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Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis

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The role of steroid treatment in drug-induced acute interstitial nephritis (DI-AIN) is controversial. We performed a multicenter retrospective study to determine the influence of steroids in 61 patients with biopsy-proven DI-AIN, 52 of whom were treated with steroids. The responsible drugs were antibiotics (56%), non-steroidal anti-inflammatory drugs (37%) or other drugs. The final serum creatinine was significantly lower in treated patients while almost half of untreated patients remained on chronic dialysis. Among treated patients, over half showed a complete recovery of baseline renal function, whereas the rest remained in renal failure. There were no significant initial differences between these two subgroups in terms of duration or dosage of steroids. After withdrawal of the presumed causative drug, we found that when steroid treatment was delayed (by an average of 34 days) renal function did not return to baseline levels compared to those who received steroid treatment within the first 2 weeks after withdrawal of the offending agent. We found a significant correlation between the delay in steroid treatment and the final serum creatinine. Renal biopsies, including three patients who underwent a second biopsy, showed a progression of interstitial fibrosis related to the delay in steroid treatment. Our study shows that steroids should be started promptly after diagnosis of DI-AIN to avoid subsequent interstitial fibrosis and an incomplete recovery of renal function.

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Drug-induced acute interstitial nephritis (DI-AIN) represents a significant cause of acute renal failure (ARF) in hospital practice.[1,2] As reported in some studies, about 15% of the renal biopsies performed in patients with ARF demonstrated a DI-AIN as the cause of the renal insufficiency.[3] Antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently implicated agents, but the list of drugs that can induce a DI-AIN is continuously increasing.[1] A general agreement exists about the discontinuation of the offending drug as the first therapeutic step in patients with DI-AIN. However, although renal function improves in a majority of patients after this measure, serum creatinine (Scr) does not return to its baseline value in a significant proportion of cases.[1,4]

Controversy persists about the role of steroids in the treatment of DI-AIN. Whereas some studies have reported a more rapid and complete recovery of baseline renal function in those patients treated with steroids,[5–7] others have failed to confirm these results.[8–10] Available information about the treatment of DI-AIN is based only on numerous case reports and observational series including a short number of cases. The absence of large retrospective series or prospective controlled studies is the main cause of the inconsistency of data regarding the most appropriate treatment for DI-AIN.

In this retrospective multicenter study, we analyzed the influence of steroid treatment and other factors that could influence the long-term outcome of DI-AIN. We gathered 61 patients with biopsy-proven DI-AIN, the largest series studied so far. All the patients had a known baseline Scr and all of them were followed during a period of time sufficient to adequately establish their long-term outcome. We found that steroid treatment induced a significant beneficial effect on the normalization of renal function. Furthermore, we found that a delay in the onset of steroid treatment after discontinuation of the responsible drug was the most significant factor to determine an incomplete recovery of baseline Scr.

RESULTS

A total of 61 biopsy-proven DI-AIN were analyzed. Demographic and clinical characteristics are expressed in Table 1. All the patients had a baseline Scr (1.1 ± 0.39; range 0.4–2.3 mg per 100 ml) obtained 7.5 ± 4.6 (range 0.5–16) months before the onset of DI-AIN. Baseline estimated glomerular filtration rate (eGFR) was 71 ± 25 (range 35–151 ml per min per 1.73 m^2). Twenty-two patients (36%) had a baseline eGFR lower than 60 ml per min per 1.73 m^2. The drug responsible for the DI-AIN episode was identified as an antibiotic in 34 patients (56%) (cephalosporins in 15 patients, quinolones in 12, and penicillins in 7), NSAIDs in 23 (37%), and other drugs (allopurinol, omeprazole, ranitidine, and pimozide) in the remaining four patients.

As expressed in Table 1, most of the patients presented some of the classic clinical characteristics of DI-AIN (fever, maculopapular rash, eosinophilia) with declining renal function, although only eight patients (13%) showed these three characteristics together. No significant differences in the incidence of rash and fever were observed between DI-AIN related to antibiotics, NSAIDs, and other drugs. Eosinophilia was significantly less common among patients with DI-AIN secondary to NSAIDs (18 vs 44% in DI-AIN not related to NSAIDs, $P < 0.05$). Most of the patients (40/61, 65%) showed proteinuria, ranging from 0.4 to 6 g/24 h, and abnormalities in the urinary sediment (microhematuria in 67% and leukocyturia in 82%). Baseline proteinuria was significantly higher in DI-AIN related to NSAIDs (1.4 ± 1.4 g/24 h) in comparison with DI-AIN secondary to other drugs (0.7 ± 0.8 g 24 h^{-1}; $P = 0.05$). Highest Scr oscillated between 1.5 and 13.3 mg per 100 ml with a mean of 5.7 ± 3.3 mg per 100 ml. Fourteen (23%) patients needed several sessions of hemodialysis due to the severity of their ARF.

