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Editorial

New challenges in tubulointerstitial nephritis induced by drugs
[[es]]Nuevos retos en las nefritis tubulointersticiales inducidas por fármacos☆

Gema M. Fernández Juárez[a,*], *Javier Villacorta Pérez*[a], *Fernando Caravaca Fontán*[b], *Clara Cases Corona*[a], *Beatriz Sánchez Alamo*[a], *Ana M. Tato Ribera*[a]

[a] *Departamento de Nefrología, Hospital Universitario Fundación Alcorcón, Alcorcón, Madrid, Spain*
[b] *Departamento Nefrología, Hospital Universitario 12 Octubre, Madrid, Spain*

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Introduction

Acute tubulointerstitial nephritis (TIN) is characterised by a diffuse inflammatory cell infiltrate in the interstitial compartment, with tubulitis and different degrees of interstitial oedema and fibrosis. It is a common pattern that can be induced by autoimmune diseases such as sarcoidosis, IgG4, Sjögren's syndrome and Dressler's syndrome, by infectious agents and by drug-mediated hypersensitivity reactions. Such drug-induced reactions are responsible for over 70% of cases.[1]

Although drug-related acute TIN was first described over 70 years ago, it continues to be a challenge for nephrologists. Renal biopsy is still the only reliable diagnostic tool and, from a therapeutic perspective, no clinical trials to help establish a treatment protocol have been published. In fact, most of the recommendations are based on retrospective observational studies and expert opinions.[2,3]

Adding to the already significant limitations in the management of acute TIN the fact that the list of potentially responsible drugs gets longer every year, and that the clinical signs are often subtle and changing, we can see the great challenges faced by nephrologists, both in terms of diagnosis and treatment.

Diagnostic challenges in acute tubulointerstitial nephritis

The first cases of drug-induced TIN were described after penicillins were incorporated into routine medical practice in the 1950s.[2] Although not all drugs induce this type of damage with the same frequency, based on the description thereof, cases were published of tubulointerstitial nephritis associated

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* *Corresponding author.*
E-mail address: gmfernandez@fhalcorcon.es (G.M. Fernández Juárez).

with most pharmacological groups, as these were marketed and became more widely used. The renal histological pattern is indistinguishable from one drug to another, but both the mechanism inducing the reaction and the accompanying clinical signs may be different. Acute TIN associated with penicillins and other antimicrobials occurs in the days/weeks following the start of treatment with the drug, and in most cases it is accompanied by some sign of systemic hypersensitivity (pyrexia, skin rash, eosinophilia).[4]

In contrast, the only manifestation of acute TIN induced by other drugs, such as nonsteroidal anti-inflammatory drugs (NSAID) and proton pump inhibitors (PPI), may be acute kidney injury alone, with no other associated signs or symptoms.[3,5] In a recent study of patients whose biopsy revealed PPI-related acute TIN, it had only been initially suspected by their treating physician in 25% of cases.[6] Less than 50% of patients had a pyrexia, less than 10% developed a rash and only a third had eosinophilia. The classic triad was present in less than 5–10% of cases.[7] Moreover, the time interval between kidney damage and the start of the drug ranged from one week to 9 months.[3]

PPI and NSAID are currently taken by millions of people around the world, sometimes for months or years, or even permanently. Although only a small percentage of patients will develop acute TIN, the spread of their use has made these drugs one of the most common causes of acute TIN worldwide. In recent years, a significant association between the use of PPI and acute and chronic kidney damage has been found in several population cohorts. In a cohort from New Zealand that included 572,661 patients, the use of PPI increased the risk of developing acute TIN by 5% compared to patients not taking PPI. The risk was much higher in the older population (aged >60) (approximately 0.2/1,000 person-years) than in the younger population (aged 15–49) (0.02/100 person-years).[8]

Although acute TIN has a good prognosis when detected early, the drug is withdrawn and, where necessary, the patient is started on early steroid therapy, undetected subclinical acute TIN can progress to renal fibrosis and eventually cause irreversible chronic kidney disease (CKD). Lazarus et al. reviewed the renal function of a cohort of 10,482 patients according to whether or not they started treatment with PPI during the observation period. Patients who took PPI had a higher risk of developing CKD (14.2/1,000 person-years) than those who did not (10.7/1,000 person-years). The increase in absolute risk was 3.3%.[9] The fact that the series also showed an increased risk of acute kidney damage in patients taking PPI would seem to suggest that acute TIN-related damage is a potential promoter of CKD. Duration of treatment and the cumulative dose appear to increase the risk of kidney damage. Similar results have subsequently been confirmed in other series.[10]

