Original Report: Patient-Oriented, Translational Research

American Journal of Nephrology

Am J Nephrol 2016;43:112–119
DOI: 10.1159/000444925

Received: December 29, 2015
Accepted: February 16, 2016
Published online: March 23, 2016

Prolonged Duration of Renal Recovery Following ANCA-Associated Glomerulonephritis

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Key Words
ANCA · Glomerulonephritis · Proteinuria · Creatinine

Abstract
Background: As renal biopsies are not routinely repeated to monitor treatment response in anti-neutrophil cytoplasm antibody (ANCA)-associated glomerulonephritis, serum creatinine (SC) and proteinuria assessed by urine protein:creatinine ratio (UPCR) measurements are relied upon to provide a non-invasive estimate of disease activity within the kidney. However, sparse information exists about the time to achieve maximal improvement in these parameters, which has important implications for treatment decisions and disease-scoring systems. ***Methods:*** We analysed patients with ANCA-associated glomerulonephritis and renal impairment from cohorts in the United Kingdom and Ireland, with the primary objective of determining actuarial time to nadir SC and UPCR. Time to disappearance of haematuria was analysed as a secondary objective. ***Results:*** Ninety-four patients fulfilled our selection criteria, with 94 (100%) and 66 (70%) having reached their nadir SC and UPCR respectively during the follow-up period. Nadir SC was achieved after a median of 88 days (95% CI 74–102), UPCR at 346 days (95% CI 205–487). Those of Indo-Asian ethnic origin reached their nadir SC faster (34 days) than other ethnicities ($p < 0.01$). There were no significant differences in time to nadir SC or UPCR on the basis of gender, clinical diagnosis, ANCA positivity or renal biopsy findings. ***Conclusion:*** In this retrospective study, nadir creatinine and proteinuria occur later than other signs of clinical remission, suggesting that ongoing renal recovery continues for a significant time after diagnosis. It may benefit disease-scoring systems to take into account SC levels beyond the initial assessment.

Introduction

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) are multisystem diseases, characterised by necrotising vasculitis of small blood vessels. They have an annual incidence in Europe of 10–20 million per year [1], but represent one of the commonest renal biopsy findings in patients biopsied for acute kidney injury [2]. AAV lead to considerable morbidity and mortality, and renal vasculitis is the most common severe manifestation, occurring at diagnosis in more than 50% of patients with granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) and microscopic polyangiitis (MPA) at presentation, and in up to 85% of patients at some point during the course of their disease

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[3]. Immunosuppressive therapies form the mainstay of treatment, and remission is achieved in more than 90% of cases, with improvement in renal function, while up to 55% of patients requiring dialysis at presentation will regain independent renal function [3–5].

Measurements of serum creatinine (SC) and proteinuria, quantified by urine protein:creatinine ratios (UPCR), provide important information about renal function and are used as non-invasive assessments of disease activity in the kidney. Improvement in renal function following diagnosis and treatment suggests that active healing and remodelling is taking place, while delay in renal recovery may suggest ongoing disease activity, requiring treatment modification. These changes should also be reflected in disease-activity scores, such as the Birmingham Vasculitis Activity Score (BVAS) [6]. Since treatment-associated toxicity is a common cause of morbidity and mortality, and almost 50% of AAV patients will suffer a relapse within 5 years from diagnosis, customising therapy based on disease activity is critical [7, 8]. While the renal biopsy is the definitive test for suspected active disease, clinical trials of novel AAV therapies and protocols frequently use renal function parameters as endpoints. Therefore, defining the tempo of renal recovery is important for interpretation of observed changes in individual patients, so as to make appropriate and necessary decisions about repeat biopsies, treatment alterations, as well as designing valid trial endpoints [9]. In particular, it is important to know how long it takes for markers of renal function to reach a nadir, indicating a return to baseline function or, as is more often the case, a new baseline following some degree of irreversible damage due to the previous vasculitic activity. It has been shown from clinical trials enrolling patients with lupus nephritis that proteinuria frequently fails to completely resolve within the first 6 months from diagnosis [10], a period much longer than initially thought, which has led to modifications in subsequent trial endpoints. If the same were true of AAV, this could have significant implications for setting trial endpoints and should alter how we score disease activity beyond the first assessment. The BVAS, typically used at diagnosis and each subsequent follow-up visit, is a good reflection of disease severity and is useful for monitoring progression or improvement. However, the renal section of the scoring system requires the clinician to score the presence of elevated SC and urinary abnormalities (proteinuria and haematuria) at initial presentation, but only urinary abnormalities on subsequent visits [6]. Since both poor renal function and urinary abnormalities could imply active disease and inflammation in the kidney, it is surprising and somewhat inconsistent that only the latter is scored as a marker of active disease. Currently, there exist only sparse data describing the tempo of renal function recovery in AAV patients [11–13].

