Drug-induced Acute Interstitial Nephritis
Pathology, Pathogenesis, and Treatment

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Drug-induced acute interstitial nephritis (DAIN) is a common cause of acute kidney injury and often presents as an unexplained rise in serum creatinine level. Kidney biopsy is therefore frequently required to make a definitive diagnosis. The hallmark pathologic features of DAIN are interstitial edema, interstitial inflammation, and tubulitis with a predominance of CD4+ T lymphocytes and mononuclear cells, with variable numbers of eosinophils. This is a result of a type B idiosyncratic non-immunoglobulin-E-mediated immune reaction marked by cell-mediated immune injury to the renal tubulointerstitium. The drug becomes immunogenic via various mechanisms such as haptenization, antigen mimicry, and neo-antigen formation. Renal interstitial dendritic cells, and renal tubular epithelial cells play an important role in further propagating this immunologic injury. Acute DAIN can progress within days to weeks to a chronic form triggered by fibroblast activation and manifested as interstitial fibrosis and tubular atrophy. The mainstay of treatment of DAIN is discontinuation of the offending drug. Incomplete renal recovery is seen in one-third of the patients and depends on the duration of injury prior to diagnosis. Use of steroids for treatment of DAIN makes biological sense, but lack of randomized controlled trials and conflicting data from retrospective studies makes the approach unclear. Positive effects include faster recovery of kidney function, more complete recovery with less chronic kidney disease, and reduced need for chronic dialysis. Therefore, it seems reasonable to employ corticosteroids in patients that do not rapidly improve 3 to 5 days following discontinuation of the offending agent.

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Review

INTRODUCTION

Acute interstitial nephritis (AIN) is a common cause of acute kidney injury (AKI) both in the outpatient and hospital settings. Various etiologies have been identified including allergic or drug-induced, infectious, autoimmune or systemic, and idiopathic forms of the disease. Acute interstitial nephritis secondary to a drug exposure is the most common form seen in clinical practice. In a 2004 report of pooled data from 3 large studies, a drug-induced etiology emerged as the most common cause of AIN, underlying 91 of the 128 cases (71.1%). Antibiotics accounted for one-third of these cases.[1] The classic triad of sterile pyuria, rash, and eosinophilia may be absent in a significant number of cases. Therefore, AIN should be considered in all cases of unexplained AKI. A renal biopsy is the gold standard for diagnosis of AIN.

In the past 10 years, there has been great progress made in understanding the immunological processes

that underlie drug-induced tubulointerstitial injury, the role of renal tubular and dendritic cells in the pathogenesis, as well as the forces that govern transformation of AIN into a chronic fibrotic irreversible process. The focus of this review will be to discuss the pathology, pathogenesis, and treatment of drug-induced AIN (DAIN) based on the current literature.

PATHOLOGY

Drug-induced tubulointerstitial kidney injury can pathologically be classified into dose-dependent renal tubular epithelial injury (acute tubular injury or necrosis) or an idiosyncratic hypersensitivity reaction that causes predominantly an interstitial pattern of injury (AIN) with inflammation subsequently extending into the tubular epithelial cells (tubulitis). The latter can be further divided into acute (develops over days to weeks) or chronic (develops over months to years), based on duration and pattern of interstitial injury.

The characteristic lesions recognized in AIN are tubulitis and interstitial inflammation with edema (Figure 1). The interstitial infiltrate often compromises of mononuclear cells, with predominance of lymphocytes (primarily CD4+ T lymphocytes) and monocytes or macrophages, intermixed with plasma cells, small numbers of eosinophils, and possibly neutrophils.[2] Presence of a large number of neutrophils, particularly as micro-abscesses, should alert one to the possibility of pyelonephritis.[3] Renal pathologists have raised the question of a drug cause when a significant eosinophilic infiltrate (> 10 eosinophils per 20× field) is present. Tubulitis refers to lymphocytes occasionally mingled with eosinophils in proximity to the outer and inner aspects of the tubular basement membrane.[4] Physiologically, this implies extension of the interstitial inflammation to the tubular epithelial cells. Tubulitis is typically accompanied by tubular degenerative changes including luminal ectasia, cytoplasmic simplification, irregular luminal contours, prominent nucleoli, loss of brush border, and apoptotic figures.[5] This can be focal or diffuse and often starts with denudation of the tubular basement membrane as opposed to acute tubular injury and necrosis, where injury often involves the villi of tubular epithelial cells with their subsequent apoptosis or necrosis. Tubulitis can also be a finding of renal allograft rejection

