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ORIGINAL ARTICLE

Long-term outcome in biopsy-proven acute interstitial nephritis treated with steroids

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Abstract

Background: There are no prospective randomized controlled trials describing the outcome of acute interstitial nephritis (AIN) treated with steroids, and retrospective studies are limited.

Methods: We identified adult patients with a diagnosis of AIN without glomerular pathology over a 14-year period. Treated patients all received oral prednisolone and three also recieved IV methylprednisolone. Data were collected retrospectively on estimated glomerular filtration rate (eGFR), change in eGFR from time of biopsy, dependence on renal replacement therapy (RRT) and mortality, and outcomes were analysed according to the treatment prescribed.

Results: A total of 187 eligible patients with AIN were identified and 158 were treated with steroids. There was no difference in median eGFR or dependence on RRT at the time of biopsy. Steroid-treated patients had significantly higher eGFR at all time points post-biopsy up to 24 months, when median eGFR was 43 mL/min in the steroid-treated group and 24 mL/min in the untreated group ($P = 0.01$). Fewer patients in the steroid-treated group were dialysis dependent by 6 months (3.2% versus 20.6%, $P = 0.0022$) and 24 months (5.1% versus 24.1%, $P = 0.0019$).

Conclusions: This large retrospective study suggests a benefit of steroids in treatment of AIN with greater improvement in eGFR and fewer patients progressing to end-stage renal disease.

Key words: acute interstitial nephritis, renal pathology, steroid therapy

Introduction

Acute interstitial nephritis (AIN) is a common cause of acute kidney injury (AKI). AIN was found in 6% of almost 4000 native renal biopsies performed at our centre between 1998 and 2011. Other large series have shown AIN to be present in 1–3% of biopsies and in those biopsied for AKI, AIN is present in up to 27% [1–3]. In patients over 60 years of age, AIN has been shown to be present in around 10% of biopsies [4]. In several case series AIN was shown to be increasing in incidence, particularly in the elderly, although this may also be due to increased rates of biopsy and detection in this group [5–9].

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AIN was classically described as related to infection, and tuberculosis (TB) remains an important cause in our series [10]. More recently, AIN has typically been described as a drug-related phenomenon, initially with methicillin and now with a broad range of medicines including antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) [11–13]. Increasingly, proton pump inhibitors (PPIs) are being identified as a common cause of AIN [14–16]. It has also been reported in association with inflammatory conditions such as sarcoidosis, IgG4-related disease and as part of the tubulointerstitial nephritis and uveitis (TINU) syndrome [17–19].

The clinical features of AIN may include those of hypersensitivity in drug-induced cases, with fever, arthralgia, skin rash and eosinophilia; however, these are not present in all patients. Urine dipstick may show haematuria or low-grade proteinuria, but these features may also be absent. Given the lack of reliable clinical signs, renal biopsy is needed for diagnosis. Biopsy typically shows an interstitial inflammatory infiltrate composed mainly of lymphocytes together with plasma cells and macrophages. As AIN progresses, interstitial fibrosis and tubular atrophy may develop, leading to chronic kidney disease and sometimes end-stage renal disease (ESRD) [20].

The role of steroids in treatment of AIN remains controversial, with no prospective randomized controlled trials and conflicting evidence from retrospective series [6, 7, 21–24]. There are several small series showing a benefit for steroids when AIN is due to sarcoidosis [25, 26]. We performed a retrospective analysis of 187 patients diagnosed with AIN on renal biopsy in our centre, the largest reported series, with the aim of evaluating the benefit of steroids in treatment.

