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**Should corticosteroids be employed to treat biopsy-proven drug-induced acute interstitial nephritis?**

**PRO**

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Acute Interstitial Nephritis (AIN) is an under-recognized cause of acute kidney injury (AKI) and occurs in 13-20% of biopsies performed for AKI (1, 2). Drug-induced AIN (DI-AIN) accounts for 70% of these (2). Although numerous drugs are implicated, proton-pump inhibitors (PPIs), antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are common culprits, especially in the elderly. Immune check point inhibitors (ICIs) have recently emerged as an important cause. AIN frequently presents insidiously, as a subacute rise in serum creatinine with minimal symptoms or urinary abnormalities (3,4). Histopathological confirmation is often necessary and may result in diagnostic delays (5). DI-AIN has a variable prognosis with 30% developing dialysis-requiring AKI and 40-60% progressing to chronic kidney disease (CKD) (2). Notably, 2% of all CKD is attributed to AIN (6, 7).

DI-AIN is characterized by a type-B idiosyncratic, cell-mediated immunological response triggered by the culprit drug, resulting in renal tubulointerstitial injury (8). Histology shows interstitial edema and a cellular infiltrate with predominance of CD4+ T lymphocytes, plasma cells and eosinophils (9). The drug acts as an allergen or lowers immune tolerance (e.g., ICIs). With ongoing drug exposure, acute cytokine mediated renal injury can rapidly progress to irreversible tubulointerstitial fibrosis (TIF), noted as early as 7-10 days after initial insult, and ultimately results in CKD (10, 11).

Immediate discontinuation of the offending drug is the first step in management of DI-AIN. Glucocorticoid therapy is frequently utilized if there is lack of renal improvement despite drug withdrawal, however its use is controversial. Data from randomized controlled trials (RCTs) is unavailable, and treatment guidelines are not standardized. Several case series and small, retrospective studies have demonstrated benefit of steroid therapy in DI-AIN (6, 10, 12-15), while others have not (16, 17). In this article, we aim to provide rationale for why glucocorticoid therapy should be strongly considered for treatment of DI-AIN.
Glucocorticoids block cytokine production via several mechanisms, including inhibition of a key proinflammatory transcription factor NF-κB (Figure 1) which has a pivotal role in promoting renal inflammation in various diseases including AIN (18, 19). Within days after the onset of tubulointerstitial inflammation, there is activation of profibrotic processes via cytokine mediated fibroblast stimulation and epithelial-mesenchymal transformation. This results in interstitial collagen deposition, irreversible tubular atrophy and interstitial fibrosis (8). Glucocorticoids suppress cytokine mediated tubulointerstitial inflammation in AIN, and if initiated early in the disease course, may prevent TIF by attenuating the initial pro-inflammatory pathways (Figure 1).