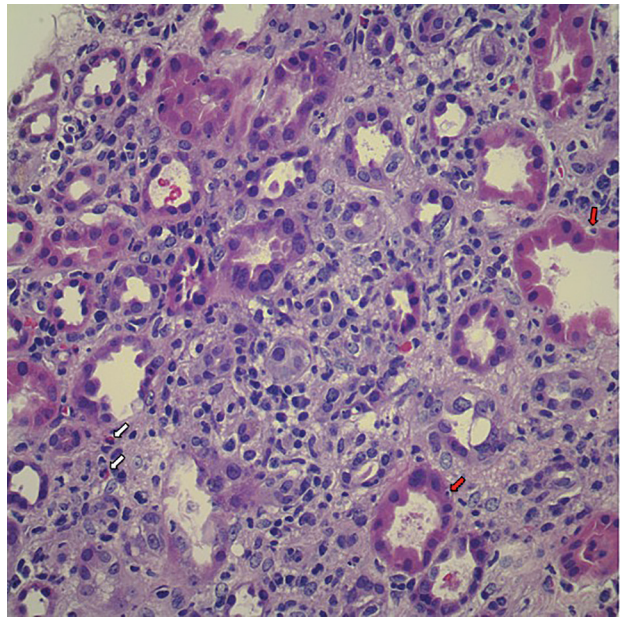

Figure 1. Pathology of drug-induced acute interstitial nephritis. Light microscopy demonstrating acute interstitial nephritis with inflammatory cells, interstitial edema, and tubulitis. Red arrows identify tubulitis while the white arrows point out eosinophils (hematoxylin-eosin, × 40).

making it sometimes difficult to differentiate allograft rejection from DAIN in kidney transplant patients. Glomeruli and blood vessels are typically spared in DAIN but can demonstrate changes of other chronic conditions such as diabetes mellitus and hypertension.

Immune complex deposits are relatively uncommon in DAIN but have been reported with drugs such as methicillin,[6] demonstrated as linear or granular staining for immunoglobulin G and C3 on tubular basement membrane (anti-TBM antibodies).

Less commonly, DAIN can present pathologically as granulomatous interstitial nephritis which is marked by the presence of hypersensitivity granulomas composed of reactive epithelioid histiocytes (macrophages) and multinucleated giant cells.[7,8] Drugs implicated include anticonvulsants, antibiotics, nonsteroidal anti-inflammatory drugs, allopurinol, and diuretics.

PATHOGENESIS

Drug-induced AIN is a type-B idiosyncratic non-immunoglobulin-E-mediated immune reaction.[9] It is marked predominantly by immune injury secondary to a cell-mediated process in the kidney.[2,4,9,10,11,12] This injury may be part of a systemic immune

response to the drug manifested in various organs and tissues such as skin eruptions, fever, interstitial nephritis, drug-induced hepatitis, pancreatitis, and interstitial lung disease, or be exclusively localized within the kidney. Drug-induced AIN can occur due to immune reactivity against endogenous renal tubular/interstitial proteins or exogenous antigenic proteins in the circulation that may have become trapped in the kidney during circulation ('planted antigen'). The nephritogenic immune response is a complex multistep process that can be divided into 4 phases[2]: antigen recognition, antigen presentation, immune regulatory, and effector phases.

Antigen Recognition Phase

The immunogenicity of drugs depends on their ability to participate in a number of processes as follows:

(1) Drugs covalently bind to larger molecules such as proteins to form antigenically active substances. These proteins can be in the circulation or could be tissue-specific (such as the kidney). Most drugs are small molecules (< 1000 Da), and are by themselves, not immunogenic. They can, however, bind to carrier proteins and become immunogenic, a process called *haptenization*.[2,9] These 'hapten-carrier complexes' are thus able to stimulate both T and B cell immune responses. Haptenization can occur in the circulation and these immunologically active compounds can get 'trapped' in the kidney during filtration or it can occur locally in the kidney where the drug binds to renal specific tubulointerstitial proteins and sets the stage for an acute interstitial nephritis to ensue.