The primary aim of this retrospective study was to determine the kinetics of SC and UPCR alteration following initiation of treatment of AAV, and to determine the duration before they reach nadir levels. The secondary objectives were to identify independent predictors of this value and to estimate the time taken for haematuria to resolve.

Materials and Methods

Inclusion Criteria

Data were gathered from patients diagnosed with AAV and followed at the vasculitis clinics at the Royal Free Hospital, London (UK cohort), Tallaght Hospital, Dublin, and Cork University Hospital, Cork (Irish cohort) between 1990 and 2013, and recruited to the Irish Rare Kidney Disease registry and UKIVAS national registry (www.ukivas.org). Patients were included if they had GPA or MPA as defined by the Chapel Hill Consensus Conference [14]. In addition, all had renal impairment due to glomerulonephritis, with SC level >110 μmol/l and/or an estimated glomerular filtration rate (eGFR) by abbreviated MDRD equation ≤90 ml/min at diagnosis [15], where diagnosis was defined as the start of immunosuppressive treatment or positive histological assessment, whichever occurred first. All patients were treated with standard induction therapy, consisting of oral prednisolone and pulsed intravenous cyclophosphamide or rituximab, with adjunctive plasmapheresis for those with severe renal failure (creatinine >500 μmol/l or dialysis dependent) or pulmonary haemorrhage, and followed by maintenance therapy with oral prednisolone and azathioprine or mycophenolate mofetil, according to published EULAR recommendations [16]. All patients were followed for at least 1 year post diagnosis, or until death if occurring sooner, prior to database query. Patients were excluded if they had less than 4 recorded SC and/or UPCR measurements, had inadequate clinical or biochemical data available from the time of diagnosis (e.g. patients diagnosed elsewhere) or remained dialysis dependent 90 days after diagnosis. In cases where patients had 4 or more recordings of only 1 or 2 of the parameters, their information was still used but excluded in the analysis of the deficient parameter (fig. 1).

We recorded demographic, clinical, biochemical and immunological data including gender, ethnicity, age at diagnosis, primary diagnosis, ANCA subtype (proteinase 3 (PR3)- or myeloperoxidase (MPO)-ANCA) status, biopsy findings according to the Berden et al. [17] histological classification, induction and maintenance immunosuppression regimen, administration of renin angiotensin system inhibitors within the first 3 months of treatment, presence or absence of haematuria on urinary dipstick testing, as well as SC and UPCR test results. UPCR was calculated from testing of urine for protein and creatinine using spot urinary samples. Haematuria was deemed to be present if the dipstick of these samples obtained during follow-up was more than 'trace' positive. Lab-

