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## Changes in the aetiology, clinical presentation and management of acute interstitial nephritis, an increasingly common cause of acute kidney injury

Manuel Praga<sup>1,2</sup>, Angel Sevillano<sup>1</sup>, Pilar Auñón<sup>1</sup> and Ester González<sup>1</sup>

<sup>1</sup>Division of Nephrology, Hospital 12 de Octubre\*, Madrid, Spain and <sup>2</sup>Department of Medicine, Complutense University, Madrid, Spain

Correspondence and offprint requests to: Manuel Praga; E-mail: mpragat@senefro.org

### ABSTRACT

Acute interstitial nephritis (AIN) is an important cause of acute kidney injury that has experienced significant epidemiological and clinical changes in the last years. The classical presentation, mostly induced by antibiotics and accompanied by evident hypersensitivity manifestations (skin rash, eosinophilia, fever) has been largely replaced by oligosymptomatic presentations that require a higher index of suspicion and are increasingly recognized in the elderly, having non-steroidal anti-inflammatory agents and proton pump inhibitors as frequent offending drugs. Drug-induced AIN continues to be the commonest type, but it requires a careful differential diagnosis with other entities (tubulointerstitial nephritis with uveitis syndrome, IgG4-related disease, drug reaction with eosinophilia and systemic symptom syndrome, sarcoidosis and other systemic diseases) that can also

induce AIN. Cortico-dependant, relapsing AIN is a recently recognized entity that poses an important therapeutic challenge. Although corticosteroids are widely used in drug-induced AIN to speed kidney function recovery and avoid chronic kidney disease, their efficacy has not been tested by randomized controlled trials. New diagnostic tests and biomarkers, as well as prospective therapeutic studies are needed to improve AIN diagnosis and management.

**Keywords:** acute interstitial nephritis, AKI in the elderly, corticosteroids, proton pump inhibitors

### INTRODUCTION

Acute kidney injury (AKI) is a growing worldwide problem with huge untoward economic and medical consequences [1]. Whereas

pre-renal AKI and acute tubular necrosis are well-known and rapidly diagnosed entities, other common causes of AKI-like acute interstitial nephritis (AIN) require a higher index of suspicion.

The true incidence of AIN is difficult to be assessed since published studies are based on retrospective analysis of kidney biopsy registries. Such estimation proves difficult because of the different kidney biopsy policies in AKI patients and the common reluctance to perform a kidney biopsy in elderly or frail patients in whom a drug-induced AIN is suspected. As shown in Table 1, the prevalence of biopsy-proven AIN seems to be similar all over the world, oscillating between 0.5 and 2.6% of all renal biopsies [2–26]. However, some retrospective registry analyses have found that AIN accounts for 5–18% of kidney biopsies performed in the setting of AKI [4, 5, 9–11, 15, 19, 20, 24, 26–29], with a tendency to increase in the last years. Such increase is apparently linked to the generalized use of antibiotics and non-steroidal anti-inflammatory agents (NSAIDs) in most countries. Assessment of differences in the aetiology of AIN is even more difficult owing to the scarcity of studies in many parts of the world. Available data, however, suggest that, whereas drug-induced AIN roughly represents two-thirds of the cases in many countries, infectious AIN are still an important cause of AIN in less developed countries (Table 1).

Important epidemiological changes in the field of drug-induced AIN and several entities mimicking drug-induced AIN have been reported in the last years. This review is aimed to summarize and to discuss the main changes reported over the last years in the aetiology, clinical presentation, diagnosis and management of AIN.

## INCREASING INCIDENCE OF AIN IN THE ELDERLY

The Spanish Registry of Glomerulonephritis [19] analysed a large number of native kidney biopsies (17 680) obtained in

the period 1994–2009. An increase in the prevalence of AIN was found, from 3.6% in the first 4 years to 10.5% in the last 4 years. Notably, the increase was particularly striking among patients >65, from 1.6 to 12.3%. A similar increase in the prevalence of AIN among elderly patients, particularly drug-related AIN, had been previously pointed out by other studies [23, 27, 28]. A recent study from the Mayo Clinic [30] analysed the causes and characteristics of AIN in 45 elderly patients (65 years and older) and in 88 younger adults (18–64 years old). The elderly had significantly more drug-induced AIN than younger patients (87 versus 64%), antibiotics and proton pump inhibitors (PPIs) being the most common culprit drugs in the former. Compared with younger patients, the elderly had higher peak creatinine and more need for dialysis.