As acute TIN is a disease with no reliable, non-invasive diagnostic test, it is possible that a considerable number of PPI-related cases go unnoticed, contributing, as mentioned, to the development of CKD. The situation is likely to be similar for other drugs with less widespread use, the study of which is even more complex. Therefore, in addition to recommending limiting the use of PPI and drugs in general to situations where there are clear indications, and only for as long as the indication persists, acute TIN should be considered among the possible diagnoses for any deterioration in renal function where the origin is not well defined, even when there is no recent drug history and no sign of associated hypersensitivity. As we shall go on to discuss, the most important prognostic factors for the recovery of renal function after an episode of acute TIN are the early withdrawal of the causative drug and the start of steroid treatment. Both measures are only possible with an early diagnosis.

The number of diagnosed cases of acute TIN has been on the rise in recent years. In the Spanish Glomerular Disease Registry, the number of renal biopsies with the diagnosis of acute TIN has tripled over the last decade, from 1.5% in the 1994–1997 period, to 4.2% in the period 2006–2009.[11] This increase is observed in all age groups, but particularly in patients aged >60. A similar increase was described in the English Registry over 20 years ago[12] and recently in the Scottish Registry.[13] There are various hypotheses to explain the increased incidence among the elderly population, including the relaxation in the criteria for indicating renal biopsy in this population over the last ten to twenty years. However, this may not be the only reason, as no similar increase has been found in other diseases diagnosed histologically since the change in policy.[14] It has been speculated that elderly people's kidneys are more susceptible to hypersensitivity-related damage. In fact, in the studies described above, the association between PPI use and kidney injury was more intense in elderly patients than in younger ones.[6,9]

Lastly, elderly patients tend to take a larger number of drugs and the chances of developing acute TIN related to any one of them is therefore greater. Polypharmacy in these patients is an additional challenge, owing to the difficulty in identifying the responsible drug. In the most recent series, the drug could not be identified in 30% of cases.

Therapeutic challenges

Early withdrawal of the causative drug is the cornerstone of the treatment of acute TIN. However, this does not always mean a complete recovery from the kidney damage; approximately 45% of patients maintain a certain degree of CKD as a sequela, and 7–10% require long-term renal replacement therapy after the acute episode.[15,16]

Drug-induced acute TIN is a consequence of a hypersensitivity reaction that promotes the onset of the inflammatory cascade in the renal parenchyma and which, if not controlled, can lead to tubular atrophy and fibrosis. Theoretically, the use of immunosuppressive medication, which includes steroids, may limit inflammation and also, therefore, the subsequent development of fibrosis. In fact, some retrospective studies have suggested that the use of steroids accelerates and intensifies renal recovery after drug-related acute TIN,[15,17] but not all studies are in agreement.[18]

Clarkson et al.[18] published a retrospective study on 60 patients diagnosed with acute TIN (92% drug-related). However, clinical data on progress were available for only 42 of the patients. They found no difference in renal function at 6 and 12 months of follow-up between patients treated with corticosteroids (60%) and those who received only supportive treatment (40%). The Madrid Interstitial Nephritis Group studied 61 patients with drug-induced acute TIN secondary diagnosed by renal biopsy. The majority (85%) received

steroids. After mean follow-up of 19 months, renal function was better in the treated patients (creatinine 2.1 mg/dl) than in the non-treated ones (creatinine 3.7 mg/dl; $p < 0.05$), and the number of patients who needed long-term renal replacement therapy was significantly lower (3.8 vs. 44.4%; $p < 0.001$).[17] In this study, the greatest benefit was obtained in patients who started steroid treatment early, and significant differences were found when it was started in the first week after stopping the causative drug.

Comparing these 2 studies, in the study in which the steroids showed no benefit over renal function,[18] the treated patients had more severe initial kidney damage than those not treated (creatinine at diagnosis 7.9 vs. 6.2 mg/dl) and steroid therapy was started late. Paradoxically, in said study the authors highlight that the steroid therapy was "early" after performing the renal biopsy (maximum interval 4 days), but the mean time between onset of symptoms and renal biopsy was four weeks, with an interquartile range between 2 and 6 weeks.

Although in both studies the authors aimed to start treatment early, they had different starting points and the results are therefore not comparable; in one, the starting point was the withdrawal of the drug, while in the other, it was the performance of the renal biopsy.