(2) In some cases though, the drug acts as a 'prohapten' and requires metabolism into a reactive compound that can then bind to specific proteins to undergo haptenization.[11] Renal proximal tubular cells have the capability to hydrolyze and metabolize exogenous antigens (drugs in this case) and present them to major histocompatibility complex (MHC)-antigen-presenting cells within the kidney.[5,13] Sulfamethoxazole has been shown to behave as a prohapten and is metabolized in the liver through various oxidative steps into nitrososulfamethoxazole which further binds to various tissue proteins (including endogenous renal tissue) and elicits an immunogenic response.[14]

(3) Drugs can sometimes produce 'neo-antigens' that cause direct toxic damage to interstitial structures and render them 'foreign' and antigenic.[15]

(4) Drugs can elicit an immune response by antigenic mimicry**.** The drug or its reactive metabolite has a structural similarity and cross-reactivity to endogenous renal interstitial or tubular proteins and may generate an immune response against them.

(5) Drugs may form antigen-antibody complexes in circulation which may deposit in the kidney and cause immune injury. This is possibly the least common form of drug-induced renal injury and often causes glomerular plus tubulointerstitial injury. An isolated AIN without glomerular involvement is rarely due to immune complex deposits or antibody-mediated immune injury. An exception is methicillin-induced AIN where granular immune complex deposits along the anti-TBM can be seen.[6]

Antigen Presentation Phase

Over the past decade, it has become increasingly well known that renal specific dendritic cells and macrophages that reside within the renal interstitium perform an exceedingly important role of antigen presentation with in the kidney.[16-20] Dendritic cells have long foot processes in close proximity to the basolateral aspects of tubular epithelial cells and peritubular capillaries, and use these dendritic extensions to continuously probe the environment and respond to any endogenous or exogenous insult or injury to the renal parenchyma.[18,19] Dendritic cells have a high capacity for antigen uptake and when activated, remarkably increase MHC class II expression and thus have the ability to propagate immune responses to inciting antigens or induce immune tolerance.[18] Macrophages have been defined as a distinct but related population of antigen-presenting cells, albeit less potent than dendritic cells, whose primary functions are maintenance of tissue homeostasis and phagocytic clearance of various native and foreign bodies.[20]

Renal tubular epithelial cells can also process proteins and act as antigen-presenting cells.[21] In vivo, they have the capacity to hydrolyze and process exogenous proteins that are filtered and to endocytose macromolecules. Tubular cells do not

express basal levels of MHC class II, but can be readily induced to do so in response to injury or antigens.[22,23] Like dendritic cells, tubular epithelial cells, when activated, also propagate further injury by inducing pro-inflammatory molecules such as cytokines, growth factors, adhesion molecules, and chemokines.[24-27] Thus, tubular cells not only are the target for injury in AIN, but orchestrate the influx of inflammatory cells and activation of T cells.

Antigen-presenting cells in the kidney process and present 'nephritogenic' antigens to T helper cells to activate the immune response, which ultimately lead to kidney injury. The uninjured kidney contains several types of T cells in the renal interstitium which can be activated locally (CD4+, CD8+, CD4-CD8-, natural killer and regulatory T cells).[28] In addition, activated renal dendritic cells migrate to regional lymph nodes and activate naive T cells which when activated, migrate back to the antigenic source in the kidney and induce immunologic injury.[18] Additional signals provided by antigen-presenting cells influence the type of T cell response that will develop. Positive costimulation through CD28 in T cells and CD80 and CD86 on antigen-presenting cells promote cytokine production and T-cell stimulation.[29]

Immune Regulatory Phase

Interstitial nephritis is a relatively uncommon immune response because activation of nephritogenic immune responses are usually self-limited by specific 'protective' immunoregulatory events. These involve activation of suppressor T cells and downregulation of MHC class II expression, the latter being necessary for T-cell activation.[10,30] The balance between these competing actions of increased pathologic immune reactivity versus the protective immunomodulatory processes ultimately determines the nature and degree of destructive outcomes of the various nephritogenic pathways.

