Treatment of Drug-Induced Acute Tubulointerstitial Nephritis

The Search for Better Evidence

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Acute tubulointerstitial nephritis (AIN) is a common cause of AKI and acute kidney disease, and it is noted to be the diagnosis in up to 20% of kidney biopsies from patients with AKI (1). Diagnosing AIN is challenging due to the absence of systemic, serum, and urine laboratory abnormalities to signal an underlying inflammatory process in the kidneys (2). Ongoing inflammation associated with unrecognized and untreated AIN leads to kidney fibrosis, and 40%–60% of patients with AIN ultimately develop CKD. Kidney injury is caused by infiltrating immune cells, and it is thought to be due to either an allergic reaction triggered by commonly used medications, such as antibiotics, proton pump inhibitors, and nonsteroidal anti-inflammatory drugs, or a loss of immune tolerance, such as occurs with immune checkpoint inhibitors. In developed countries, over 70% of all AIN is caused by medications, and it is thus the primary focus of studies evaluating therapies for this disease. The current standard of care for drug-induced AIN management includes early identification of this disease (*via* histologic examination of kidney biopsy tissue) and prompt discontinuation of the culprit medication. Given the underlying immune-mediated damage in drug-induced AIN, corticosteroid therapy has also been used since the 1970s. However, there is a lack of high-quality evidence to support this practice.

The efficacy of corticosteroids for treatment of drug-induced AIN has not been evaluated in a randomized, controlled trial. All of the data were from retrospective studies, which were often small, single-center, uncontrolled, and unadjusted analyses of data from biopsy registries. Such data have several limitations. The decision to use corticosteroids in these studies was made by the treating physician, which introduces selection bias in the observed association of corticosteroids with outcomes. On the one hand, patients selected to receive corticosteroids might be expected to derive more benefit, because the clinician "feels" that they have salvageable kidney function (*i.e.*, less kidney fibrosis). Therapy may be withheld from patients deemed "too sick for corticosteroids" due to other comorbidities. In both of the above scenarios, corticosteroid therapy may seem beneficial for some patients compared with those who are not treated, regardless of its true effect on the disease. Alternatively, patients with more severe features of drug-induced AIN (*i.e.*, those with higher serum creatinine concentrations or higher degrees of infiltrate on biopsy) may be selected for corticosteroid treatment, whereas those with milder disease may be treated with drug withdrawal alone, which biases the analysis toward observed harm with corticosteroid therapy. Regardless, this significant selection bias hampers our ability to judge the true effects of corticosteroids on outcomes in these patients. Moreover, many centers in the United States, including our own, administer corticosteroids to nearly all eligible patients with drug-induced AIN as a standard of care, which makes it harder to compare drug efficacy from retrospective analyses. As a result, retrospective evaluation of the effect of corticosteroid use on long-term kidney function outside of a randomized setting is highly confounded.

Within these limitations, several retrospective studies attempted to examine the effectiveness of corticosteroids in patients with drug-induced AIN and showed contradictory results (Table 1). In a study of 187 patients with AIN (25% with drug-induced AIN, 48% with "unknown" cause), corticosteroid-treated patients had better kidney function at 2 years and lower dialysis dependence compared with those who did not receive these drugs (3). Similar outcomes were observed in other studies (4–6). Early identification of drug-induced AIN and treatment with corticosteroids were associated with better kidney function and lower need for dialysis in some studies (4,6). In a study of 171 patients with drug-induced AIN (73% with drug-induced AIN), the authors found no improvement in kidney function in those treated with corticosteroids compared with untreated controls; however, patients in the corticosteroid-treated group were older and had significantly reduced kidney function at the time of biopsy (7). Once again, these studies highlight the perils of retrospective analyses in AIN treatment. Despite these deficiencies, the available evidence seems to support a potential benefit of early corticosteroid administration on long-term recovery of kidney function in those without significant fibrosis on the kidney biopsy.