Materials and methods

Subjects

All patients with AIN on renal biopsy were identified from our biopsy database over a 14-year period. The criteria for diagnosis were the presence of an interstitial inflammatory cell infiltrate around non-atrophic tubules, with tubulitis in the absence of ascending bacterial infection. A retrospective analysis of medical records and biopsy reports was carried out and data collected on age, gender, ethnicity, biopsy features, estimated glomerular filtration rate (eGFR) and the need for RRT at the time of biopsy. Drug-induced AIN was only documented if this was clearly defined in the notes by the clinician responsible and the drug concerned discontinued. Patients were excluded if already on maintenance steroids, if there was a co-existing glomerulonephritis present on the biopsy, if they had <3 months follow up or if insufficient clinical information was available. The MDRD-4 calculation was used for eGFR and for analysis patients were divided into categories of eGFR >60 mL/min, 30–60 mL/min, 15–30 mL/min, <15 mL/min and requiring RRT.

Treatment and outcomes

The patients were divided into those treated with steroids and those not treated. The dose and duration of steroid therapy were determined by clinician choice and documented when available. Response to treatment was assessed by both absolute values for eGFR and change from baseline eGFR. Timepoints 1, 3, 6, 12 and 24 months, and final (last value documented for each patient) were used for follow up. For 6 and 12 month time points, results 1 month either side were allowed; for 24 months this was extended to 2 months either side. Dependence on RRT and mortality data were collected. Patients with documented drug-induced AIN and those with TB were analysed as subgroups.

Statistics

Data are reported as median values with range unless otherwise stated. Mann–Whitney U test was used for continuous variables and chi-squared for the difference in proportions between two groups. Results are reported as significant when $P < 0.05$. The Kaplan–Meier analysis was used to calculate probabilities of survival. In order to attempt to control for a number of possible confounding factors, a matched group was identified using variables that gave a propensity for patients to be treated with steroids or not. Patients in the steroid-untreated group were matched with a patient in the treated group according to diabetic status, category of renal function at the time of presentation and the closest match for age possible.

Results

Over the 14-year period analysed, 3983 native renal biopsies were performed in our centre. We identified 238 patients with AIN; 51 of these were excluded (28 had insufficient clinical information, 11 with co-existing glomerular pathology, 4 already on maintenance prednisolone and 8 with length of follow up <3 months), leaving 187 patients for analysis. The median age of the patients at presentation was 52.4 years (range 16.4–87.8 years). In all, 98 patients were males and 89 females. The median duration of follow up was 39 months (3–164 months). The most common aetiology was drug-induced AIN (D-AIN); however, its true incidence was probably underestimated as aetiology was only documented as drug induced if there was clear documentation of a putative causative agent that was promptly discontinued (Figure 1). Patients diagnosed with AIN caused by TB were treated with quadruple anti-tuberculous (TB) therapy in addition to steroids if used.

One hundred and fifty-eight patients were treated with steroids and 29 were managed conservatively. Patients receiving steroids were all treated with oral prednisolone and three patients received methylprednisolone prior to oral prednisolone. Dose and duration of treatment were variable as this was determined by clinician choice; however, most patients were prescribed either 40 mg or 60 mg of oral prednisolone daily. There was wide variation in duration of steroid therapy; 20.8% were still on steroids at their last appointment and of these 10 patients required steroids for an underlying or unrelated inflammatory condition. Thirty-two patients (20.2%) were off steroids by 3 months and the median duration of treatment was 6 months (1 week–5 years).

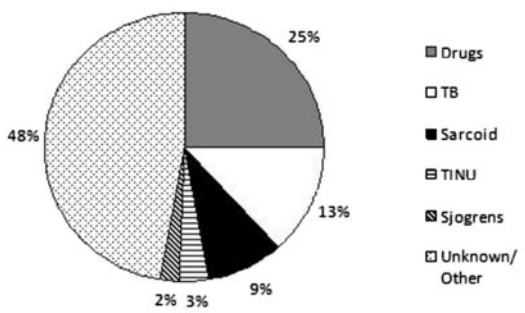

Fig. 1. Aetiology of AIN in this series. The proportion with D-AIN is probably underestimated due to strict inclusion criteria.