Taken together, these retrospective studies suggest that older people might present an increased susceptibility to drug-induced AIN and that ageing kidneys might be more vulnerable to the harmful effects of the interstitial inflammation that characterizes AIN. Although prospective studies are needed for confirmation, this increasing prevalence of AIN among elderly patients poses a number of important clinical questions. Chronic poly medication is common among old people, including PPIs and anti-inflammatory drugs, and this fact, together with the frequent cognitive impairment that accompanies ageing, makes problematic an accurate identification of the offending drug in many elderly patients with AIN. Kidney biopsies are generally deemed too aggressive a procedure in frail elderly patients and empirical approaches (drug withdrawal, corticosteroids) are frequently preferred. On the other hand, old people are remarkably prone to serious side effects of corticosteroids and ageing kidneys could be more sensitive to the development of chronic kidney disease (CKD) when the diagnosis and treatment of AIN is delayed.

**Table 1. Prevalence of biopsy-proven AIN in different parts of the world**

	Asia (n = 24075)				Africa [7–11] (n = 2518) <sup>a</sup>	Europa [12–14] (n = 50568) <sup>b</sup>	South America [15] (n = 9617) <sup>c</sup>	North America [16, 17] (n = 7834) <sup>d</sup>
	India and Pakistan [2–3] (n = 3642)	China [4] (n = 13519)	Japan [5] (n = 2400)	South Korea [6] (n = 4514)				
AIN (all renal biopsies)	1.1%	1.1%	1%	0.6%	2.6%	1.9%	0.5%	1.8%
AIN (renal biopsies in the setting of AKI)	5.4%				10.4%	11.5%		18.6%
Drug-induced	53% <sup>e</sup>				50% <sup>f</sup>	78% <sup>g</sup>		71%
‘Infectious’	40% <sup>e</sup>				50% <sup>f</sup>	6% <sup>g</sup>		4%
‘Associated with systemic diseases’						5% <sup>g</sup>		20%
‘Other/idiopathic’	7% <sup>e</sup>					11% <sup>g</sup>		5%

<sup>a</sup>Pooled data from Egypt and South Africa.

<sup>b</sup>Pooled data from Belgium, Croatia, Germany, Ireland, Italy, Portugal, Serbia, Spain, the Netherlands and UK.

<sup>c</sup>Data from Brazil.

<sup>d</sup>Data from USA.

<sup>e</sup>Data from India.

<sup>f</sup>Data from Egypt.

<sup>g</sup>Data from Germany and UK.

## DRUG-INDUCED AIN: THE EMERGING ROLE OF DRUGS OTHER THAN ANTIBIOTICS AND NSAIDS

Drug-induced cases represent more than two thirds of AIN in many countries (Table 1). Although theoretically any drug can elicit the typical allergic response characteristic of AIN, antibiotics and NSAIDs are considered the most frequently involved drugs (reviewed in [31, 32]). However, in the last years, the important role of other commonly prescribed drugs has been raised.

### Proton pump inhibitors

PPIs are one of the most prescribed drugs worldwide. Their efficacy in acid-related gastrointestinal diseases and the very low number of side effects have contributed to their massive prescription. Nevertheless, PPI treatment is frequently unjustified and over the counter. The first report of AIN associated with PPI was published in 1992 and thenceforth, several dozens of PPI-related AIN have been published [32, 33]. The interval between drug initiation and the onset of kidney abnormalities can oscillate between 1 week and 9 months, although a time frame of 10–11 weeks was the commonest. As in other types of drug-induced AIN, leucocyturia, haematuria and non-nephrotic proteinuria are commonly observed but the classical triad of fever, skin rash and eosinophilia has been found in less than 10% of the patients [31–33]. Non-specific complaints like low-grade fever, malaise and anorexia are common and AKI of variable severity, virtually universal. In the above mentioned Mayo Clinic study [30], PPI-induced AIN had less severe AKI than antibiotic-induced cases, but the probability of recovery by 6 months was significantly lower.