Data supporting early glucocorticoid use was first provided by González et al in a multicenter, retrospective study of 61 cases of biopsy proven DI-AIN (majority were antibiotic or NSAID induced) (10). At 18-months, the glucocorticoid group (52/61 patients) had a lower serum creatinine (2.1 vs. 3.7 mg/dl), more complete renal recovery and lower dialysis dependency (3.8% vs. 44%) compared to controls. No significant steroid adverse effects were noted with a treatment duration of 8-12 weeks. A delay in steroid initiation (13 vs. 34 days) was associated with poor renal recovery. Compared to the initial renal biopsy, there was evidence of markedly less cellular infiltrate and more TIF on repeat biopsies in three patients that received delayed steroid treatment. This study suggested that prompt initiation of glucocorticoids (within 7 days) in patients with DI-AIN may improve extent and rate of renal recovery and lower TIF and risk of future CKD. Raza et al demonstrated greater improvement in serum creatinine (3.4-fold vs. 2.1-fold, p < 0.05) in the steroid group (37/49 patients) as well as less likelihood of needing dialysis, but the latter did not reach statistical significance (P=0.06) (12). Muriithi et al evaluated renal outcomes at 6-months post-biopsy in 83 DI-AIN patients treated with steroids (vs. 12 controls) (6). Although there was no difference in outcomes at 6 months (likely due to the small size of the control group), the steroid group achieved 49% complete and 39% partial renal recovery, despite having lower baseline eGFRs and more severe AKI. Longer drug exposure and a delay in initiating
glucocorticoid therapy (8 vs. 11 vs. 35 days for complete, partial and no renal recovery respectively, P=0.05), correlated with suboptimal renal recovery. Prendecki et al evaluated the effect of steroids in a large retrospective study with a 2 year follow up of patients with AIN (N=187, 158/187 were treated with steroids and 48 of those had DI-AIN) (13). Despite a lower eGFR in the steroid group compared to the non-steroid group at the time of biopsy (17 mL/min vs. 38 mL/min), the steroid group exhibited greater improvement in eGFR at 6, 12 and 24 months (median eGFR 43ml/min vs. 24ml/min at 24 months, P=0.01), with fewer patients progressing to end-stage kidney disease (5.1% vs. 24.1%, p=0.0019). Notably, those with DI-AIN had a worse eGFR at the time of biopsy but a higher eGFR at all time points post-biopsy, demonstrating a better steroid response in those with DI-AIN compared to non-drug etiologies. Fernandez-Juarez et al recently published a large, retrospective, multicenter study evaluating severe biopsy-proven DI-AIN (N=182, 19% requiring dialysis), who received at least 2 weeks of corticosteroids (average dose of 0.8 +/- 0.2 mg/kg/d) followed by 9-week taper. At 6 months, the mean recovered eGFR was 34 +/- 26ml/min with 41% achieving complete, 46% partial and 13% no renal recovery. Delayed initiation of steroids (>29 days) correlated with poor renal recovery at 6 months. This study confirms previous findings suggesting importance of early steroid therapy in DI-AIN. Furthermore, 74% of patients initiated on RRT in this study recovered renal function demonstrating a beneficial role of steroids in severe, dialysis-requiring DI-AIN. Duration of steroid treatment did not independently impact renal recovery, and no additional benefit was seen with treatment with high dose steroids for > 3 weeks or total treatment duration of > 8 weeks. This study provides some guidance on appropriate duration of steroid treatment. Huang et al recently conducted a retrospective analysis of 72 patients with severe DI-AIN requiring dialysis at diagnosis (15). At 6 months, 59/72 recovered renal function, whereas 13/72 progressed to CKD (eGFR<60ml/min). Longer interval to treatment with corticosteroids was an independent risk factor for progression to CKD (OR= 1.183, 95% CI 1.035, 1.352, p=0.014) and a delay > 22.5 days had the best predictive value for progression to CKD. This study again demonstrates that
severe DI-AIN can have improved renal outcomes with timely initiation of steroids. Given the irreversibility of established TIF, several of these studies have noted poor renal recovery despite steroids, in patients with higher degrees of fibrosis (6,10).

In contrast to above, other retrospective studies have found lack of benefit of glucocorticoids in DI-AIN (16, 17). There are several potential explanations for these results. a. Selection bias in these retrospective studies would generally favor outcomes in those not treated with steroids, as steroids would be trialed in patients that fail to improve with drug discontinuation. b. Delay in initiating steroid treatment and c. Presence of higher degree of TIF on renal biopsy would predict lower steroid responsiveness.

Clarkson et al showed no difference in 1 year outcome with early steroid use in biopsy proven AIN (26 controls vs 16 steroid-treated) (16). In addition to being a small study, 33% of the patients had severe TIF, which could explain the absence of observed benefit from steroids. A larger, multicenter study (N=171) by Valluri et al found a trend towards complete renal recovery in the glucocorticoid group vs. controls (48% vs 41%) although this was not statistically significant (17). A high percentage of patients in this study had an unclear duration of AKI and only 14% had a time course of less than 3 weeks which suggests that the majority may have developed significant TIF. Additionally, 35% of patients had DI-AIN attributed to PPIs. PPI induced AIN is particularly notable for poorer prognosis due to its insidious onset, delay in diagnosis, as well as baseline CKD in the elderly who are more likely to be on chronic PPI therapy (20). Finally, glucocorticoid-treated patients had a higher severity of AKI at baseline (4.0 mg/dL Cr vs. 3.2 mg/dL), therefore, similar creatinine levels in the two groups on follow up could suggest a higher magnitude of improvement in renal function in those that received glucocorticoids.