Table 1. Baseline characteristics of steroid-treated and not treated groups

	Steroid treated	Not treated
N	158	29
M/F	80/78	18/11
Age (years)	52.2 (16.4–85.3)	53.8 (19.2–87.8)
Length of follow up (months)	39.9 (3–164)	35 (4–121)
Aetiology [*n* (%)]	Drugs 44 (27%), TINU 6 (3.7%), sarcoid-16 (10%), TB 19 (11.9%), Sjogrens-4 (2.5%)	Drugs 3 (13.8%), sarcoid 1 (3.4%), TB 6 (20.7%)
Granulomatous TIN [*n* (%)]	40 (25.3%)	6 (20.7%)
eGFR at biopsy (mL/min)	20.5 (5–110)	25 (5–59)
Median category of renal function at presentation (mL/min)	15–30	30–60
RRT dependent at presentation [*n* (%)]	19 (12.0%)	4 (13.8%)
Diabetic at presentation [*n* (%)]	20 (12.6%)	10 (34.5%)
Tubular atrophy (%)	30 (0–80), $n = 115$	30 (0–90), $n = 27$

Values are given as median with range unless otherwise indicated.

The baseline characteristics of the two groups according to treatment were comparable and are shown in Table 1. The groups were well matched in terms of age, gender, length of follow up, eGFR at biopsy and dependence on RRT at biopsy, although there was a greater proportion of patients with diabetes at diagnosis in the group not treated with steroids. Degree of tubular atrophy was harder to assess as biopsy reports often did not record this, but where data were available the percentage of tubular atrophy was similar between groups. There were relatively more patients with the D-AIN in the steroid-treated group and more with TB in the untreated group.

The steroid-treated group had a significantly higher eGFR at 6, 12 and 24 months and at final follow up, as shown in Figure 2. In an attempt to control for selection bias, we compared the group not treated with steroids with a matched group of 29 steroid-treated patients. The patients were matched by category of eGFR at biopsy, diabetic status and age. Matched steroid-treated patients had a higher eGFR compared with untreated patients; however, this was not statistically significant (except for final follow up), possibly due to the smaller numbers (Figure 2).

The improvement in eGFR from time of biopsy to all time points was also better in the steroid-treated group, with a median change in eGFR of 0 mL/min at all-time points in the untreated group, and of +10 mL/min by 3 months ($P < 0.0001$), +16 mL/min by 6 months ($P < 0.0001$) and +13 mL/min by 24 months ($P < 0.0001$) in the treated group.

Patients treated with steroids were more likely to maintain or recover independent renal function; a lower proportion of patients in the steroid-treated group were dependent on some form of RRT at 6 months (3.2% versus 20.6%, $P = 0.0022$) and 24 months (5.1% versus 24.1%, $P = 0.0019$). At last follow up, 9.4% of the steroid-treated patients and 34.4% of the untreated patients were dependent on RRT ($P = 0.0011$) (Figure 3). Within the matched steroid-treated group 6.9% of patients were dependent on RRT at both 6 and 24 months and 13.7% of patients were dependent on RRT at last follow up (Figure 3). Despite the large difference in outcome from the group not treated with steroids (data shown above) this was not statistically significant. There were also fewer deaths by 3 years in the steroid-treated group (6.9% versus 27.6%, $P = 0.0029$) (Figure 4).

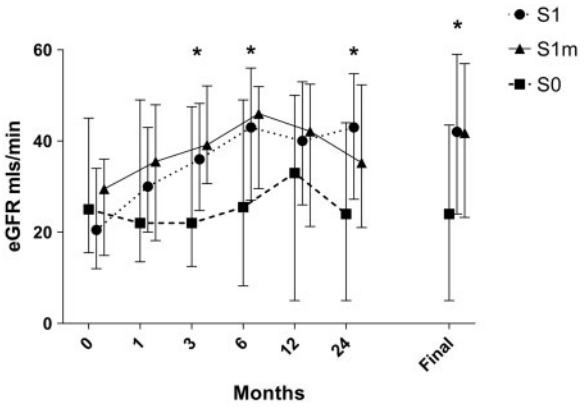

Fig. 2. Median eGFR with interquartile range at serial time points following biopsy and last documented follow up. S0: patients not treated with steroids; S1: all patients treated with steroids; S1m: matched group of patients treated with steroids. P-values refer to comparison of S0 and S1 except for last documented follow up, at which both S0 compared with S1 and S0 compared with S1m were significant. *$P < 0.05$.

