cells, that play a central pathogenetic role in crescent formation.[1,31] Overall, these findings, if replicated, may provide a solid basis to use kidney histology as a guide to personalize immunosuppressive treatment.

Although these results are intriguing, they should be interpreted with great caution, because the stratified analysis presented is exploratory by design, carries a nonnegligible risk of type 1 error, and the observed effects were only nonsignificant trends or borderline statistically significant. Other important limitations need to be accounted for as well. Despite being one of the largest case series of biopsy-proven ANCA-glomerulonephritis, this study remained substantially underpowered to fully address our research question. Only 17% of patients received RTX monotherapy, resulting in < 15 patients per stratum of histological class, which greatly limits the generalizability of the findings. Furthermore, retrospective data collection and missing data did not allow us to fully account for other factors potentially affecting kidney outcomes and confounding the results, such as use of plasma exchange, GC dosing,[32] and maintenance immunosuppression. Additional limitations include possible bias in treatment assignment and lack of centralized review of the biopsies. Moreover, though we adopted the Berden classification because of the possibility to robustly collect this data retrospectively, our dataset did not include other important histological parameters with well-established prognostic value, such as interstitial fibrosis and tubular atrophy.[7] In addition, it is conceivable that new histological scoring systems, specifically developed for this purpose, may be better able to predict response to different immunosuppressants. Overall, we cannot exclude the possibility of significant bias in our findings, which warrants cautious interpretation.

Additional considerations are needed for patients with a sclerotic class. In this group, eGFR recovery was notably poor across all treatment regimens, suggesting that the immunosuppressive approach should be carefully tailored. A regimen based on RTX, given its potentially lower risk of side effects, may therefore be a preferable option in this context.

Another interesting finding was that older age was independently associated with lower chances of eGFR recovery, despite controlling for baseline eGFR and histological class. This is in line with the well-established observation that recovery of kidney function after acute kidney injury is impaired in older individuals.[33] The molecular mechanisms at play remain incompletely understood and probably include different age-associated alterations in the kidneys, such as impaired angiogenesis, deceased proliferative capacity, cellular senescence, and a proinflammatory milieu (the so-called inflammageing).[34] A better understanding of the molecular underpinnings that regulate the transition from acute kidney injury to chronic kidney disease may pave the way to modulating these processes for therapeutic purposes, thus improving kidney outcomes across different acute kidney injury etiologies, including immune-mediated diseases such as AAV.

In conclusion, our study provides several key considerations. First, kidney biopsy remains a crucial prognostic tool in patients with ANCA-glomerulonephritis. Second, kidney biopsy may provide key information to guide immunosuppressive treatment choices. Our data suggest that RTX monotherapy may be suboptimal to tackle active crescentic lesions, resulting in potentially impaired eGFR recovery compared with CYC-based regimens. Our work supports the hypothesis that induction regimens may not all be equal, at least when active crescentic lesions prevail. This is in contrast with currently available evidence from clinical trials and retrospective data, in which no distinctions based on kidney pathology were made. Nonetheless, as previously highlighted, this work has substantial limitations and should be considered hypothesis-generating rather than providing definitive evidence. Additional data are needed, ideally from prospective studies in larger cohorts, because these findings could have important implications for clinical practice. In particular, the CYC-RTX combination may be a particularly appealing therapeutic option for crescentic glomerulonephritis, with the potential to exploit the quick efficacy of CYC, while limiting the cumulative dose and toxicity. Retrospective data on CYC–RTX combination therapy are very promising[35,36]; however, there is a strong need for high-quality prospective studies, integrating kidney histopathology. Moreover, the recent addition of the complement inhibitor, avacopan, to the therapeutic arsenal for AAV may favorably impact kidney outcomes, and these hypotheses should therefore be tested in avacopan-treated cohorts.[37,38]

Future work will be needed to better understand how to personalize treatment based on kidney histopathology and, ideally, other noninvasive biomarkers and clinical features, to tackle at best both acute inflammation and maladaptive repair mechanisms.

DISCLOSURE

FM reported support for attending meetings or travel from CSL Vifor. JS reported lecture fees from CSL Vifor. AJ reported honoraria from CSL Vifor and Nordic AAV Forum and support for attending meetings/travel from CSL Vifor. SRB reported grant support from NIHR, KfL, and VUK; honoraria from CSL Vifor and Otsuka; support for attending meetings or travel from CSL Vifor; and leadership or fiduciary roles in UKKA and UKIVAS. AK reported grant support from CSL Vifor, Novartis, and Otsuka; consulting fees from Amgen, Novartis, AstraZeneca, Novo Nordisk, Boehringer Ingelheim, Otsuka, CSL Vifor, Roche, Delta4, Sobi, GlaxoSmithKline, Walden Biosciences, and Argenx; honoraria from CSL Vifor, Miltenyi Biotec, and Otsuka; support for attending meetings or travel from CSL Vifor; participation on a data safety monitoring or advisory board for Walden Biosciences; and participation in the IWG of ERA. AB reported consulting fees from Alexion, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, CSL-Vifor, Stada, and Otsuka; honoraria from Alexion, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Chemocentryx, CSL Vifor, Fresenius, GSK, and Otsuka; participation on data safety monitoring or advisory board for Intercept trial (transplantation) DSMB; and leadership or fiduciary roles in ERA SAB, ERA IWG, and the Swedish Renal Fund. RAS reported consulting fees from Roche and Vifor. SPM reported grants from AstraZeneca and Senya Therapeutics; consulting fees from Alexion, AstraZeneca, and Alentis; honoraria from CSL Vifor; and leadership role in UKIVAS. DJ reported grant support from CSL Vifor; consulting fees from Alentis, Amgen, AstraZeneca, Boehringer, GSK, Novartis, Otsuka, Roche, and CSL Vifor; honoraria from CSL Vifor and Otsuka; participation on data safety monitoring or advisory board for GSK, Hansa, and Novartis; stocks of Alentis and Aurinia. FA reported consulting fees from CSL Vifor, Alexion and Novartis; honoraria from CSL Vifor and support for attending meetings/travel from CSL Vifor.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

AUTHOR CONTRIBUTIONS

FA conceived the study. All the authors selected eligible patients and recorded histological and clinical data in a dedicated database. FA, FM, and MU conceived and conducted the statistical analysis. All the authors were involved in drafting the article or revising it critically for important intellectual content and approved the final version to be published.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Proportions of kidney remission rates at 6 months according to induction immunosuppression in subgroups stratified by Berden histopathological classes.

Figure S2. eGFR at baseline, 6 and 12 months after induction in the cohort stratified by Berden histopathological classes.

Figure S3. Kaplan Meier curves showing time to the kidney failure outcome in the cohort stratified by Berden histopathological classes.

Table S1. Clinical features of the study cohort in subgroups by Berden histopathological class and according by induction treatment.

Table S2. eGFR at baseline, 6 and 12 months and changes in eGFR from baseline at 6 and 12 months in the overall cohort and in groups stratified by Berden histological classes.

Table S3. eGFR at baseline, 6 and 12 months and changes in eGFR from baseline at 6 and 12 months, according to induction treatment and after stratification by Berden histological classes.

Table S4. Multivariable logistic regression model predicting eGFR recovery 6 months after induction therapy.

Table S5. Multivariable Firth's penalized logistic regression models to predict eGFR recovery in patient subgroups by Berden class.

Table S6. Multivariable Cox regression model with Firth's penalized partial likelihood predicting the kidney failure outcome.

Table S7. Multivariable Cox regression models with Firth's penalized partial likelihood to predict kidney failure in patient subgroups by Berden class.

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