Although some studies have suggested that PPI could be numerically the first cause of drug-induced AIN, the variable interval between drug initiation and AIN and the frequently irregular or over-the-counter use of these drugs make it difficult to establish a clear correlation between PPI treatment and AIN in many cases. In this regard, recent epidemiological studies have provided convincing data in support of the important role of PPI as causative agents in AIN [30, 34, 35]. Blank *et al.* [36] performed a population-based case-control study nested in a cohort of 572 661 New Zealand patients receiving PPI. The unadjusted odds ratio of AIN was 5.16 [95% confidence interval (CI) 2.21–12.05] for current use of any PPI compared with past use. Importantly, the absolute risk in current users who were 60 years or older was considerably higher than for younger current users: for every 100 000 PPI users in the >60 age group, about 20 per year developed AIN when compared with 2 per year in those aged 15–49 years.

### 5-Aminosalicylates

The 5-aminosalicylates (sulphasalazine, mesalazine, olsalazine) are frequently used for the treatment of inflammatory bowel diseases (IBD). Several types of kidney involvement have been reported both in Crohn disease and in ulcerative colitis. Ambruzs *et al.* reviewed a series of 83 kidney biopsies performed in patients with IBD [37]. IgA nephropathy was the most common diagnosis (24%), followed by interstitial

nephritis (19%). More than half of patients with interstitial nephritis had current or recent past exposure to aminosalicylates. This report is in line with other studies that have stressed the appearance of AIN in patients receiving these drugs [38, 39]. The incidence of renal impairment among patients taking 5-aminosalicylates has been estimated in 1 in 200–500 patients. Some patients develop AIN accompanied by hypersensitivity symptoms (rash, fever, eosinophilia) in the first year after the onset of aminosalicylates, whereas others present a chronic and progressive kidney injury with no clear chronological relationship with aminosalicylates [39]. On the other hand, several cases of AIN in therapy-naive patients have been reported, suggesting the possibility of AIN as an extraintestinal manifestation of IBD (reviewed in [40, 41]). Therefore, monitoring of kidney function is advised in all patients with IBD, particularly in those treated with aminosalicylates.

## AIN IN HIV INFECTION AND IN ONCOLOGIC PATIENTS

HIV-infected patients are particularly prone to AIN. Hypersensitivity reactions to drugs, anti-retroviral-induced direct tubulointerstitial damage, infections (tuberculosis, candida, cryptococcus, viruses) or immunologic syndromes associated with HIV infection as diffuse infiltrative lymphocytosis syndrome or immune reconstitution inflammatory syndrome are the causative entities in the majority of patients. Parkhie *et al.* [42] reviewed 262 biopsies performed in HIV patients in the period 1995–2008. AIN without HIV-associated nephropathy was identified in 29 patients (11%). Mostly (72%) were caused by drugs, NSAIDs and sulphamethoxazole/trimethoprim being the most common offending agents. Interestingly, none of the patients presented with the classic triad of fever, rash and pyuria. Zaidan *et al.* [43] found tubulointerstitial nephropathies in 26% of 222 kidney biopsies in HIV-infected patients. Half of them presented predominant tubular lesions, whereas interstitial nephritis was observed in the remaining half. Drug-related nephrotoxicity (52.5%), infections (15.2%), dysimmune disorders (8.5%), malignancies (3.4%) and tubulointerstitial nephropathies of undetermined origin (20.4%) were the commonest diagnosis. In agreement with other studies, the typical characteristic findings of drug-induced AIN (rash, eosinophilia) were rare or absent. In summary, AIN represents a common cause of AKI in HIV patients, is associated with a broad spectrum of aetiologies and frequently requires the performance of renal biopsy to establish an accurate diagnosis.

Drug-induced AIN might also be a neglected problem among cancer patients. Airy *et al.* [44] have recently published a literature review of 44 patients and provided another 12 documented cases of acute and chronic tubulointerstitial nephropathies related to different types of anti-cancer drugs. A prompt diagnosis, rapid drug withdrawal and a short course of corticosteroids were associated with a more favourable outcome.