Table 1 | Clinical characteristics of the patients

Characteristic	Value
Age (years)	57.7 ± 17.4 (range 18–81)
Gender (M/F)	39/22
Baseline Scr (mg per 100 ml)	1.1 ± 0.39 (range 0.4–2.3)
Baseline eGFR (ml per min per 1.73 m^2)	71 ± 25 (range 35–151)
Highest Scr (mg per 100 ml)	5.7 ± 3.3 (range 1.5–13.3)
Oliguria	14 (23%)
Skin rash	14 (23%)
Fever	26 (42%)
Eosinophilia (> 500 eosinophils/mm^3)	21 (34%)
Proteinuria (g/24 h)	0.9 ± 1.1 (range 0–6)
Microhematuria	41 (67%)
Leukocyturia	50 (82%)

eGFR, estimated glomerular filtration rate; F, female; M, male; Scr, serum creatinine.

Comparison between patients treated (Group 1) and untreated (Group 2) with steroids

Fifty-two patients were treated with steroids 23 ± 17 (range 2–68) days after the withdrawal of the offending drug (Group 1). Although steroid doses and duration of the treatment were not uniform due to the multicenter character of the study, the most common scheme of treatment consisted of intravenous pulses of methylprednisolone (250–500 mg daily for 3–4 consecutive days) followed by oral prednisone (1 mg/kg/day) tapering off over 8–12 weeks. The remaining nine patients did not receive steroids (Group 2). As expressed in Table 2, there were no differences in baseline characteristics (age, gender, baseline Scr and eGFR, type of offending drug, duration of treatment, highest Scr and proteinuria, or the interval between the withdrawal of the responsible drug and the performance of renal biopsy) between Group 1 and Group 2 patients. The final outcome of Group 1 patients (steroid treatment) was significantly better than that of Group 2 (no steroid treatment); as shown in Table 2, final Scr was significantly lower in Group 1 patients and a significantly higher proportion of Group 2 patients remained on chronic dialysis after the DI-AIN episode (44.4 vs 3.8%). No side effects attributable to steroid treatment were observed.

Comparison between steroid-treated patients who showed a complete (Group 1a) or an incomplete (Group 1b) recovery of baseline renal function

Twenty-eight out of 52 patients in Group 1 showed a complete recovery of baseline renal function after steroid treatment (Group 1a), whereas in the remaining 24 patients (Group 1b) renal function did not reach the baseline values. As expressed in Table 3, there were no significant differences

Table 2 | Characteristics of Group 1 (steroid treatment) and Group 2 (no steroid treatment)

	Group 1 (*n*=52)	Group 2 (*n*=9)	*P*-value
Age (years)	57.6 ± 17.5	58.1 ± 18	NS
Gender (M/F) (%)	61.5/38.5	77.8/22.2	NS
Baseline Scr (mg per 100 ml)	1.14 ± 0.4	1.13 ± 0.37	NS
Baseline eGFR (ml per min per 1.73 m^2)	71 ± 26	70 ± 25	NS
Offending drug (antibiotics/NSAIDs/others) (%)	53.8/34.6/11.5	66.7/33.3/0	NS
Duration of the treatment (days)	13.4 ± (r 3–60)	12.6 ± (range 4–30)	NS
Highest Scr (mg per 100 ml)	5.9 ± 3.4	4.9 ± 2.1	NS
Proteinuria (g/24 h)	1 ± 1.2 (range 0–6)	0.6 ± 0.6 (range 0–1.7)	NS
Complete recovery of renal function	28 (54%)	3 (33%)	NS
Chronic dialysis	2 (3.8 %)	4 (44.4 %)	< 0.001
Final Scr (mg per 100 ml)	2.1 ± 2.1 (range 0.7–12.7)	3.7 ± 2.9 (range 0.7–8.9)	< 0.05
Follow-up (months)	19 ± 19 (range 6–60)	18 ± 18 (range 6–56)	NS

eGFR, estimated glomerular filtration rate; F, female; M, male; NS, not significant; NSAID, non-steroidal anti-inflammatory drug; Scr, serum creatinine.