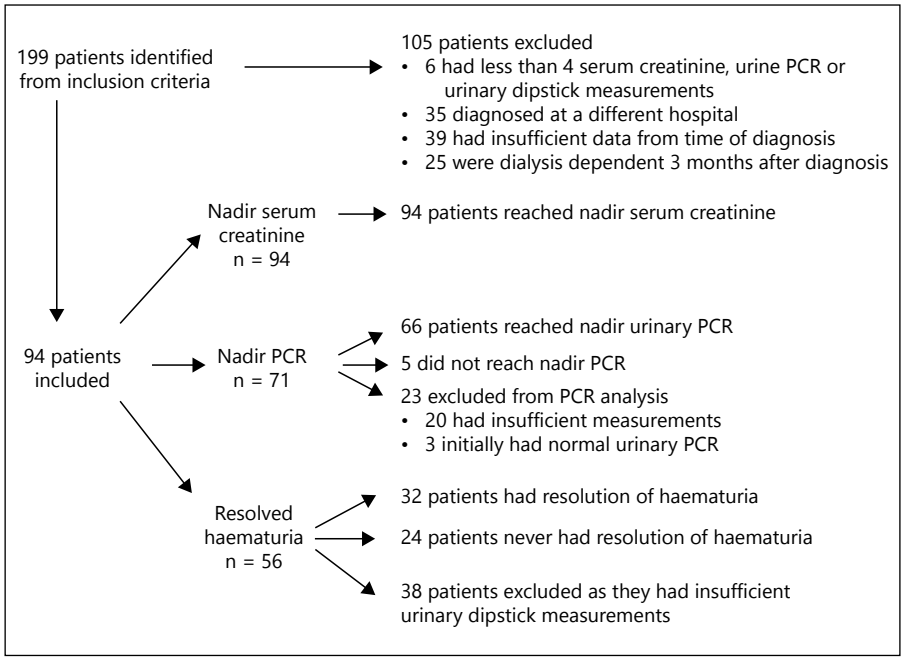

Fig. 1. Flowchart of patients screened and included in the study.

oratory quantification of the number of erythrocytes was not done. Where data were missing from registry entries, a thorough review of the hospital laboratory databases, patient notes and clinic letters was conducted.

Analysis of Nadir Values

Nadir SC and urinary PCR values were defined as the earliest point at which the difference between 2 consecutive test results was less than 5%. Similarly, resolution of haematuria was defined as 2 consecutively negative results, with haematuria being considered present if measured as greater than trace positivity on dipstick testing. Time to nadir was therefore expressed as the number of days from date of diagnosis to the earliest date at which the value in question plateaued.

Statistical Analysis

Statistical analysis with actuarial life table survival analysis was performed to construct Kaplan–Meier curves, which were compared using the log-rank test. Nadir values were expressed as median and 95% CI. SPSS version 22 (IBM) was used to perform statistical analyses.

Results

We screened 199 patients from which a total of 94 patients were identified from the 3 sites; these patients satisfied the entry criteria (fig. 1). All recruits provided informed consent for enrolment into UKIVAS (NRES 10/H/1102/77) or the Irish Rare Disease registry (REC Ref 2012138104).

Nadir SC

All 94 included cases reached a nadir creatinine (table 1). The median starting creatinine in this cohort was 308 μmol/l (range 100–1,116 μmol/l) and the median nadir creatinine was 133 μmol/l (range 72–341 μmol/l). Significant differences between starting creatinines in the sub-groups existed only between male and female patients, in those patients who received plasma exchange and those who did not, and in patients who were given or not given methylprednisolone. Differences in the absolute nadir creatinine achieved between the sub-groups existed between males and females, MPO- and PR3-ANCA and between MPA and GPA. The median time taken to achieve the nadir was 88 days (95% CI 74–102 days; fig. 2a), with no significant differences existing between males and females (88 vs. 93 days, respectively). There was no difference in time to nadir according to clinical vasculitic syndrome (GPA vs. MPA), antibody specificity (MPO- vs. PR3-ANCA), type of induction regimen (cyclophosphamide vs. non-cyclophosphamide, including rituximab); additional methylprednisolone vs. no methylprednisolone; adjunctive plasmapheresis vs. no plasmapheresis, Berden class, or use of maintenance renin angiotensin aldosterone system (RAAS) blockers. However, there was a significant difference found according to self-reported ethnicity (fig. 2b). Asian patients had a significantly shorter median time to nadir SC when compared to Caucasian or 'other' patients (34 vs. 94 and 86 days, respectively, $p < 0.001$).

