Incidence and outcomes of acute kidney injury in a referred chronic kidney disease cohort

Jean-Philippe Lafrance1,2, Ognjenka Djurdjev3 and Adeera Levin3,4

1Service de Néphrologie, Hôpital Maisonneuve-Rosemont, Montréal, Canada, 2Département de Médecine, Université de Montréal, Montréal, Canada, 3British Columbia Provincial Renal Agency, Vancouver, Canada and 4Division of Nephrology, University of British Columbia, Vancouver, Canada

Correspondence and offprint requests to: Jean-Philippe Lafrance; E-mail: jean-philippe.lafrance@umontreal.ca

Abstract

Background. Whilst chronic kidney disease (CKD) has been identified as a risk factor for the development of acute kidney injury (AKI), little has been published about the incidence and outcomes of those acute injuries on chronic stable kidney disease and even less in a referred cohort of CKD patients followed up by nephrologists.

Methods. We followed up 6862 patients registered as CKD in British Columbia, Canada, for a median time of 19.4 months after they achieved an estimated glomerular filtration rate (eGFR) value ≤30 mL/min/1.73 m². AKI was defined as a decrease in eGFR of ≥25% compared to a moving baseline eGFR within 25 days.

Results. Of the CKD patients, 44.9% had at least one AKI episode. Crude incidence rate for a first AKI event was 34.8 per 100 person-years. Older age [adjusted relative risks (RR) = 0.93 by 10 years, 95% confidence intervals (CI) = 0.90, 0.95] was associated with a lower risk of AKI. Of the patients, 15.3% died before dialysis and 18.1% initiated dialysis. AKI was associated with both a higher risk of death (adjusted RR = 2.32, 95% CI = 2.04, 2.64) and an increased risk of dialysis (adjusted RR = 2.33, 95% CI = 2.07, 2.61).

Conclusions. In a referred CKD population, AKI was a frequent event and associated with higher risks of dialysis and mortality. The incidence of AKI appears to be less with older age in this population. Quantification of AKI incidence and its risk factors in different populations is important for clinicians and planners, so that appropriate identification, prevention and treatment strategies can be tested.

Keywords: dialysis; epidemiology; kidney failure, acute; kidney failure, chronic; mortality

Introduction

Both chronic kidney disease (CKD) and acute kidney injury (AKI) are devastating conditions with respect to human and financial costs. CKD, affecting more than 13% of the United States population, is associated with a higher risk of mortality [1,2]. AKI is also associated with an increased risk of mortality, and its community-based incidence increased by 60% between 1996 and 2003 [3,4]. Although each of these two diseases has been extensively studied, investigations evaluating the combination of both diseases are less frequent. Indeed, whilst CKD has been identified as a risk factor for the development of AKI, little has been published about the incidence and outcomes of those acute injuries on chronic stable kidney disease and even less in a cohort of patients followed up by nephrologists [3,5,6]. Whilst structured, multidisciplinary nephrology teams may stabilize or slow the progression of CKD [7], the incidence and impact of AKI events on those patients being cared for in this way is not known.

The aims of this study were to (i) estimate the incidence and predictors of AKI in a referred cohort of CKD patients and (ii) determine the risk of end-stage renal disease (ESRD) and mortality prior to dialysis associated with AKI in such a cohort. The purpose of such an analysis would be to inform clinicians as to the incidence and impact of changes in serum creatinine/estimated glomerular filtration rate (eGFR), which may help in prognostication and long-term treatment adjustments.

Materials and methods

Data source

For this study, we used the provincial CKD registry (Patient Registration and Outcomes Management Information System) that includes all patients referred to nephrologists or on dialysis therapy in British Columbia, the third largest province in Canada with a population with more than 4 million persons.