Effector Phase

Drug-induced AIN is marked predominantly by immune injury secondary to a cell-mediated process in the kidney. Drug-specific T cells have been identified in the peripheral blood of patients with biopsy proven DAIN with simultaneous demonstration of these T lymphocytes in the renal interstitium on immunohistochemistry analysis of respective renal biopsy specimens.[11] The T cells orchestrating injury can be activated locally in the kidney by resident antigen-presenting cells or migrate from neighboring lymph nodes as explained above, to cause a cascade of inflammatory interstitial reaction marked by cytokine release and subsequent tubulointerstitial injury. The actual pattern of injury manifested in each organ depends on the specific type of T cell activated and the nature of cytokines released.[11,12,31,32] Drug-induced delayed hypersensitivity reactions have been recently classified into 4 subclasses based on the pattern of cell-mediated injury.[12,31] Although this was originally described in relation to skin manifestations, given the systemic nature of drug-induced injury, this can likely be extended to other organs such as the kidney as well (Table 1).[11] A T-helper-2-mediated type IVb reaction with subsequent interleukin-5 production and

Table 1. Drug-induced Hypersensitivity Reaction Classification

Classification	Description
Type IVa	T helper 1 cell Interferon-γ/Interleukin-12 - Monocyte/macrophage stimulation - Synthesis of complement-fixing antibody and complement-mediated injury - Co-stimulation of pro-inflammatory responses (tumor necrosis factor, interleukin-12) -Co-stimulation of CD8 T-cell responses
Type IVb	T helper 2 cell Interleukin-4, interleukin-5, inerleukin-13 - B-cell production of IgE and IgG4 - Macrophage deactivation - Mast cell and eosinophil responses
Type IVc	Cytotoxic T cells - Injury via perforin/granzyme and Fas ligand-dependent processes
Type IVd	T cell (interleukin-8 and granulocyte monocyte-colony stimulating factor) - Neutrophil-mediated inflammation/'sterile polymorphonuclear-rich inflammation'

eosinophilia has been most commonly described in the classic allergic acute DAIN, but all four types have been reported in the literature.[11] For example, the predominant inflammatory cells in omeprazole-induced AIN were shown to be of a T helper 1 to T helper 17 lineage, suggesting this is the major type of cell-mediated inflammatory process rather than a T-helper-2-mediated response. Also, lack of a substantial eosinophilic infiltrate argues against a T-helper-2-mediated mechanism for proton pump inhibitors.[32] As described above, renal tubular cells, when injured or activated can produce pro-inflammatory cytokines, thereby both being a target and effector for further interstitial injury.

Irrespective of the type of T cells and immune injury involved, the final common pathway in AIN is acute interstitial inflammation and tubular injury mediated via infiltration of inflammatory cells such as lymphocytes, neutrophils, macrophages, mast cells, eosinophils, etc, producing either direct injury or via production of various inflammatory cytokines (Figure 2).