Table 1. Demonstrating presenting creatinine, actual nadir SC achieved and time to reach nadir with statistical analysis of time to reach nadir between sub-groups

Sub-group	Number	Initial creatinine, μmol/l, median (IQR)	Nadir creatinine, μmol/l, median (IQR)	Time to nadir creatinine, days, median (95% CI)	Log-rank test, p value
All patients	94	308 (222–525)	133 (108–180)	88 (74–102)	
Gender					0.9
Female	41	279 (185–357)	119 (103–157)	93 (62–124)	
Male	53	383 (229–592)	140 (117–212)	88 (76–100)	
Race					<0.001
Caucasian	75	309 (222–548)	135 (111–193)	94 (77–111)	(comparing all
Asian	7	262 (228–280)	136 (112–219)	34 (0–70)	3 groups)
Other	12	353 (195–558)	108 (91–123)	86 (64–108)	
Diagnosis					0.13
MPA	59	339 (256–521)	153 (110–211)	87 (72–102)	
GPA	35	240 (159–529)	123 (107–135)	100 (56–144)	
Biopsy findings					0.24
Not done	23	320 (132–500)	134 (101–205)	129 (57–200)	(comparing
All biopsied	71	307 (226–557)	133 (108–180)	86 (73–99)	only the
Crescentic	24	358 (266–631)	129 (105–173)	98 (49–147)	groups with
Mixed	20	303 (210–500)	137 (108–179)	86 (71–101)	known biopsy
Sclerotic	8	281 (167–438)	184 (113–223)	44 (39–47)	results)
Focal	19	262 (226–584)	128 (112–171)	49 (23–75)	
ANCA					0.3
MPO	51	339 (231–498)	155 (112–211)	88 (72–104)	(comparing all
PR3	38	285 (194–592)	124 (102–136)	85 (50–120)	3 groups)
Negative	5	279 (177–751)	130 (90–233)	182 (6–358)	
Induction regime[∞]					0.08
Cyclophos	83	309 (222–557)	131 (107–178)	91 (78–104)	
Non-cyclo	7	224 (147–339)	161 (90–179)	38 (20–56)	
Steroid induction[Δ]					0.69
Methylpred	56	355 (228–601)	137 (110–180)	86 (76–96)	
Non-methyl	31	240 (141–448)	119 (89–175)	77 (14–140)	
Plasma exchange[¥]					0.41
Yes	27	523 (348–674)	137 (110–181)	94 (65–122)	
No	62	280 (191–408)	130 (104–176)	83 (54–112)	
ACEi/ARB use?[T]					0.79
Yes	37	355 (236–559)	134 (109–197)	87 (62–112)	
No	56	286 (202–500)	133 (107–178)	91 (73–109)	

[∞] This information was unavailable for 4 patients. [Δ] This information was unavailable for 7 patients. [¥] This information was unavailable for 5 patients. [T] This information was unavailable for 1 patient.

Nadir UPCR

Of the 94 patients in the cohort, sufficient data on UPCR were available for 71 patients; of these 66 (93%) reached nadir proteinuria after a median time of 346 days (95% CI 205–487). Those not reaching nadir UPCR were followed up for a median time of 303 days (interquartile range (IQR) 177–811). There were no significant differences in time to nadir UPCR when making comparisons based on gender, ethnicity, ANCA specificity, clinical diagnosis, type of induction regimen, Berden histological class or use of maintenance RAAS blockade (table 2). Overall, 57 of 71 patients (80%) achieved nadir UPCR of less than 50 mg/mmol, demonstrating near normalisation of urinary protein excretion.