Cohort definition

We created an analytic cohort of all subjects registered as having CKD between November 2002 and November 2007 who, after being registered, had been followed up for at least 6 months and had at least three eGFR values. These restrictions were applied to ensure inclusion of only long-term patients seen by nephrologists. To ensure a certain degree of homo-
Fig. 1. Definition of AKI and cohort follow-up diagram: follow-up started at the first eGFR value ≤30 mL/min/1.73 m² (index eGFR); the index eGFR could occur anywhere during the follow-up (it could be the first eGFR value in the registry or a further value without being limited to three); patients were followed up from the index eGFR until the earliest of the following event: dialysis, kidney transplantation, death, lost to follow-up or end of the study; after cohort entry, each longitudinal eGFR value was compared to a baseline eGFR to identify a possible AKI event; the baseline eGFR value was calculated as the average of the last eGFR values (maximum three values) found in a time period from 25 up to 180 days prior to the eGFR being evaluated (nth eGFR value in the diagram), thus the baseline assessment period was moving along with follow-up; AKI was defined as a decrease in eGFR of at least 25% and of more than 5 mL/min/1.73 m² (AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate).

Definition of covariates
Baseline variables included age, sex, eGFR and time before cohort entry (interval between entry in the CKD registry and the first eGFR value ≤30 mL/min/1.73 m²). An eGFR values were captured by automatic uploading from provincial and public laboratory databases and were thus inclusive of all blood work ordered in that patient group.

Definition of outcomes
No definition has been clearly validated for AKI occurring in a cohort of CKD patients. Traditionally, retrospective observational studies used the International Classification of Disease, Ninth Revision (ICD-9) codes, but those are known to have a poor sensitivity and are dependent on the coding physician’s definition of AKI leading to a heterogeneous set of outcomes [9]. Recently, some laboratory-based AKI definitions have been proposed by the Acute Kidney Injury Network, but those definitions were designed for a prospective use in a hospital setting and include urine output [10]. Moreover, the authors recognized that those criteria may not be applicable to patients with CKD and removed the “acute on chronic disease” category that was present in the previous definitions [10,11]. However, we adapted those definitions to be used in our longitudinal cohort since they are currently the most widely used definitions. We defined AKI as a decrease in eGFR of at least 25% and of more than 5 mL/min/1.73 m² compared to a baseline eGFR (Figure 1). Since CKD is a progressing disease, the baseline eGFR was computed as a moving average (i.e. recalculated at every new eGFR value during follow-up) of the last eGFR values (maximum of three values). All baseline eGFR values used to compute the baseline were taken at least 25 days (but no more than 180 days) prior to the considered time. Based on the fact that stable patients may have eGFR measurements with a frequency of up to once a month, inserting a 25-day gap ensured that the baseline comparison was similar for every subject and was not dependent on the frequency of laboratory tests during the AKI event (e.g. during hospitalization, an information not available in the database). The maximum look-back time period (180 days) for the baseline eGFR was set to ensure that patients with rapid progression of kidney disease were not considered cases of AKI. In order to evaluate the occurrence of multiple events, patients were considered susceptible for another AKI event when, as a proxy for return to a stable eGFR, the intervals between eGFR tests were of at least 25 days. When computing the baseline eGFR for the possibility of a recurring event, values occurring prior to or defining the previous AKI episode were excluded. Initiation of dialysis and pre-dialysis mortality were other outcomes.

Continuous variables are reported as the mean and standard deviation or the median with the first and third quartiles, as appropriate. Incidence rates of AKI were calculated by dividing the number of cases by the total person-time in follow-up. Confidence intervals (CI) for the incidence rates were calculated using Poisson regression. Relative risks (RR) associated with predictors of the first AKI were estimated using multivariable Cox proportional hazards models. Models were adjusted for sex, age, baseline eGFR and time in registry before cohort entry. The inclusion of this last variable aimed at reducing referral bias (selection bias). The determination of death and initiation of dialysis was estimated with multivariable time-dependent Cox proportional hazards models. In those models, AKI status was updated at the time of AKI. As a sensitivity analysis, we repeated all analyses where the maximum look-back time period for the baseline eGFR was set to 90 days instead of the 180 days used in the main analysis, in order to minimize even more the misclassification of ‘rapid CKD progressors’ as cases of AKI. Restricting the look-back period ensures that all creatinine values used for the baseline eGFR are no more than 3 months prior to the event and, consequently, that the eGFR decrease is acute.

We used a cut point of $\alpha = 0.05$ for statistical significance and we present the 95% CI. All statistical analyses were performed using R, version 2.9.1 (R Foundation for Statistical Computing, Vienna, Austria).

The study was approved by the University of British Columbia and the Providence Health Care Research Ethics Board.