Immune complex deposits are relatively

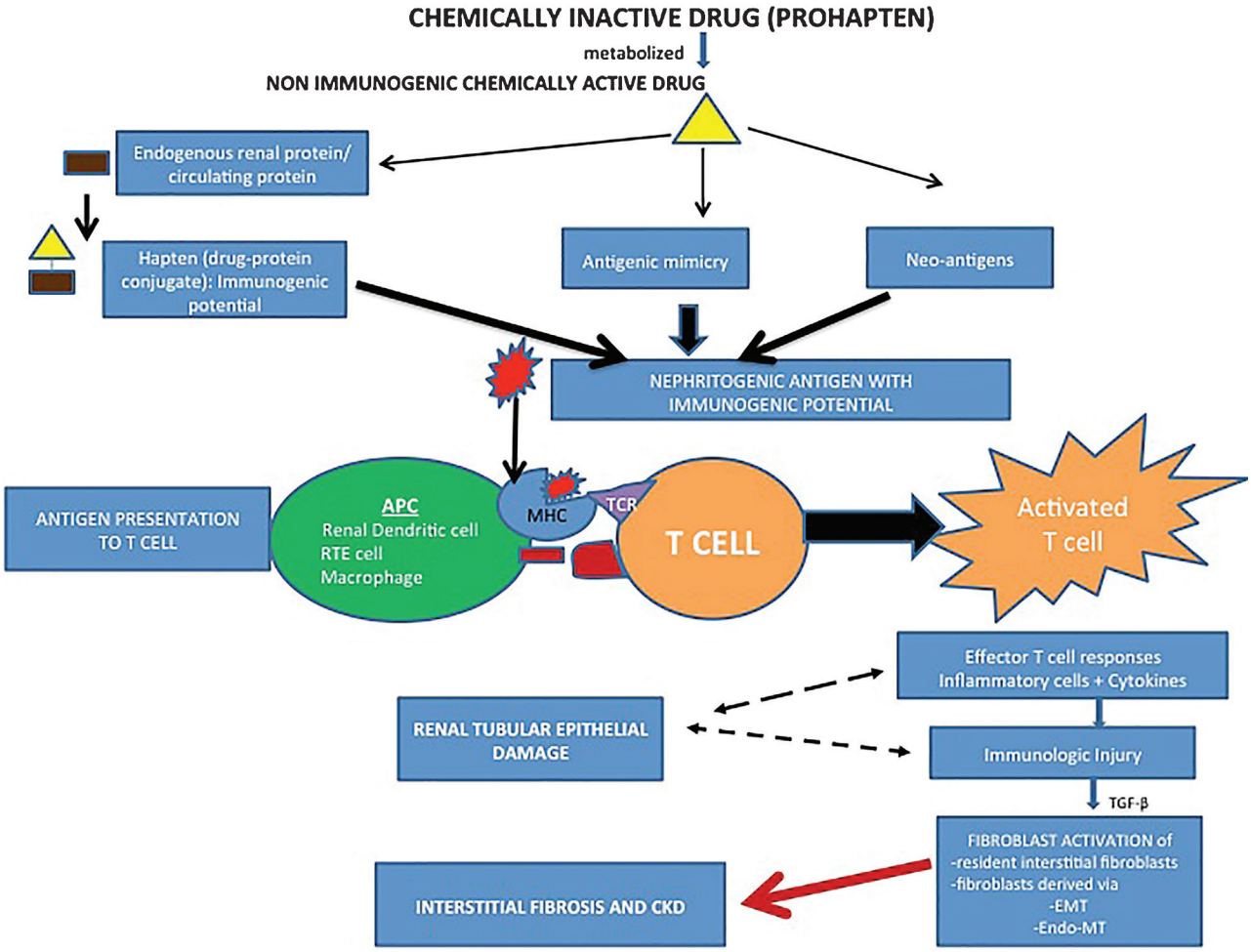

Figure 2. Pathogenesis of drug-induced acute interstitial nephritis. A chemically active but non-immunogenic drug may be rendered immunogenic by haptenization, molecular mimicry, or direct toxicity and formation of neo-antigens. These nephritogenic antigens are then processed by antigen-presenting cells such as renal dendritic cells, macrophages and renal tubular epithelial cells and presented to effector T cells via major histocompatibility complex that resides on antigen-presenting cells cell surface. Activated T cell propagates an intense inflammatory response marked by infiltration of inflammatory cells and cytokine production. The nature of this response depends on the type of the T cell stimulated. Consequent renal tubular epithelial cell damage in turn causes more cytokine release by tubular cells and further inflammation and injury. Renal tubular epithelial cells are both target and effector cells for kidney injury. Subsequent fibroblast activation ultimately causes interstitial fibrosis. TCR indicates T cell receptor; EMT, epithelial-mesenchymal transition; Endo-MT, Endothelial mesenchymal transition; MHC, major histocompatibility complex; APC, antigen-presenting cell; TGF-β, transforming growth factor-β; RTE, renal tubular epithelial cell; and CKD, chronic kidney disease.

uncommon in DAIN, but have been reported with drugs such as methicillin, rifampin, allopurinol, and phenytoin,[6,33-36,37] demonstrated as linear or granular staining for immunoglobulin G and complement C3 on anti-TBM antibodies. Antibodies are formed against a TBM protein (anti-TBM) possibly due to drug-protein hapten conjugates and induction of autoimmunity. For example, methicillin is secreted in large amounts by tubular epithelial cells, therefore exposing tubular basement membrane proteins to high concentration of the drug making it conducive for these drug-protein conjugates to form.[6] Antibodies found in the interstitium likely form complexes as an in situ process rather than due to deposition of preformed circulating antigen-antibody complexes, as the latter would likely appear first in the glomerulus, which is rarely the case in AIN. These antigen-antibody complexes, once formed, mediate injury by complement activation,[38] inducing chemotaxis,[39] invoking tubular injury by direct cytotoxic effects,[40] or via antibody-dependent cell-mediated cytotoxicity.[41]