## INFECTIOUS AIN. THE CHANGING PATTERN OF KIDNEY TUBERCULOSIS

Infection-related AIN accounts for 5–10% of the cases [31, 32], although its incidence seems to be higher in less developed countries (Table 1). Multiple organisms can precipitate AIN, but it has not been clarified yet whether the infection elicits the characteristic inflammatory interstitial reaction by direct invasion or by the release of proinflammatory cytokines from distant organs.

Kidney involvement was one of the most serious and frequent complications of tuberculosis. Classical kidney tuberculosis is characterized by lower urinary symptoms and radiographic evidence of upper and lower urinary tract involvement, with calycial erosions and narrowings, ureteral strictures and papillary necrosis, finally leading to massive parenchyma scarring and calcification (mastic kidney). Some recent reports suggest that the predominant clinical presentation of kidney tuberculosis could be changing into an AIN pattern [45–47]. Chapagain *et al.* [45] describe 25 patients with active tuberculosis and significant renal disease. Kidney biopsy showed interstitial inflammation with eosinophils and granulomas. Anti-tuberculous therapy was followed by renal function improvement in the majority, although some patients with very advanced disease finally required chronic dialysis. The pathogenesis of these new presentations of kidney tuberculosis is unknown. Although extrarenal infection by *Mycobacterium tuberculosis* was demonstrated in all the patients reported by Chapagain *et al.* [45], Ziehl–Neelsen staining and *M. tuberculosis* PCR were negative in renal tissue. Therefore, immune responses against *M. tuberculosis*, without direct kidney invasion, could precipitate AIN. In this way, glomerulonephritis and AIN likely mediated by immune phenomena have been found in a significant proportion of patients infected by *Mycobacterium leprae* [48]. Interestingly, all the patients in Chapagain's report were treated with corticosteroids in addition to anti-tuberculous therapy, although two patients who received corticosteroids for the treatment of AIN, without concomitant complete anti-tuberculous therapy, developed disseminated tuberculosis [45]. On the other hand, several reports suggest that this type of tuberculosis-induced AIN is more prevalent among patients of Indo-Asian origin [49].

## DIFFERENTIAL DIAGNOSIS OF AIN

The absence of hypersensitivity manifestations and a normal urinary sediment are important features to distinguish acute tubular necrosis from AIN but an important number of AIN has, nowadays, an oligosymptomatic presentation. Clinical suspicion of AIN in patients with AKI usually relies on the presence of general symptoms (malaise, anorexia, arthralgias), hypersensitivity manifestations (low-grade fever, skin rash, eosinophilia) and urinalysis findings typical of AIN (reviewed in [31, 32]): microhaematuria (rarely macroscopic or accompanied by erythrocyte casts), non-nephrotic proteinuria (although some patients with NSAIDs-related AIN can present complete

nephrotic syndrome) and leucocyturia. Sterile pyuria and leucocyte casts have been pointed out as important clues for the diagnostic of AIN in patients with AKI [31, 32], but, in the end, kidney biopsy is still needed to confirm AIN diagnosis.

Eosinophiluria has long been considered a useful diagnostic test for drug-induced AIN. An important recent study, however, has greatly undermined this belief. Muriithi *et al.* [50] reviewed 566 patients in whom urinalysis searching for eosinophils and a renal biopsy had been performed simultaneously. Eosinophiluria was found in a variety of diagnoses. Ninety-one patients had AIN, 80% of them drug-induced. Using a >1% urinary eosinophils cut-off, only 31% of AIN patients was identified, with a similar rate in acute tubular necrosis (29%). The sensitivity and specificity for urinary eosinophils >1% were 30 and 68%, respectively. Even using a 5% cut-off, eosinophiluria was a poor test to discriminate AIN and acute tubular necrosis.

Although most of AIN are induced by drugs, it should always be kept in mind that AIN can also be caused by infections, systemic diseases and idiopathic forms (reviewed in [31]). A rapid differential diagnosis is mandatory in order to prescribe the most appropriate treatment. Table 2 summarizes clinical and histological findings that could help in the differential diagnosis of AIN.