Results
We identified 11395 patients registered as having CKD. Among those, 4533 subjects did not satisfy the inclusion criteria and were excluded, leaving 6862 subjects included in the analysis (see Figure 2). One hundred fifty-nine subjects had no subsequent eGFR values after their first value ≤30 mL/min/1.73 m².

Table 1 describes the demographics of the cohort in total and according to those who did and did not have an episode of AKI. The mean age was 69.8 (13.3) years, the proportion of females was 46.0%, the mean baseline eGFR was 23.6 (5.8) and the median time in the registry before entry in the cohort was 4.1 (1.8, 12.1) months (Table 1). Subjects were followed up for a median time of 19.4 months.
(11.1, 32.4) months and had a median number of 14 (7, 26) eGFR tests. The median number of days between eGFR tests was 28 (7, 47), and only 300 (4.4%) patients had at least one interval >1 year.

Incidence of AKI

We identified 3079 patients (44.9%) with at least one AKI event. Whilst most of those had only one event (n = 1987), 678 had two events and 414 had three or more events, for a total of 4785 events. Baseline characteristics for cases and non-cases of AKI are presented in Table 1. For AKI episodes (n = 4785), the median moving average baseline eGFR was 28.0 (22.0, 35.6), the median decrease in eGFR was 9.2 mL/min/1.73 m² (7.0, 12.8) and the median percentage eGFR reduction was 32.5% (28.1, 40.7%). Crude AKI incidence rates were 39.6 (95% CI = 38.5, 40.8) and 34.8 (95% CI = 33.6, 36.0) per 100 person-years for all events and first event, respectively. Incidence rates for the first AKI event stratified by age categories and sex are presented in Figure 3. According to Figures 3 and 4, AKI incidence tends to be lower in older age groups, with a more pronounced effect in males.

In the multivariable survival models of time to the first AKI event, older age (adjusted RR = 0.93 by 10 years, 95% CI = 0.90, 0.95) and eGFR (RR = 0.92 by 5 mL/min/1.73 m², 95% CI = 0.89, 0.95) were associated with a lower risk of AKI (Table 2). The protective effect of age tended to be greater among males compared to females (RR = 0.91 in males versus RR = 0.95 in females).

Outcomes of AKI

During follow-up, 1047 patients died (15.3%) before dialysis and 1244 initiated dialysis (18.1%). The proportions appeared to be slightly different among cases of AKI (deaths = 18.0%, dialysis = 23.1%) than among non-cases (deaths = 13.0%, dialysis = 14.1%). Predicted and adjusted Nelson–Aalen curves of dialysis-free survival and mortality are presented in Figure 5.

In multivariable survival models (Table 3), AKI (RR = 2.32, 95% CI = 2.04, 2.64) and older age (RR = 1.87 by 10 years, 95% CI = 1.75, 2.00) were associated with a higher

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**Table 1.** Baseline characteristics of study subjects

<table>
<thead>
<tr>
<th></th>
<th>All (n = 6862)</th>
<th>AKI (n = 3079)</th>
<th>No AKI (n = 3783)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>69.8 (13.3)</td>
<td>68.0 (13.2)</td>
<td>70.6 (13.4)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>46.0</td>
<td>45.4</td>
<td>46.6</td>
</tr>
<tr>
<td>Mean baseline eGFR (mL/min/1.73 m²)</td>
<td>23.6 (5.8)</td>
<td>23.7 (5.5)</td>
<td>23.6 (6.0)</td>
</tr>
<tr>
<td>Median time in registry before cohort entry (months)</td>
<td>4.1 (1.8, 12.1)</td>
<td>3.9 (1.8, 11.2)</td>
<td>4.3 (1.9, 12.6)</td>
</tr>
<tr>
<td>Median follow-up time (months)</td>
<td>19.4 (11.1, 32.4)</td>
<td>22.9 (13.4, 36.3)</td>
<td>17.0 (9.5, 28.9)</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury.

**Fig. 2.** Derivation of patient cohort from all CKD patients registered between 2002 and 2007 in British Columbia (BC, British Columbia; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate).

**Fig. 3.** Incidence rates for the first AKI event by sex and age categories (error bars on the graph represent 95% CI for the rates; AKI, acute kidney injury).