Haematuria

Of the 94 recruits, sufficient results of urinary dipstick testing were available for 56 patients, of whom 32 (57%) had complete resolution of haematuria after a median of 448 days (95% CI 341–595). Those not reaching this endpoint were followed for a median time of 798 days (IQR 130–1,616). None of the covariates were significant-

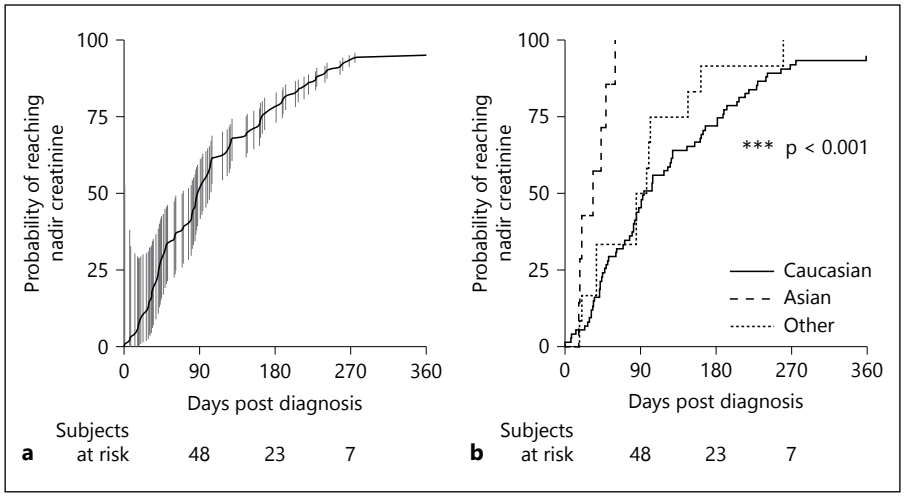

Fig. 2. Kaplan–Meier curves demonstrating the probability of reaching nadir creatinine over time. **a** Full cohort, n = 94; error bars represent the 95% CI. **b** Probability of reaching nadir creatinine stratified by ethnicity.

ly associated with time to cessation of haematuria. Figure 3 summarises the 3 parameters on one Kaplan–Meier plot.

Cohort Validation: UK vs. Irish

To validate our results, we compared the time to nadir SC and UPCR between the UK and Irish cohorts (fig. 4). Respectively, the median time to nadir SC was 80 (n = 53) and 123 days (n = 41), p = 0.017 and to nadir UPCR was 427 (n = 42) vs. 322 (n = 29) days, p = 0.44. This difference in time to nadir creatinine between the UK and Irish cohorts was lost when the analysis was restricted to Caucasian patients (p = 0.12), given that the Irish cohort was fully Caucasian and that we have identified a reduced time to nadir in Asian patients looking at the GPA and MPA sub-group, and the MPO-ANCA and PR3-ANCA sub-group.

Discussion

The time taken to reach nadir SC and UPCR is significantly longer than previously reported [13], with creatinine stabilising at a median of approximately 3 months post diagnosis, and proteinuria plateauing much later at a median of approximately 1 year post diagnosis.

We found that these patterns were similar across different clinical syndromes, ANCA specificities, induction regimens and histological classes. Surprisingly, the use of RAAS blockade with ACE inhibitors or Angiotensin receptor blockers did not significantly impact on time to achieve nadir creatinine or UPCR, although the number of subjects in this sub-group analysis was small. Only ethnicity exerted a significant effect on time to achieve nadir creatinine, with Asian subjects achieving this in the fastest time.

The reason why time taken to achieve a nadir SC was different in Asians is intriguing and not easily explained. While this may well be an artefact due to a small sample size of just 7 patients, it may represent a true difference in rates of renal resolution that may be hard to validate using clinical trial data, in which a vast majority of enrolled subjects have to date been Caucasian. Analysis of longitudinal registry data or validation from a study of larger Indo-Asian patient population may be more informative in this respect. Although there may be a greater degree of chronic renal damage found in patients with MPA/MPO-ANCA at presentation, there was no difference in time to achieve nadir in the GPA group compared to the MPA group [18]. In addition, no difference was found when we analysed the outcome according to histological classification, which likely reflects the classification groups, which currently focuses only on glomerular and not on tubulointerstitial damage.