In summary, despite lack of data from RCTs, there is compelling evidence favoring early use of glucocorticoid therapy in patients with DI-AIN (ideally within 7-10 days of diagnosis). This includes
patients with severe AKI, but without severe TIF on histopathology. Timely therapy may allow faster and more complete renal recovery and lower risk of residual CKD. Situations in which withdrawal of the drug may be detrimental (such as life-saving antibiotics or ICIs), treatment with glucocorticoids and drug rechallenge, may be the only option (21). A short course of high dose steroids (2-3 weeks), followed by a taper over the next 6-8 weeks is a reasonable approach. Those patients with DI-AIN that respond favorably to steroids are likely to do so by 4 weeks, and treatment beyond 6-8 weeks may increase the adverse effects with minimal additional benefit (5, 10). ICIs may require longer treatment (3-6 months) and a slower taper (21). Although intravenous pulse steroids can be used for severe AKI, there does not appear to be an advantage of intravenous protocols over high dose oral steroids (22). Finally, factors such as age, frailty, comorbidities, and overall risk vs. benefit of glucocorticoid therapy in the individual patient should be considered. A prospective, open-label RCT is underway to compare prednisolone vs. supportive care in patients with incident, biopsy proven AIN and should provide further guidance (23).

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Figure 1: Proposed mechanism of the effect of glucocorticoids on T-lymphocytes in treatment of drug induced acute interstitial nephritis. Drug acts as an antigen and induces a delayed type 4 hypersensitivity response with activation of T-lymphocytes and other immune cells. This results in a cascade of cytokine-mediated renal tubulointerstitial inflammation which ultimately results in activation of fibroblasts leading to tissue fibrosis and irreversible renal damage. Glucocorticoids (GC) can prevent activation of inflammatory pathways via their effects on genomic transcription of proteins as illustrated. GC bind to their respective cytoplasmic receptor (GR). The GR-GC complex can bind to the glucocorticoid response element (GRE) within the T lymphocyte DNA, resulting in the upregulation of mRNA transcription and translation of anti-inflammatory proteins (shown in green arrow). The GR-GC complex can also bind to the Nuclear factor kappa B element (NF-κBE) which results in inhibition of mRNA and inflammatory protein synthesis (shown in red arrows). Abbreviations: NF-κB (Nuclear factor kappa B), NF-κBE (Nuclear factor kappa B element), GR (Glucocorticoid receptor), GRE (Glucocorticoid response element), TGFα (Transforming growth factor alpha), TNFα (Tumor necrosis factor alpha), GM-CSF (Granulocyte-macrophage colony-stimulating factor), MMP (Matrix metalloproteinase), TIMP-1 (Tissue inhibitor of metalloproteinases 1), ROS (Reactive oxygen species), TGF-β (Transforming growth factor beta), EMT- epithelial mesenchymal transformation.
Macrophage

T-Lymphocyte

T-Cell/Macrophage Activation
Response: Pro-Inflammatory: (IL-6, IL-8, TGFβ, TNFα, GM-CSF).
Cytotoxic: (MMP, TIMP-1, ROS)

Antigen/Hapten (Drug)

Renal Antigen Presenting Cell

Neutrophil

Neutrophil Extravasation

Renal Tubulo-interstitium

Fibroblast

Fibrosis

Fibroblast Activation and EMT: TGF-β, TNF, IL-1, Laminin, Fibronectin

GC stimulate synthesis of anti-inflammatory proteins

GC inhibit synthesis of inflammatory proteins

NF-κB activating signals

GRE

NF-κBE

mRNA

GR-GC

GC

+