### Sarcoidosis

AIN is a recognized manifestation of sarcoidosis [51, 52]. The finding of non-caseating granulomas, in addition to the characteristic inflammatory interstitial infiltrates, is characteristic of the disease. AIN may be the first manifestation of sarcoidosis and, in these cases, the presence of pulmonary involvement (hyaline adenopathies, pulmonary infiltrates), hypercalcaemia or elevated serum levels of angiotensin-converting enzyme are useful clues for a prompt and correct diagnosis. Mostly patients present a rapid improvement with corticosteroids, usually administered at a dose of 0.5–1 mg/kg/day and tapered down in 3–4 weeks. However, relapses are common and some patients need prolonged corticosteroid treatment. In such cases, azathioprine and mycophenolate mofetil can be useful corticosteroid-saving options [53, 54]. In cortico-resistant, cortico-dependant or in patients in whom corticosteroids are contraindicated, anti-TNF drugs like Infliximab or Adalimumab may be useful [53].

### Tubulointerstitial nephritis with uveitis

Tubulointerstitial nephritis with uveitis (TINU) syndrome is characterized by AIN with anterior uveitis, usually bilateral [55]. Since the first description in 1975, over 200 cases have been described in the literature. Usually, AIN precedes uveitis, but some patients present both uveitis and AIN concurrently and in a few cases uveitis can precede kidney involvement. Corticosteroids are commonly prescribed and most patients recover kidney function, although relapses can occur. The pathogenic role of antibodies against modified C-reactive protein has been postulated recently [56].



**Table 2. Differential diagnosis of AIN**

	Age/sex	Renal laboratory findings	Hypersensitivity manifestations <sup>a</sup>	Extrarenal manifestations	Histopathological features	Treatment	Prognosis
Drug-induced AIN	Any. increasing incidence among elderly	AKI (100%), non-nephrotic proteinuria (90%), leukocyturia and leukocyte casts (80%), haematuria (70%)	Relatively common in antibiotic-induced cases. Rare in NSAIDs, PPI and aminosalicilate-induced	Arthralgias, malaise, elevated liver transaminases	Interstitial infiltrates composed by lymphocytes, macrophages, eosinophils, and plasma cells. Interstitial granulomas occasionally seen	Rapid removal of the offending drug. Early corticosteroid treatment facilitates the recovery of renal function	Variable, mainly related to delay in diagnosis and treatment
Infectious AIN	Any	Similar to drug-induced AIN	Absent	High-grade fever, clinical picture of the responsible infection	Interstitial infiltration by neutrophils. Granulomas in <i>M. tuberculosis</i> , fungi and parasites	Treatment of the responsible infection	Favourable when infection is resolved
Sarcoidosis	More common in young adults	Similar to drug-induced AIN	Absent	Pulmonary infiltrates, lymphadenopathies, hypercalcaemia	Interstitial granulomas commonly observed	Corticosteroids	Favourable, but relapses are common
TINU syndrome	Young women	Similar to drug-induced AIN	Absent	Uveitis preceding, coinciding or following AIN	Interstitial granulomas commonly observed	Corticosteroids	Favourable but relapses can occur
IgG4-related disease	Any	Similar to drug-induced AIN	Absent	Pancreatitis, sialadenitis, retroperitoneal fibrosis, lung interstitial disease	Interstitial cellular infiltrates rich in IgG4+ plasma cells. Storiform, interstitial irregular fibrosis	Corticosteroids	Favourable but relapses are common
DRESS syndrome	Any	Similar to drug-induced AIN	Very common and severe. Skin eruption can progress to exfoliative dermatitis	Hepatitis, pneumonitis, myocarditis	Similar to drug-induced AIN	Rapid removal of the offending drug, supportive measures, corticosteroids	5–10% mortality. Relapses are common

<sup>a</sup>Eosinophilia, skin rash, low-grade fever.

### IgG4-related disease

IgG4-related disease (reviewed in [57–59]) is a systemic disorder characterized by the appearance of cellular infiltrates, rich in IgG4-positive plasma cells, in multiple organs. Kidney involvement was reported for the first time in 2004 and consists of dense lymphoplasmacytic infiltrates with an increased number of IgG4-positive plasma cells. A characteristic type of storiform, irregular fibrosis, is another typical finding [58]. High serum levels of total IgG, IgG4 and IgE, as well as hypocomplementaemia are frequently found. Radiologically, low-density lesions, cortical nodules or diffuse patchy involvement, sometimes mimicking malignancies, can be observed. Extrarenal organ manifestations are common and include autoimmune pancreatitis, sialadenitis, retroperitoneal fibrosis, lymphadenopathy, lung interstitial disease and sclerosing cholangitis [57–59]. These past or concurrent manifestations can be important clues for a correct diagnosis in patients with AIN of apparently unknown aetiology.