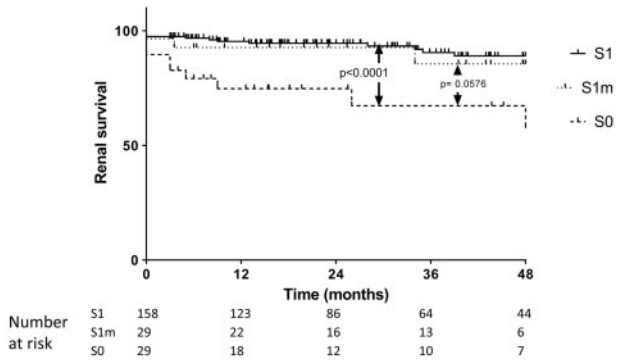

Fig. 3. Kaplan–Meier curve showing survival with independent renal function in all patients treated with steroids (S1), matched group of steroid-treated patients (S1m) and those not treated (S0).

Drug-induced AIN

Forty-eight of the patients had clearly defined D-AIN. The most common drugs implicated were antibiotics ($n = 17$, 36.2%), NSAIDs ($n = 12$, 25.5%) and PPI ($n = 5$, 10%). Relatively more of these patients were treated with steroids ($n = 45$, 93.8%) compared with the non-drug-induced group ($n = 113$, 81.4%), although this did not reach statistical significance ($P = 0.061$). An equal proportion of patients required RRT at presentation in the drug-induced and non-drug-induced groups ($P = 1.00$).

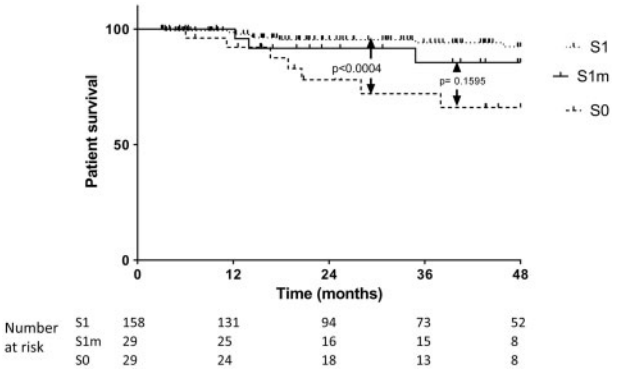

Fig. 4. Kaplan–Meier curve showing patient survival in all patients treated with steroids (S1), matched group of steroid-treated patients (S1m) and those not treated (S0).

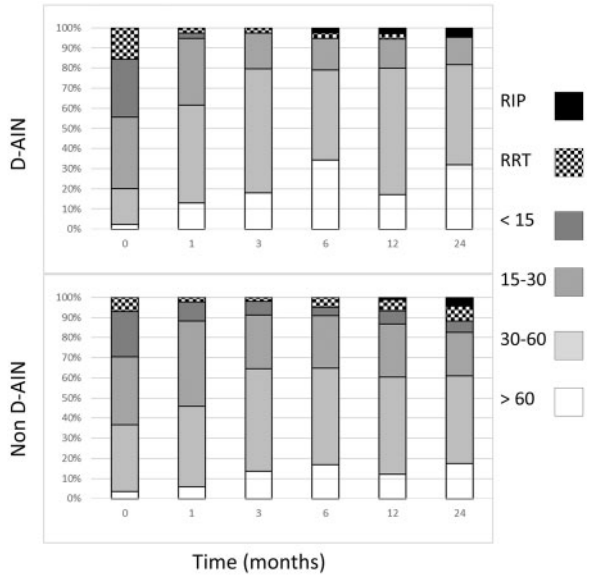

Fig. 5. Category of eGFR in steroid-treated patients with D-AIN and those treated but with another cause for AIN.