**Fig. 4.** Nelson–Aalen cumulative incidence function of death for all patients.
risk of death, whereas female sex (RR = 0.75, 95% CI = 0.67, 0.86) and eGFR (RR = 0.81 by 5 mL/min/1.73 m², 95% CI = 0.76, 0.85) was associated with a lower risk of death. AKI (RR = 2.33, 95% CI = 2.07, 2.61) was also associated with an increased risk of dialysis, whereas older age (RR = 0.78 by 10 years, 95% CI = 0.75, 0.81), female sex (RR = 0.76, 95% CI = 0.68, 0.85) and eGFR (RR = 0.63 by 5 mL/min/1.73 m², 95% CI = 0.60, 0.65) were associated with a lower risk of dialysis initiation. The association between AKI and dialysis or death did not appear to be only due to severe cases of AKI since the results were similar when we kept only the AKI events defined as an eGFR decrease between 25 and 50% (RR of death = 2.27, 95% CI = 1.99, 2.60 and RR of dialysis = 2.59, 95% CI = 2.29, 2.92). The risk of death or dialysis initiation associated with AKI tended to be lower in patients with a baseline eGFR between 10 and 20 mL/min/1.73 m² (RR of death = 2.00, 95% CI = 1.56, 2.55 and RR of dialysis = 1.28, 95% CI = 1.07, 1.53) compared to above 20 mL/min/1.73 m² (RR of death = 2.52, 95% CI = 2.17, 2.94 and RR of dialysis = 4.88, 95% CI = 4.08, 5.84). Due to small numbers, we could not evaluate the group with a baseline eGFR below 10 mL/min/1.73 m². In the

<table>
<thead>
<tr>
<th>Table 2. Multivariable survival models of time to AKI</th>
</tr>
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<tbody>
<tr>
<td>All</td>
</tr>
<tr>
<td>Adjusted RR</td>
</tr>
<tr>
<td>Age (by 10 years)</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>eGFR (by 5 mL/min/1.73 m²)</td>
</tr>
<tr>
<td>Time in registry before cohort entry (years)</td>
</tr>
</tbody>
</table>

CI, confidence interval; eGFR, estimated glomerular filtration rate; RR, relative risk.
Table 3. Multivariable survival models of time to pre-dialysis mortality and time to dialysis initiation

<table>
<thead>
<tr>
<th>Risk of pre-dialysis mortality</th>
<th>Risk of dialysis initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted RR</td>
</tr>
<tr>
<td>AKI</td>
<td>2.32</td>
</tr>
<tr>
<td>Age (by 10 years)</td>
<td>1.87</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (by 5 mL/min/1.73 m²)</td>
<td>0.81</td>
</tr>
<tr>
<td>Time in registry before cohort entry (by year)</td>
<td>1.15</td>
</tr>
</tbody>
</table>

CI, confidence interval; eGFR, estimated glomerular filtration rate; RR, relative risk.

Discussion

To our knowledge, this is the first study to evaluate the incidence and outcomes of AKI in a referred cohort of CKD patients under the active care of nephrologists. We found a relatively high incidence of AKI and that younger age and male sex are associated with a higher risk of AKI. Our study was able to show that the incident event of AKI is associated with a future higher risk of both dialysis and mortality prior to dialysis in this referred cohort of CKD patients.

Until recently, the epidemiology of AKI has been almost exclusively studied among hospitalized patients, mostly in intensive care units [12–17]. There are a few recent studies which have evaluated the incidence of AKI at a population level showing incidence rates varying from 181 to 522 per 100,000 person-years, depending on the AKI definition [3,4,18]. However, few studies have evaluated the incidence of AKI in CKD patients. Ali et al. [3] reported a lower incidence of acute on chronic kidney injury (33.6 per 100,000 person-years), but this estimate used the entire population as the denominator and not the subgroup of CKD patients. Among Medicare patients discharged alive, the incidence of AKI was 2.3% in non-CKD patients versus 8.8% in CKD patients [17]. In addition, again using administrative data, CKD was also found as a strong predictor of dialysis-requiring AKI in hospitalized patients, the risk rising from approximately 2-fold up to 40-fold with increasing severity of kidney disease [5]. Given this background, it is not surprising that we found higher incidence rates of AKI in our population of CKD patients than the estimates previously reported at a population level. Note that our definition does not rely on administrative data, but rather on actual changes in serum creatinine or eGFR within a fixed time period.