Corticosteroids are usually the first line of therapy. Response is satisfactory in the majority of patients, with the exception of those with advanced degrees of interstitial fibrosis. Relapses are common and mycophenolate mofetil, azathioprine and methotrexate have been used as corticosteroid-sparing agents. Rituximab has been useful in some patients refractory to other treatments [57–59].

### DRESS syndrome

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare drug-induced hypersensitivity reaction with severe and diffuse erythematous skin eruption that can progress to exfoliative dermatitis, accompanied by fever, eosinophilia, atypical lymphocytosis and organ involvement (lung, liver, kidney) [60, 61]. Allopurinol and anti-epileptic drugs are the most frequently involved agents. A long latency period (3–8 weeks) between drug exposure and onset of symptoms differentiates DRESS from other drug-induced hypersensitivity syndromes.

Kidney involvement occurs in 10–30% of patients, most of them related to allopurinol [62]. Rapid drug withdrawal, supportive measures and corticosteroids induce a recovery of renal function and resolution of symptoms in a majority of cases, although DRESS can be a life-threatening disease in some patients with severe skin affection. Relapse of AIN can occur after corticosteroid discontinuation without re-exposure to the offending drug [60–62].

### Other systemic diseases causing AIN

Although rarely, AIN can be a clinical manifestation of systemic diseases such as systemic lupus erythematosus and vasculitis. Chronic tubulointerstitial nephritis is the commonest type of renal involvement in Sjögren's syndrome, but, in some patients, the typical lymphoplasmacytic interstitial infiltration

that characterizes this disease develops abruptly, causing an AKI that fulfils AIN criteria [63]. Characteristic ocular and salivary involvement (that should be carefully differentiated from IgG4-related disease), and positive serologies for SSA and SSB lead towards the correct diagnosis.

### THE PROBLEM OF CORTICOSTEROID-DEPENDANT AIN

Occasionally, AIN patients who had shown a positive response to corticosteroids, present a relapse coinciding with treatment discontinuation. In some of these patients, a diagnosis of sarcoidosis, TINU syndrome or IgG4-related disease can be established but in others relapsing AIN cannot be attributed to any particular disease. Interestingly, in the author's experience, some of these patients had received an initial diagnosis of drug-induced AIN, based on a clear chronologic relationship with a drug and the presence of hypersensitivity manifestations. The possibility that a drug-induced AIN can later evolve into a relapsing cortico-dependant AIN not related to the initially precipitating drug has been clearly documented in DRESS syndrome. A tendency to suffer this disease has been associated with some HLA haplotypes [64]. Expansion of activated T lymphocytes in the blood and the presence of atypical CD8 lymphocytes that can persist for months after offending drug discontinuation have been demonstrated in some patients [65]. On the other hand, very interesting studies have connected DRESS syndrome with viral reactivations: amplification of regulatory T cells, induced by a drug-specific immune reaction, could contribute to virus reactivation by unknown mechanisms, and asymptomatic viral reactivations could induce, in turn, an expansion of T cells cross-reacting with the drug [66, 67]. In support of these hypotheses, an increase in antibody titres against human herpesvirus-6 (HHV-6) was detected in 60 of 100 patients with DRESS syndrome, and active viral replication was found in a substantial proportion of cases [68]. Importantly, clinical relapses coincided with the detection of HHV-6 DNA in peripheral blood [68]. These pathogenic issues warrant investigation in patients with drug-induced AIN, particularly in those with a relapsing clinical course.

Cortico-dependant AIN poses an important therapeutic challenge, owing to the serious side effects related to long corticosteroid treatments. Mycophenolate mofetil has been successfully used as a corticosteroid-sparing agent in a number of patients [69, 70], maintaining stable remission for long periods.