All of the above studies (except for the study by González *et al.* [4]) were single-center studies, and none controlled for confounders or evaluated duration of

Table 1. Studies examining corticosteroid therapy in acute tubulointerstitial nephritis

Author, Year (Reference)	Sample Size		Peak sCr, mg/dl		Final sCr, mg/dl		Follow-Up, mo	Comment
	Steroid	No Steroid	Steroid	No Steroid	Steroid	No Steroid		
Clarkson *et al.* (11)	26	16	7.9	6.1	1.6	1.6	12	Patients received CS late after diagnosis (median delay >3 wk)
González *et al.* (4)	52	9	5.9	4.9	2.1	3.7	19	CS-treated patients with complete recovery had shorter delay to CS (13 d) compared with those without complete recovery (34 d)
Raza *et al.* (5)	37	12	6.5	5.2	2.8	3.4	19	Improved eGFR with CS versus control ($P<0.05$); no difference in kidney outcomes on the basis of CS timing
Muriithi *et al.* (6)	83	12	3.0	4.5	1.4	1.5	6	CS-treated patients had better kidney outcomes with early versus late CS therapy
Valluri *et al.* (7)	73	51	4.03	3.16	N/A	N/A	12	Worse kidney function in CS-treated patients versus controls at biopsy (sCr 4.2 versus 3.3 mg/dl); CS-treated patients had complete recovery (48%) versus control group (41%); final sCr was not different at 1 yr
Prendecki *et al.* (3)	158	29	21 ml/min (eGFR)	25 ml/min (eGFR)	43 ml/min (eGFR)	24 ml/min (eGFR)	24	CS-treated patients had better eGFR at 2 yr and less dialysis (5% versus 24%); dose, duration, and time to CS initiation were variable
Fernandez-Juarez *et al.* 2018 (8)	182	0	5.7	N/A	1.7–2.2	N/A	6	Duration of CS therapy was not associated with 6-mo recovery of eGFR; shorter interval between diagnosis and CS initiation was associated with greater recovery of kidney function at 6 mo

sCr, serum creatinine concentration; CS, corticosteroid; N/A, not available.

therapy. The study by Fernandez-Juarez *et al.* (8), published in this issue of the *Clinical Journal of the American Society of Nephrology*, evaluated 182 patients with biopsy-proven cases of drug-induced AIN from 13 centers in Spain. All patients developed acute kidney disease, mean (SD) serum creatinine concentration was 5.7 (±3.5) mg/dl, and 35 (19%) patients were on dialysis. Only a minority of patients had systemic findings of an allergic reaction, such as rash, fever, or eosinophilia. Leukocyturia was observed in three quarters of the patients, and microhematuria was present in approximately one half of the patients. Nonsteroidal anti-inflammatory drugs, antibiotics, and proton pump inhibitors were the top three causes of drug-induced AIN, accounting for just over one half of all patients with drug-induced AIN. All patients were treated with corticosteroids. Approximately 41% of the participants recovered >75% of kidney function lost during the AIN episode by 6 months, whereas 13% only recovered <25%. The authors evaluated factors independently associated with recovery of kidney function. They found that more patients with >75% recovery of kidney function were treated with corticosteroids within 15 days of diagnosis than those who recovered <25% of kidney function (70% versus 29%; $P=0.002$). This association was independent of kidney function at biopsy and the degree of interstitial fibrosis, which were both also associated with kidney function recovery. The time elapsed between clinical diagnosis of drug-induced AIN and corticosteroid initiation was correlated with interval from diagnosis to culprit drug withdrawal

(coefficient r=0.48) and kidney biopsy(r=0.83); however, these factors were not controlled for in the multivariable analysis. On average, patients received 13 weeks of corticosteroid therapy, and the duration of therapy was not associated with recovery of kidney function on univariable or multivariable analyses.

The biggest strength of this study is the large number of patients, which allowed the authors to evaluate factors independently associated with kidney function recovery after AIN in a multivariable model. Although the finding that early initiation of corticosteroids was associated with better outcomes is not novel, this study confirms the findings noted in several previous studies (4,6). Other interesting findings from this study include confirmation of the low accuracy of clinical and laboratory features considered typical of drug-induced AIN diagnosis. The most novel finding of this study may be the observation that the duration of corticosteroid therapy was not associated with kidney function recovery. However, patients who received shorter duration of steroids (<8 weeks) tended to have lower peak serum creatinine concentrations at biopsy, indicating milder disease than those with longer duration (>11 weeks). Serum creatinine concentrations at 1-month follow-up were also lower in the shorter duration group. Both of these observations indicate that clinicians likely tailored duration of therapy on the basis of initial severity and clinical improvement. Thus, the conclusion that shorter duration of therapy may be equivalent to longer duration is far from definitive.