These data have implications for patient management, disease scoring and trial design. For example, half the number of patients continue to experience improvement in excretory kidney function after 3 months, a point at which induction therapy is switched to maintenance therapy. Although trial evidence suggests that, overall, this duration of therapy is sufficient, it is likely that there are specific individuals with ongoing renal inflammation at this stage. The currently unmet challenge in providing personalised care will be identifying these patients. Moreover, the use of proteinuria or haematuria as an indicator of active disease is less helpful within the first 300 days,

Table 2. Demonstrating actual nadir UPCR achieved and time to reach nadir with statistical analysis of time to reach nadir between sub-groups

Sub-group	Number	Nadir PCR, mg/mmol, median (IQR)	Time to nadir PCR, days, median (95% CI)	Log-rank test, p value
All patients	71	23 (10–39)	346 (205–487)	
Gender				0.60
Male	38	26 (14–49)	321 (222–420)	
Female	33	18 (10–37)	427 (242–611)	
Race				0.50 (comparing all 3 groups)
Caucasian	54	23 (10–50)	346 (255–437)	
Asian	6	17 (10–34)	274 (0–674)	
Other	11	20 (10–37)	445 (209–681)	
Diagnosis				0.25
MPA	45	23 (10–47)	346 (174–518)	
GPA	26	19 (10–32)	349 (167–531)	
Biopsy findings				0.18 (comparing only the groups with known biopsy results)
Not done	20	27 (10–62)	240 (179–301)	
All biopsied	51	20 (10–37)	427 (290–564)	
Crescentic	19	18 (10–49)	571 (353–789)	
Mixed	17	28 (10–41)	231 (161–301)	
Sclerotic	5	23 (10–59)	274 (177–371)	
Focal	10	19 (12–35)	287 (208–366)	
ANCA				0.34 (comparing all 3 groups)
MPO	39	23 (10–49)	346 (181–511)	
PR3	28	20 (10–33)	349 (158–540)	
Negative	4	17 (10–35)	287 (0–771)	
Induction regime[∞]				0.58
Cyclophos	63	21 (10–38)	370 (213–527)	
Non-cyclo	6	32 (16–130)	156 (0–351)	
Steroid induction[Δ]				0.48
Methylpred	45	23 (11–39)	442 (328–556)	
Non-methyl	23	14 (10–37)	226 (162–290)	
Plasma exchange[¥]				0.72
Yes	21	21 (10–37)	321 (196–446)	
No	48	22 (10–44)	421 (241–601)	
ACEi/ARB use?				0.11
Yes	31	20 (10–38)	443 (246–640)	
No	40	23 (12–44)	293 (192–394)	

[∞] This information was unavailable for 2 patients. [Δ] This information was unavailable for 3 patients. [¥] This information was unavailable for 2 patients.

meaning that to prevent or treat 'grumbling' subclinical renal inflammation and progression to ESRD in a significant number of patients [19], we may have to consider more aggressive biopsy policies early on following induction therapy. With respect to disease scoring with BVAS, our data support the concept that SC, proteinuria and haematuria should be regarded in the same fashion, scoring them at initial presentation only or at each visit. Finally, with respect to trial design, one could consider assessing change in SC at 6 months, but use of proteinuria would require a later time point to better separate responders from non-responders.

There are caveats to consider when interpreting these data. First, data were collected retrospectively, and a similar analysis using prospective clinical trial data where renal function has been very closely monitored may be helpful in confirming the results. Second, the frequency of testing may explain some of the difference between creatinine, proteinuria and haematuria data. There were numerous creatinine data points in our analysis, but less fre-

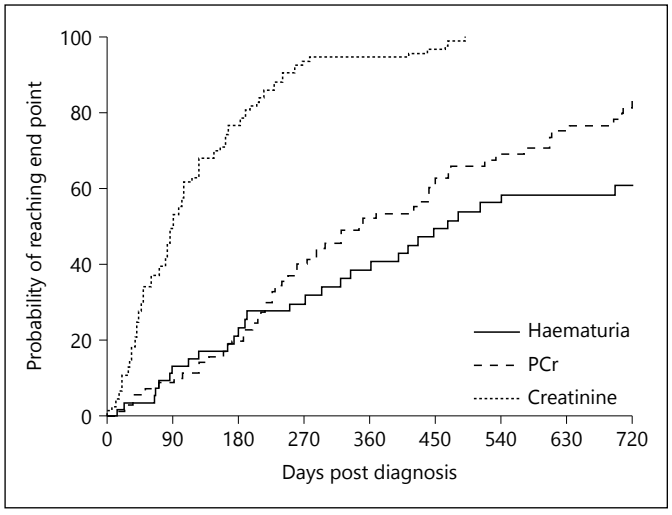

Fig. 3. Graphical comparison of time to nadir creatinine, nadir PCR and disappearance of haematuria in the study cohort. The dotted lines indicate 95% CIs.