Once acute interstitial inflammation sets in, it can progress very rapidly to a less reversible, more destructive fibrogenic process that is eventually marked by increased interstitial matrix, ischemia, tubular atrophy, and interstitial fibrosis.[42-44] Increase in the interstitial matrix has been noted as early as 7 days after the onset of acute inflammation.[43] The key step in this process is fibroblast stimulation-proliferation and conversion to a 'myofibroblast' phenotype, which expresses alpha smooth muscle actin and has the ability to produce excessive amounts of collagen and extracellular matrix.[42,44] This may occur by activation of resident fibroblasts within the interstitium after injury or may originate from bone marrow derived circulating precursors.[45] There is also data to suggest that other cells such as renal tubular cells via a process of epithelial-mesenchymal transition or endothelial cells via a process of endothelial-mesenchymal transition,[46-48] may acquire a fibroblast phenotype and function. Transforming growth factor-β/Smad signaling is the most important pro-fibrotic stimulus and facilitates epithelial-mesenchymal transition, epithelial apoptosis, and initiation of fibrogenic foci.[49] Mast cell infiltration, chronic hypoxia, reactive oxygen species, and angiotensin II are a few of the other pro-fibrotic stimuli that play an important role in this process.[50,51] Clinically, the degree of chronic injury to the tubulointerstitial compartment is the best determinant of residual renal function and development of chronic kidney disease (CKD).[52,53]

TREATMENT

The immunologic mechanisms underlying AIN support the use of corticosteroids as an effective treatment option; however, the actual data supporting their efficacy is mixed. The mainstay of treatment for DAIN is discontinuation of the offending agent, which can be a challenging task in patients receiving multiple medications. In general, the timing of drug exposure as well as the clinical and laboratory manifestations will sometimes point to the offending agent. As an example, the presence of hypersensitivity may incriminate drugs such as the β-lactams or sulfonamides. While the majority of patients recover kidney function with early recognition of AIN and prompt drug withdrawal, some patients may only gain partial recovery. In this circumstance, kidney recovery appears to depend primarily on the duration of injury prior to diagnosis, with less than two weeks associated with better return of kidney function. Overall, a significant number of patients, approximately one-third, are left with some level of CKD.[1]

It is attractive for clinicians to consider the use of immunosuppressive agents for DAIN as it is an allergic inflammatory process. A prime immunologic example for successful steroid use is acute cell-mediated rejection in kidney transplant allografts. High-dose corticosteroids rapidly melt away the T-cell infiltrate and improve kidney function. However, the case for steroid use in AIN is not so clear. Importantly, there are no randomized controlled trials available to substantiate steroid efficacy in patients with DAIN. All of the early studies consist primarily of anecdotal reports and small case series suggesting that corticosteroid therapy is beneficial in some patients.

A small study described more rapid recovery to baseline kidney function in 7 patients treated with prednisone for a mean of 9.3 days compared with 54 days in 2 untreated patients.[54] A retrospective study of 20 patients with AIN observed that steroid treatment in 7 patients was associated with better renal outcomes than in 13 patients managed conservatively.[55] In another study of 27 AIN patients, drug withdrawal alone lad to kidney

function recovery to baseline in 17 patients.[56] The remaining 10 patients that did not respond to conservative management were treated with corticosteroids and kidney function improved in all patients, with 6 returning back to baseline.[56] In contrast, 7 nonrandomized retrospective studies (n = 100) were reviewed and no clear benefit of corticosteroids was observed.[38] In this compilation of studies, 58% of 52 steroid treated patients recovered kidney function to a serum creatinine less than 1.3 mg/dL and 17% developed CKD as defined by a serum creatinine greater than 2.3 mg/dL. In patients treated conservatively, 52% of patients recovered to baseline and 19% developed CKD. However, it is worth noting that steroid treated patients in this review had more severe AKI at the time of therapy with a mean peak serum creatinine of 9.3 mg/dL versus 6.5 mg/dL in the conservative group.