In view of the results of this study, we maintain our previous recommendation that, when corticosteroids are considered in treatment of drug-induced AIN, they should be started early and continued for at least a month (9). Subsequent therapy should be guided by clinical improvement, and no absolute recommendation on duration can be on the basis of the results of this study. There are several important questions in drug-induced AIN that remain unanswered and could be the focus of future research. First, a multicenter, randomized, controlled trial is needed to study the effect, duration, and dose of corticosteroids. Second, a better understanding of the pathophysiology of drug-induced AIN could guide more targeted and potentially corticosteroid-sparing therapies, such as the ones developed in other immune-mediated kidney diseases. For example, given the role of mast cells in allergies and AIN (10), would targeting of therapy toward these cells yield better outcomes than with corticosteroids? Results from such studies could ultimately help reduce the burden of CKD resulting from drug-induced AIN.

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Disclosures

None.

References

1. Goicoechea M, Rivera F, López-Gómez JM; Spanish Registry of Glomerulonephritis: Increased prevalence of acute tubulointerstitial nephritis. *Nephrol Dial Transplant* 28: 112–115, 2013
2. Perazella MA: Clinical approach to diagnosing acute and chronic tubulointerstitial disease. *Adv Chronic Kidney Dis* 24: 57–63, 2017
3. Prendecki M, Tanna A, Salama AD, Tam FW, Cairns T, Taube D, Cook HT, Ashby D, Duncan ND, Pusey CD: Long-term outcome in biopsy-proven acute interstitial nephritis treated with steroids. *Clin Kidney J* 10: 233–239, 2017
4. González E, Gutiérrez E, Galeano C, Chevia C, de Sequera P, Bernis C, Parra EG, Delgado R, Sanz M, Ortiz M, Goicoechea M, Quereda C, Olea T, Bouarich H, Hernández Y, Segovia B, Praga M; Grupo Madrileño De Nefritis Intersticiales: Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. *Kidney Int* 73: 940–946, 2008
5. Raza MN, Hadid M, Keen CE, Bingham C, Salmon AH: Acute tubulointerstitial nephritis, treatment with steroid and impact on renal outcomes. *Nephrology (Carlton)* 17: 748–753, 2012
6. Muriithi AK, Leung N, Valeri AM, Cornell LD, Sethi S, Fidler ME, Nasr SH: Biopsy-proven acute interstitial nephritis, 1993-2011: A case series. *Am J Kidney Dis* 64: 558–566, 2014
7. Valluri A, Hetherington L, Mcquarrie E, Fleming S, Kipgen D, Geddes CC, Mackinnon B, Bell S: Acute tubulointerstitial nephritis in Scotland. *QJM* 108: 527–532, 2015
8. Fernandez-Juarez G, Perez JV, Caravaca-Fontan F, Quintana L, Shabaka A, Rodriguez E, Gadola L, de Lorenzo A, Gobo MA, Oliet A, Sierra M, Cobelo C, Iglesias E, Blasco M, Galeano C, Cordon A, Oliva J, Praga M; Spanish Group for the Study of Glomerular Disease: Duration of treatment with corticosteroids and recovery of kidney function in acute interstitial nephritis. *Clin J Am Soc Nephrol* 13: 1851–1858, 2018
9. Moledina DG, Perazella MA: Drug-induced acute interstitial nephritis. *Clin J Am Soc Nephrol* 12: 2046–2049, 2017
10. Zand L, Monaghan M, Griffin BR, Wagner SJ, Criaci IM, Kamal A, Raissian Y, Grande JP, Lim KG, Garovic VD: The role of type I hypersensitivity reaction and IgE-mediated mast cell activation in acute interstitial nephritis. *Clin Nephrol* 84: 138–144, 2015
11. Clarkson MR, Giblin L, O'Connell FP, O'Kelly P, Walshe JJ, Conlon P, O'Meara Y, Dormon A, Campbell E, Donohoe J: Acute interstitial nephritis: Clinical features and response to corticosteroid therapy. *Nephrol Dial Transplant* 19: 2778–2783, 2004

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