By stratifying community-based incidence rates of AKI, Hsu et al. [4] showed higher rates in males compared to females and increasing rates with older age. Whilst we also found a higher risk of AKI with male sex, older age was a protective factor in our study. This may be explained by the different populations under study and the underlying kidney disease. Since our cohort includes only patients with relatively severe CKD (≤30 mL/min/1.73 m²), to be included at a younger age is probably associated with various comorbidities and a more aggressive underlying kidney disease, thus potentially increasing the probability of AKI events.

AKI has been associated with a higher risk of in-hospital mortality, mostly if dialysis is needed or in conjunction with multi-organ failure [19,20]. However, there have been conflicting reports whether CKD increases this risk or not: among hospitalized patients with AKI, the 6-month mortality risk was higher in the subgroup of patients with CKD than those without [3], whereas, in a study using the Nationwide Inpatient Sample, in-hospital mortality associated with AKI was lower in patients with CKD compared to patients without CKD [18]. In another study, AKI was associated with an increased risk of ESRD, and this risk was higher in the subgroup of patients with CKD than those without [17]. Finally, in hospitalized patients with an eGFR <45 mL/min/1.73 m², dialysis-requiring AKI was associated with an increased risk of death and ESRD [6].

Of note, in this referred population, only a minority of patients will die before initiating dialysis, which is different from population-based studies where death before dialysis is more common [2]. Again, the differences between referred cohorts receiving care by expert teams and the impact that it has on outcomes must be acknowledged. We have previously reported the variability in kidney disease progression within a referred cohort. We identified that 25% of patients have no progression and the remainder has progression rates that are variable, with approximately 47% of the cohort having loss of eGFR of between 1 and 5 mL/min/1.73 m² per year [21].

Our study differs from the previous studies in many ways. One strength is that it includes a relatively large population of CKD patients who have achieved Stage 4 and 5 and in whom a substantial follow-up period exists. The current report is unique in that we have purposefully evaluated outcomes after an AKI event in a referred CKD cohort, which has not previously been done. Availability of longitudinal outpatient and inpatient laboratory data by automatic uploading is also a strength of this dataset, since it allows identification of AKI events in an outpatient setting (no requirement for hospitalization) and using a laboratory-based definition which is more sensitive than...
ICD-9 codes [9]. Indeed, many studies investigating AKI on CKD were limited by those codes [5,17,18]. Moreover, our definition of AKI using patient-level data and actual serum creatinine values (calibrated and standardized to eGFR estimates) did not require the identification by the physician of AKI with billing coded accordingly, as is the case in previous studies on AKI using codes. Our estimate of AKI (using the definition of change of >25% from baseline within a fixed time period) reflects the current uncertainty that exists in the literature regarding best definitions, but is concurrent with the definitions. As well, there remains some controversy around the meaning of small changes in serum creatinine in those with already abnormal kidney function, thus again our justification for using this definition. We describe a high incidence of significant AKI episodes wherein the GFR dropped by ≥25% and >5 mL/min within a short period. These conservative definitions attempt to differentiate AKI from ‘rapid progressors’ as their rates are usually <10 mL/min over a 12-month period. The fact that the results are similar in the sensitivity analysis where the look-back period was set to 90 days increases our confidence that true AKI cases were identified.

The clinical utility of this study is that it provides a threshold cut-off which can be used by clinicians and researchers which helps to define AKI within CKD populations. The fluctuations in serum creatinine (and thus eGFR) seen over time in chronic patients have not been previously systematically evaluated using this approach. For clinicians that follow up those patients, knowing the frequency and impact of those acute outpatient drops of eGFR may well be important for prognostication and perhaps for identifying those with ‘lower renal reserve’ and thus susceptible to external insults.