From a practical point of view, although we acknowledge the difficulties involved, time of onset of symptoms or the increase in nitrogen products should be considered as starting point, regardless of the time of renal biopsy or drug withdrawal. Taking these premises into account, in a study of 182 patients diagnosed with acute TIN by renal biopsy and treated with steroids, those treated in the first 2 weeks after kidney injury had better renal recovery. In contrast, treatment started beyond 4 weeks had hardly any benefit on final renal function.[15]

Steroid treatment is not without side effects, especially in the elderly population. Optimising the dose and, above all, the duration of treatment, is therefore essential. In one study, it was observed that prolonging steroid therapy at full doses for more than 3 weeks, or the reducing regimen for more than 5 weeks, even in the most severe forms, did not improve the renal prognosis.[15] As had been observed in other studies,[19] recovery of the glomerular filtration rate occurred mainly in the first weeks after the damage (4–5 weeks), with subsequent recovery being far more modest or non-existent, even prolonging the steroid therapy. Several studies have found that rapid recovery of the glomerular filtration rate carries more weight in the final renal prognosis than the original severity of the kidney damage.[19,20] Precisely to obtain a quick response, a number of reviews have proposed incorporating steroid boluses.[3] However, no studies have been able to demonstrate the potential benefit.[15]

From a histological perspective, there is consensus about the severity of interstitial fibrosis being a determining factor in the reversibility of the condition.[21] The recognised partiality of the renal biopsy in estimating interstitial fibrosis and the difficulty in standardising the quantification of the interstitium may explain why it has not been possible to establish a cut-off point for the degree of fibrosis that determines a point of no return, from which treatment will provide no benefits, and which might be of help for making therapeutic decisions.[15] No other histological characteristic has been found to have prognostic value.

Lastly, the role of immunosuppressants other than steroids has scarcely been studied. Some clinical cases and small series have been published on the use of mofetil mycophenolate or ciclosporin in a situation of steroid dependence, steroid resistance or non-tolerance to corticosteroids. The most extensive series published to date included 8 patients diagnosed with acute TIN who had received steroids for at least 6 months and who, due to one of the circumstances described above, were switched to mycophenolate. Improvement of renal function was observed in 6 patients and stabilisation in 2. The applicability of these results to drug-induced acute TIN is limited, however, as only 2 patients in the series had that diagnosis. The majority had an underlying autoimmune disease.[22]

Future challenges

A new pharmacological group, the so-called immune control inhibitors (ICI), is attracting great attention as a range of new therapeutic agents against cancer, due to their efficacy in various types of malignancy.[23] There are 2 different types, according to their mechanism of action: inhibitors of the cytotoxic T-lymphocyte-4 (CTLA-4); and the programmed cell death protein (PD-1) and its PD-L1 ligand. Ipilimumab was the first ICI to be approved by the FDA, followed by 2 anti-PD-1 antibodies (nivolumab and pembrolizumab) and two other anti-PD-L1 antibodies (atezolizumab and durvalumab).

These agents reactivate cytotoxic T cells, and cause cancer cell lysis by overloading the immune system's braking mechanisms. Owing to their intrinsic mechanism of action, they induce an interruption of immune tolerance, and in some patients a condition that histologically mimics an acute TIN. In clinical trials, this side effect occurs in 1.7% of treated patients, with a higher incidence when these drugs are used in combination.[23] The toxicity can also be found in other organs: the skin; the gastrointestinal system; and the endocrine system (pituitary gland, pancreas, etc.). The time interval from onset of toxicity to the onset of kidney damage can vary greatly, from the first dose to several months. It is virtually never associated with systemic hypersensitivity (rash, eosinophilia, etc).[24]

Acute TIN induced by these new drugs presents an additional challenge; the decision to withdraw the therapy is complex, particularly when an oncological response has been achieved. The use of concomitant corticosteroids is limited, as the steroids cancel out their mechanism of action.

Conclusions

Acute TIN should be considered in the differential diagnosis of all cases of acute kidney damage. Withdrawal of the drug potentially responsible is the essential point of treatment.

It should not be forgotten that the beneficial effect of steroids is optimal only when they are started within the first 2 weeks of the injury, any benefit being doubtful if started beyond 4 weeks. The effect of the steroids is achieved in the first days/weeks after starting therapy, and they should be discontinued as soon as renal function recovers, or after com-

pleting 3 weeks of treatment. Extending the treatment beyond that point, or for more than 5 weeks, has not been shown to improve renal prognosis, but simply to increase the associated side effects.

Dealing with a disorder like drug-induced acute TIN, which is so prevalent and has such severe repercussions from a renal point of view, we urgently need to seek biomarkers to help with early diagnosis, and to conduct clinical trials to help optimise the current treatment regimens. In the meantime, we must rely on the expertise of the nephrologists as our only weapon against the challenges this disorder will continue to pose.

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