Of all patients treated with steroids, we compared those identified as having D-AIN with all other aetiologies. Those with D-AIN had significantly worse eGFR category at the time of biopsy but a higher eGFR category at all time points following biopsy, demonstrating a relatively better response to treatment (Figure 5).

The baseline characteristics of the drug-induced group according to treatment were similar, with median age 55.1 years and 59% of male patients in the steroid-treated group ($n = 45$), and 52.8 years and 33.3% of male in the untreated group ($n = 3$). The median length of follow up was 20 months (range 3–150) in the steroid-treated group and 19 months (12–25) in the untreated group. Six of the 44 (13.65%) patients treated with steroids required RRT at the time of biopsy and none of the untreated patients required RRT. Moreover, eGFR in the treated group was worse at biopsy than in those not treated with steroids [17 mL/min (5–62) versus 38 mL/min (12–51)].

Statistical analysis was not performed due to small numbers of untreated patients. Due to the worse eGFR at the time of biopsy, absolute values for eGFR were lower in the steroid-treated group at 6 months (48 mL/min versus 55 mL/min), but by 12 months the eGFR in the treated group was higher (47 mL/min versus 42 mL/min). The steroid-treated group showed more improvement in creatinine from baseline to 6 months than the untreated group (+29.5 mL/min versus +13 mL/min), baseline to 12 months (+21 mL/min versus −1 mL/min) and baseline to last follow up (+25 mL/min versus −2 mL/min). Of the six patients requiring RRT at biopsy in the steroid-treated group, five regained independent renal function. One further treated patient developed ESRD although he was noted to be non-adherent with steroid therapy.

AIN related to TB

Twenty-six patients were diagnosed as having TB and treated with full-dose anti-TB therapy for at least 6 months. Twelve (46.1%) patients were of Indian ethnicity, four (15.4%) Pakistani, three (11.5%) other Asian, three (11.5%) African, one (3.8%) British and three (11.5%) other or unspecified ethnicity. One patient was already receiving anti-TB therapy at the time of biopsy, the others all began treatment post-biopsy. Twenty-three (88.4%) patients had granulomatous interstitial nephritis. No patients had evidence of acid fast bacilli on renal biopsy and diagnosis of TB was made on the basis of the clinical findings and other investigations. Twenty of these patients were treated with steroids and six were not. Eight of the steroid-treated patients and four of the untreated patients were male. The median age was 38.4 years in the steroid-treated group and 55.0 years in the untreated group. eGFR at the time of biopsy was 25 mL/min and 19 mL/min in steroid-treated and untreated groups, respectively, and two patients in each group were dependent on dialysis at time of biopsy.

Statistical analysis was not performed due to the small numbers, but patients treated with steroids in addition to anti-TB therapy had higher eGFR than the untreated patients at 1 month (28.5 mL/min versus 21.5 mL/min), 3 months (31.0 mL/min versus 20.0 mL/min), 6 months (27.0 mL/min versus 17.5 mL/min), 12 months (27.0 mL/min versus 17.0 mL/min) and 24 months (26.0 mL/min versus 19.5 mL/min). The improvement in eGFR from the time of biopsy to all time points was also better in the steroid-treated group, with a greater median change in eGFR at 6 months (+10.5 mL/min versus −0.5 mL/min) and 12 months (+7.0 mL/min versus +3.0 mL/min). A lower proportion of the steroid-treated patients were dependent on dialysis at 6 months (5% versus 33.3%) and 24 months (10% versus 33.3%).

Discussion

AIN is a common cause of AKI, possibly with increasing incidence over recent years [8, 27]. D-AIN is the most common aetiology, but there is a broad range of other causes [6].