Several subsequent retrospective studies have also examined the utility of steroids for DAIN (Table 2). To no surprise, they have again reached discordant results and are subsequently reviewed from oldest to newest by publication date. In 2004, Clarkson and colleagues studied 67 patients with biopsy-proven AIN, of which 92% drug-induced who were either treated conservatively or received steroids as intravenous pulse followed by oral dosing.[57] The timing of drug withdrawal and steroid administration are not described, but the time from symptoms to kidney biopsy was wide ranging from 2 to 6 weeks, suggesting that steroid administration may have been later in the disease course. The authors examined kidney function over a 12-month period in 42 patients with complete data. The authors observed no difference in serum creatinine concentration between the 2 groups at 1, 6, and 12 months. Only 2 out of 35 patients were dialysis-dependent, although many were left with some level of CKD as the mean serum creatinine for the group was 1.6 mg/dL. It is important to point out 2 facts that may have diminished the potential beneficial effect of corticosteroid therapy. First, the steroid group had a higher mean peak serum creatinine (7.9 mg/dL versus 6.1 mg/dL), although it was not statistically different, and steroid administration was likely delayed from time of drug withdrawal to actual therapy. As will be seen, this second point may be important for renal response and recovery.

Four years later, Gonzalez and coworkers found a beneficial effect in 61 patients with biopsy-proven DAIN.[58] In this multicenter, retrospective study, 52 patients were treated with steroids while 9 patients were considered untreated controls. Intravenous methylprednisolone pulse doses of 250 mg to 500 mg for 3 to 4 days followed by oral prednisone (1 mg/kg) tapered over 8 to 12 weeks was the typical regimen. The groups had similar baseline kidney function although the steroid-treated patients had slightly higher peak serum creatinine concentrations (5.9 mg/dL versus 4.9 mg/dL). At a mean of 19-month follow-up, treated patients recovered more fully (54% versus 33%),

Table 2. Retrospective Studies Examining the Utility of Steroids in Drug-induced Acute Interstitial Nephritis

Study	Year	Patients	Peak serum Creatinine, mg/dL	Final serum Creatinine, mg/dL; Dialysis	Follow-up, mo	Comments
Clarkson et al[57]	2004	n = 42 Steroids, 35 Control, 7	Steroids, 7.9 Control, 6.1	Steroids, 1.6; 5.4% Control, 1.6; 0%	12	Patients received steroids late (median delay > 3 weeks) after diagnosis.
Gonzalez et al[58]	2008	n = 61 Steroids, 52 Control, 9	Steroids, 5.9 Control, 4.9	Steroids, 2.1; 3.8% Control, 3.7; 44.4%	19	Steroid-treated patients had better renal outcomes with early (13 days) versus late (34 days) steroid therapy.
Raza et al[59]	2012	n = 49 Steroids, 37 Control, 12	Steroids, 6.5 Control, 5.2	Steroids, 2.8; 16% Control, 3.4; 42%	19	There was no difference in renal outcomes based on steroid timing. Steroid treated patients received steroids early following diagnosis.
Muriithi et al[60]	2014	n = 95 Steroids, 83 Control, 12	Steroids, 3.0 Control, 4.5	Steroids, 1.4; 7% Control, 1.5; 0%	6	Steroid-treated patients had better renal outcomes with early (6 days) versus late (14 days) steroid therapy

had better kidney function (2.1 mg/dL versus 3.7 mg/dL), and only 2 patients required chronic dialysis (3.8%) as compared with 4 of 9 (44.4%) treated conservatively. Importantly, in those who received steroids, the time from drug withdrawal to steroid administration (13 days versus 34 days) significantly influenced recovery of kidney function. In those that recovered fully (13 days) versus those who did not (34 days), earlier treatment was critical. In addition, a smaller degree of interstitial fibrosis was seen on kidney biopsy with earlier steroid administration, which was also associated with a greater chance of recovery of kidney function.

In 2012, Raza and coworkers undertook a retrospective study in 49 patients with biopsy-proven AIN, of which 67% were associated with a medication.[59] All of the patients had AKI and 37 patient received steroids for a mean of 5 months, while 12 did not. The steroid regimen utilized was not described. In regards to timing of steroid administration, mean time from hospital admission to kidney biopsy was 2.9 days (range, zero to 28 days) with more than half performed within 24 hours of admission. Thus, most patients received steroids fairly early and the authors noted no difference in outcomes based on timing of steroids. Mean peak serum creatinine in the treated group was 6.5 mg/dL and 5.2 mg/dL in the control group. At a mean follow-up period of 19 months, the steroid-treated group had a mean serum creatinine of 2.78 mg/dL while the serum creatinine in the untreated group was 3.4 mg/dL. The control group also required more dialysis at follow-up (42%) as compared with the steroid group (16%). Similar positive results were noted when patients with DAIN were analyzed separately.