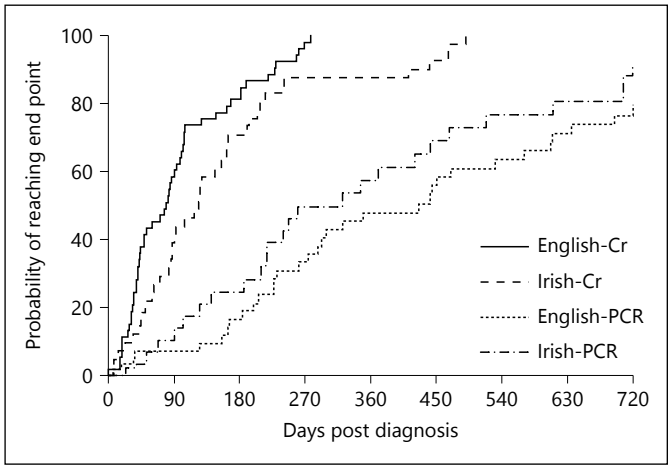

Fig. 4. Comparison of all patients in the UK and Irish cohorts for time taken to achieve nadir SC and urine PCR.

quently documented assessments of urinary protein quantification and haematuria, which may mean that the time to proteinuria nadir and resolution of haematuria may be later on as a result of measurement artefact rather than true effect. However, it is also likely that the resolution of proteinuria and haematuria is delayed compared to SC as they represent different components of renal inflammation and repair, with the former predominantly reflecting glomerular disease activity, while the latter may include the effect of acute tubular injury which generally recovers more rapidly. Additionally, proteinuria and haematuria may persist due to significant focal glomerular scarring or chronic tubular damage, while excretory renal function may be less affected in these settings. Finally, other reasons for haematuria may co-exist, which have not been considered in this analysis.

Limited published data on resolution of urinary abnormalities in AAV exist. Using a smaller cohort of AAV patients, one study demonstrated that the time for haematuria resolution (divided into less than or greater than 90 days) was not predictive of eGFR at 1 year, while only pANCA and lower baseline eGFR were predictive of persistent haematuria, suggesting that persistent haematuria was more likely associated with chronic rather than active damage. Analysis of the persistence of proteinuria was limited, as only dipstick results were analysed [11]. Magrey et al. [12] reported complete resolution of haematuria in 19 patients treated for MPO-ANCA-associated crescentic glomerulonephritis within 4 months of treatment, whereas, more in keeping with our findings, Lillieebladh et al. [13] demonstrated prolonged haematuria in long-term remission patients, with half the number of subjects displaying haematuria for more than 6 months and a quarter of them showing persistent haematuria at a median of 38 months follow-up.

Overall, our data show that the time taken to achieve a levelling off of urinary abnormalities is considerably prolonged and the time taken to achieve a stable nadir creatinine is also later than other markers of disease activity. Timely diagnosis of sub-clinical, smouldering or relapsing ANCA associated glomerulonephritis may therefore require a more aggressive biopsy policy, so that prompt intervention may be initiated with the aim of preventing progression to ESRD, seen in half the number of these patient cohorts and often considered to be due to a progression of established chronic kidney disease.

Disclosure Statement

M.A.L. supported by Science Foundation Ireland (grant 11/Y/B2093). A.O. is an NIHR academic clinical fellow.

Acknowledgements

We are grateful to the UKIVAS and Rare Kidney Disease steering committees for permitting analysis of UKIVAS recruited cohorts.

Conflicts of Interest

None of the authors have any conflicts.

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