### CORTICOSTEROIDS IN DRUG-INDUCED AIN

Rapid identification and withdrawal of the causative drug is the mainstay of treatment in drug-induced AIN. Most patients show an improvement of renal function after drug withdrawal but, in many cases, such improvement stops before the complete recovery of renal function, the patient remaining with different degrees of CKD. Several observational studies and

**Table 3. Current therapeutic protocol for Drug-induced AIN at the Hospital 12 de Octubre**

- (1) Rapid identification and withdrawal of the offending group
- (2) Early administration of corticosteroids (<5 days after diagnosis) unless rapid renal function recovery after drug withdrawal in mild cases.
- (3) Scheme of corticosteroid treatment:
  - IV Methylprednisolone pulses (250 mg each), for 3 consecutive days
  - Oral prednisone, 1 mg/kg/day for 1–2 weeks after IV pulses
  - Prednisone tapered down for 4–6 weeks
- (4) When renal function does not improve after 2 weeks of treatment, corticosteroids are discontinued more rapidly
- (5) In patients who relapse after corticosteroid discontinuation (after other causes of AIN have been excluded), mycophenolate mofetil, starting with 1.5–2 g/day and slowly reduced over 12–24 months. Corticosteroids administered at the lowest possible doses or withdrawn.

case reports (reviewed in [31]) suggest that corticosteroid treatment can accelerate renal function recovery in drug-induced AIN, but the lack of a prospective, randomized, controlled trial makes corticosteroid treatment still controversial. In addition, some retrospective studies have not confirmed the beneficial influence of corticosteroids [15, 71]. Clarkson *et al.* [15] performed a retrospective study in 60 patients with biopsy-proven AIN (drug-induced in 92%). Of them, 60% received corticosteroids and 40% supportive care. No difference in renal function was observed between the two groups after 1 year of follow-up, although a significant proportion of patients in both groups exhibited CKD. Of note, median delay between the onset of AIN and corticosteroid treatment was longer than 3 weeks. The Grupo Madrileño de Nefritis Intersticiales performed a retrospective multicentre study in 61 patients with biopsy-proven drug-induced AIN [72]. A majority of patients (85%) received corticosteroids and their long-term outcome was significantly better than that of patients who did not (need of chronic dialysis 3.8 versus 44%). But the most important finding in this study was the close correlation between the delay in the onset of corticosteroids and renal function recovery. Among the patients who had received corticosteroids, a complete recovery of baseline renal function was observed in 53%. When comparing these patients with the remaining 47% in whom renal function recovery had been only partial, no differences in baseline characteristics nor in the doses or duration of corticosteroids were found. However, a significant difference in the interval between drug withdrawal and onset of corticosteroid treatment was observed ( $13 \pm 10$  versus  $34 \pm 17$  days) as well as a significant correlation between the delay in corticosteroid treatment and the final serum creatinine. By multivariate analysis, an interval longer than 7 days between drug withdrawal and onset of corticosteroid treatment and the severity of interstitial fibrosis were the only clinical factors that significantly increased the risk of an incomplete recovery of baseline renal function. Repeated renal biopsies in this study showed a rapid transformation of interstitial infiltrates into areas of irreversible fibrosis [72]. Therefore, the rationale for

early corticosteroid treatment would be based on the recognized efficacy of corticosteroids to resolve cellular interstitial infiltrates and to avoid subsequent fibrosis. Table 3 presents our current therapeutic protocol in patients with drug-induced AIN.

It has been recently reported that the response to corticosteroids in elderly patients (>65 years) presenting an AIN is similar to that observed in younger patients and that the number of complications attributable to this treatment was relatively small [30]. Delays in initiating corticosteroids correlated with a poorer recovery of AIN in the elderly [30].

## CONCLUSIONS

Important epidemiological and clinical changes in AIN have occurred over the last years, including an increasing incidence in elderly patients, an emerging role of PPIs and 5-aminosalicylates as precipitating causes of drug-induced AIN and an increasing number of sub-clinical, asymptomatic presentations that require a high index of suspicion. The characteristics of several infectious and systemic diseases that should be distinguished from drug-induced AIN have been better defined in the last years. Corticosteroids are widely used in drug-induced AIN, but their efficacy has not been tested by means of randomized, controlled trials. Therefore, further studies, ideally prospective, are needed in search of new diagnostic tests and biomarkers and in order to establish the most appropriate management of this still largely neglected cause of AKI.

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## CONFLICT OF INTEREST STATEMENT

None declared.

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