Most recently in 2014, Muriithi and colleagues published their experience with 133 cases of biopsy-proven AIN, of which 95 (70%) were drug-induced.[60] All of these patients underwent kidney biopsy for AKI with a mean peak serum creatinine of 4.3 mg/dL. As in all studies examining this question, steroid use was based on clinical judgment. Eighty-three patients were treated with corticosteroids (no specific regimen) for a relatively brief duration (mean 5 weeks), while 12 patients were managed conservatively. Mean peak serum creatinine in the steroid group was 4.5 mg/dL and 3.0 mg/dL in the control group. At mean follow-up of 6 months, there was no difference in serum creatinine concentration between the groups (1.4 mg/dL versus 1.5 mg/dL) and 6 steroid treated patients required dialysis. Analysis of all patients that received steroids revealed that a shorter interval from drug withdrawal to steroid administration (6 days versus 14 days) was associated with recovery of kidney function.

Given the lack of randomized, prospective trials and conflicting data from retrospective studies, the benefit of corticosteroids in the treatment of DAIN is unclear and the best approach remains elusive. One can argue that the overall published data modestly supports that steroids, when employed in certain cases, are potentially beneficial. Such positive effects include faster recovery of kidney function, more complete recovery with less CKD, and reduced need for chronic dialysis. Is there an explanation for the conflicting results in the 4 larger retrospective studies published since 2004? In the studies that show no benefit, the steroid-treated patients tended to have more severe kidney injury (higher peak mean serum creatinine) at the time of biopsy and initiation of therapy. In addition, steroids appeared to be administered later in the course of disease as compared with the favorable studies. In the retrospective study by Gonzalez and associates that showed a beneficial effect of steroids, the severity of AKI at the time of biopsy and initiation of steroid therapy were similar and the steroids were administered early (7 to 14 days) in the course of disease.[58]

Based on the immunologic mechanism of kidney disease and potential utility of steroids, other immunosuppressive drugs have been utilized to treat AIN, primarily to spare patients from adverse effects of corticosteroids. The immunosuppressive agent mycophenolate mofetil, which is employed to prevent rejection in transplanted kidneys and treat other aberrant immunologic diseases (systemic lupus erythematosus, vasculitis, etc) has been utilized for AIN.[61] Acute interstitial nephritis of various etiologies in 8 patients (drug-induced in 2) who were either steroid dependent or resistant were effectively treated with this drug. Of the 8 patients given mycophenolate mofetil (500 mg to 1000 mg twice daily), 6 manifested an improvement of kidney function, while kidney function stabilized in the 2 others.

Despite the discordant study results and paucity of prospective, controlled data on the efficacy

of steroid therapy, a reasonable approach to the management of DAIN would be as follows: (1) consider AIN in the differential diagnosis of unexplained AKI and withdraw the offending agent; (2) in the absence of improvement in kidney function within 5 days, kidney biopsy should be considered; (3) if the duration of AKI is less than three weeks, there is minimal interstitial fibrosis on biopsy, and there are no major drug contraindications, a trial of corticosteroids appears warranted (intravenous steroids or oral prednisone at 1 mg/kg a day); (4) if kidney function improves, steroid therapy should be maintained for 4 to 6 weeks, and the dosage then tapered over the next 4 weeks; and (5) if there is no meaningful improvement in kidney function after 3 to 4 weeks of high-dose therapy, steroids should be discontinued. Patients who are intolerant of steroids may benefit from treatment with mycophenolate mofetil.

In conclusion, based on the underlying allergic nature of DAIN it seems reasonable to employ corticosteroids in patients that do not rapidly improve (3 to 5 days) following discontinuation of the offending agent. As there is a reasonable amount on uncertainty about the utility of steroids for DAIN, it is fair to consider undertaking a randomized prospective trial to test this recommendation.

CONFLICT OF INTEREST

None declared.

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