The role for steroid therapy remains controversial, with no prospective trials. There is conflicting evidence from retrospective series, with some studies suggesting a benefit for steroids, with faster and greater recovery of renal function [12, 22], whereas other studies have showed no benefit of steroid treatment [5, 7, 24]. The outcomes of recent published series are summarized in Table 2. In this study, we report a large retrospective series with a long median follow up (39 months). We show that steroids lead to improvement in eGFR and fewer patients requiring RRT. There was also improved survival of patients treated with steroids, perhaps because fewer of them developed ESRD. When we attempted to control for selection bias by comparing a matched group of steroid-treated patients with those not treated with steroids there was a trend towards greater improvement in eGFR and RRT-free survival. These

Table 2. Summary and outcome of larger published series of AIN

Reference	Year	Cases	Aetiology	Treatment	Severity of renal dysfunction	Proportion steroid treated	Outcome
Clarkson *et al.* [24]	2004	60	92% drug induced	Methylprednisolone 500 mg IV 2-4 days, oral prednisolone 0.75 mg/kg tapered over 3–6 weeks	58% RRT dependent, median peak creatinine 670 μmol/L	60%	No difference in serum creatinine at 1 year
Gonzalez *et al.* [22]	2008	61	100% drug induced	Methylprednisolone 250–500 mg IV for 3–4 days, oral prednisolone 1 mg/kg tapered over 8–12 weeks	23% RRT dependent, mean peak creatinine 504 μmol/L	85%	Higher serum creatinine at last follow up in those not steroid treated (327 μmol/L versus 185 μmol/L), more patients RRT dependent (44.4% versus 3.8%)
Raza *et al.* [28]	2012	49	67% drug induced	Oral prednisolone 1 mg/kg to maximum 60 mg/day	22.4% RRT dependent, mean creatinine 548 μmol/L	75%	Greater improvement in creatinine in steroid-treated patients (3.4-fold versus 2.1-fold)
Muriithi *et al.* [5]	2014	133	70% drug induced	21% received IV methylprednisolone initially, median starting dose of oral prednisolone 60 mg for median 7.5 weeks	22% RRT dependent, median peak creatinine 335 μmol/L (24% RRT and peak creatinine 380 μmol/L in D-AIN group)	86% (87% in D-AIN group)	Within D-AIN group, no difference in recovery of renal function within the first 6 months in steroid-treated group
Valluri *et al.* [7]	2015	171	73% drug induced	Prednisolone dose not stated. Median duration of treatment 3 months	19% RRT dependent, median creatinine 327 μmol/L at time of biopsy	63% (59% in D-AIN group)	Within D-AIN group, no difference in median creatinine at 1, 3 or 6 months. No difference in proportion of patients experiencing complete renal recovery (48% of steroid treated, 41% of steroid untreated. More severe AKI in those treated with steroids, median creatinine at biopsy 356 μmol/L compared to 280 μmol/L in those not treated)

results were not statistically significant, possibly due to small group size.

Gonzalez *et al.* [22] described a benefit from steroid treatment. They reported 61 patients with D-AIN; the most common drugs implicated were antibiotics. The 52 patients who were treated with steroids showed greater improvement in final serum creatinine and fewer patients requiring RRT. The authors also demonstrated that time to starting steroid treatment was important; those who completely recovered renal function started steroids at an earlier time point than those who had incomplete recovery. A more recent series by Raza *et al.* [28] reports 49 patients with AIN, 37 of whom were treated with steroids. They report a greater improvement in eGFR in patients treated with steroids; mean improvement in eGFR was 3.4-fold in the steroid-treated group compared with 2.0-fold in the untreated group.