Our study has several limitations, as do all observational cohort studies. As previously noted, intervals between eGFR tests were determined on a clinical basis and not pre-specified, so that there may have been decreases in eGFR which occurred within shorter or longer periods of time and some of the episodes of AKI might have been missed. This would serve to conservatively bias our results regarding incidence. We were particularly cautious about identifying further AKI events after the first one, so again we may have missed true distinct events, again underestimating true incidence. Irrespective, multiple events were not used in any of the models, thus we are unable to appropriately determine the impact of more than one episode of AKI on outcomes, but do demonstrate the profound impact of that event. Our referred cohort is a selected population, which was the purpose of this study. Whilst this may limit the generalizability of our results to other populations, there are a large number of Stage 4 and 5 patients followed up by nephrology teams and the results can be applied to those patients. Finally, because a limited number of covariates were included in the multivariable models, the associations we found with some factors may not be direct, but those factors may be markers for unmeasured variables and be confounded. Nonetheless, the consistency of our results with those of others makes this a relative limitation.

This study showed that AKI, defined conservatively, is a frequent event in a referred CKD population. The risk appears to be less with older age in this population. Quantification of AKI incidence and its risk factors in different populations is important for clinicians and planners, so that appropriate identification, prevention and treatment strategies can be tested. Reduction of AKI incidence may benefit survival and delay dialysis initiation. Further studies are needed to evaluate triggers and/or causes of AKI in this population and how AKI can be prevented.

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Conflict of interest statement. None declared.

References
Serum IL-17 and IL-23 levels and autoantigen-specific Th17 cells are elevated in patients with ANCA-associated vasculitis

Estela Nogueira 1,2,*, Sally Hamour 1,*, Devika Sawant 1, Scott Henderson 1, Nicholas Mansfield 1, Konstantia-Maria Chavele 1, Charles D. Pusey 1 and Alan D. Salama 1

1 Imperial College Kidney and Transplant Institute, Division of Medicine, Imperial College London, Hammersmith Hospital, London, UK and 2 Servico de Nefrologia, Centro Hospitalar de Vila Nova de Gaia/Espinho, Porto, Portugal

*Equal contribution.

Abstract

Background. The Th17 subset has been implicated in the pathogenesis of a number of autoimmune diseases. However, little is known about its role in anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV). We measured serum levels of IL-17A and the associated upstream cytokines and the frequency of IL-17-producing autoantigen-specific T cells in patients with AAV.

Methods. ELISA on sera from acute (n = 28) and convalescent (n = 65) patients with AAV from Hammersmith Hospital was performed for IL-17A and the associated upstream cytokines IL-23, IL-6 and IL-1β, as well as the Th1 cytokine IFN-γ. ELISPOT was performed to measure autoantigen-specific recall T cell responses in convalescent patients and the frequency of IL-17- and IFN-γ-producing cells.

Results. Serum IL-17A and IL-23 levels were significantly elevated in patients compared to healthy controls (P < 0.01 and P < 0.001, respectively), but importantly, remained elevated in a proportion of convalescent patients. By contrast, no significant differences in IFN-γ levels were detected between patient groups and controls. Patients with elevated levels of IL-23 compared to those with low IL-23 had more active disease as measured by Birmingham Vasculitis Activity Score (P < 0.05) and had higher ANCA titres (P < 0.05). Critically, immunosuppressive therapy did not always effectively suppress IL-23 or IL-17 production. Additionally, autoantigen-specific IL-17-producing, but not IFN-γ-producing, cells were significantly elevated in patients during disease convalescence compared to healthy controls.

Conclusions. These data implicate the Th17 axis and specifically IL-23 as mediators of more severe disease in AAV. Their persistence despite conventional treatment may contribute to high relapse rates.

Keywords: ANCA; cytokines; IL-17; IL-23; Th17; vasculitis

Introduction

Wegener’s granulomatosis (WG), microscopic polyangiitis (MPA) and Churg–Strauss syndrome (CSS) are idiopathic multi-system vasculitides affecting small-calibre blood vessels. They are characterized by the production of anti-neutrophil cytoplasm antibodies (ANCA), reactive to either proteinase-3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA), constituents of neutrophil granules and monocyte lysosomes. Over 70% of patients with ANCA-associated vasculitis (AAV) have renal involvement ranging from indolent disease to rapidly progressive glomerulonephritis and end-stage renal failure. Renal disease is the most important prognostic feature and renal failure constitutes the commonest cause of death after treatment-related infection. Despite advances in immunosuppression regimes, relapse rates in AAV remain high.

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