The series reported by Clarkson *et al.* [24] showed no benefit for steroid treatment. They included complete data on 42 patients, 26 treated with steroids. The most common aetiology was D-AIN in 90% of cases. There was no difference in serum creatinine between the two groups at 1, 6 or 12 months. However, patients who developed ESRD were excluded from this analysis (7% of all patients). Valluri *et al.* [7] reported no significant difference in serum creatinine in steroid-treated and untreated patients with D-AIN. Steroid-treated patients had more severe AKI at the time of biopsy, suggesting greater improvement in renal function in these patients compared with those not treated. The series reported by Muriithi *et al.* [5] also showed no improvement in rates of renal recovery when patients with D-AIN were treated with steroids compared with those untreated. Again, the patients treated with steroids had lower baseline eGFR.

There was a lower incidence of D-AIN in our study than in other recent published series. This is most likely due to our stringent definition for inclusion in this group and the fact that cases were identified retrospectively from a biopsy database. It is likely that a significant proportion of the patients with an unknown cause for their AIN actually had D-AIN. When we analysed the subgroup of patients with D-AIN we again showed a benefit for steroid treatment, with greater improvement in eGFR in those treated with steroids compared with those not treated (although numbers were small). When steroid-treated patients

with D-AIN were compared with those treated, but with any other aetiology, they had a higher eGFR at all time points post-biopsy, despite having a lower eGFR at thetime of biopsy, suggesting a particular benefit of steroids in D-AIN.

There also seems to be a benefit for steroids in patients with AIN related to TB. The incidence of TB in our study was high, reflecting the high incidence of TB in our catchment area. London as a whole contributed 39% of the TB notifications in the UK in 2014; the highest rates of TB in London were within North West London; and of the top five local authorities for TB notification rates three are served by our referring hospitals [29]. Steroid-treated patients had a higher eGFR at all time points post-biopsy and a lower proportion of steroid-treated patients became dependent on RRT. Our patients with TB generally had worse outcomes when compared with patients with other causes for AIN. When the groups were compared (including both steroid-treated and untreated patients) there was a smaller median improvement in eGFR in the group with TB compared with other causes. The relatively poor prognosis of TB-related AIN has been described in other case series [30]. The mechanism by which TB causes a granulomatous interstitial nephritis, generally without evidence of acid fast bacilli on biopsy, remains unknown [31]. We would suggest that patients with AIN due to TB are treated with steroids in addition to anti-TB therapy.

Patients in our series were treated with higher total doses of steroids than in the Gonzalez series [22], which also showed a benefit of treatment. In a small number of patients, a rise in creatinine following rapid weaning of steroids prompted re-biopsy and re-introduction of steroids. We did not see a significant number of complications despite a more prolonged steroid course. Of the 171 patients for whom data were available, only eight patients (4.7%) were documented to have developed diabetes. Of these eight, two patients required chronic steroid treatment for other conditions and three of the eight had steroid courses that were of 4 months duration or less. All were aged 55 years or older at the time of biopsy.

There are several limitations to our study; in particular this is a retrospective series with some missing data. In addition, multiple clinicians at our centre treated patients with AIN with no defined protocol for steroid use, due to the lack of evidence. Decision to treat with steroids or not was down to clinician choice; however, propensity analysis identified that diabetic status, baseline renal function and age (non-significantly) correlated with whether or not patients received steroids. We therefore report a heterogeneous group of patients with considerable variation in steroid dose and duration. There was also variation in time to introduction of steroids, from within hours of biopsy to a few weeks. More patients were treated with steroids than not, which makes statistical analysis of subgroups difficult due to small numbers in the non-steroid-treated groups.

Despite the limitations, the outcome of this large series of patients with long-term follow up showing improvement in renal function, and some patients becoming dialysis independent during follow up, provides further evidence for the benefit of steroid therapy in AIN. Based on our results, we would suggest the use of oral prednisolone at 1 mg/kg with maximum dose 60 mg daily for treatment of AIN, to prevent development of chronic renal impairment and ESRD. Ideally, steroids should be rapidly weaned over the next 8–12 weeks to avoid the recognized complications. A randomized controlled trial of steroids in AIN would be required to provide stronger evidence for this approach.

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Conflict of interest statement

None declared.

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