When to use steroid treatment for those patients with drug-induced acute interstitial nephritis?

E. González[1], M. Praga[1]. Interstitial Nephritis Group of Madrid[2]

[1] Nephrology Department. 12 de Octubre Hospital. Madrid, Spain

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Drug-Induced Acute Interstitial Nephritis (DIAIN) represents a high percentage of acute renal failure in clinical practice.[1,2] Some studies indicate that around 15% of biopsies with acute renal failure have DIAIN as the responsible injury for renal failure.[3] To this, it must be added that many DIAIN cases are not biopsied and the diagnosis is based on clinical data and recent history of a new drug administration which as described below, sometimes is not so easy to identify. Although numerous drugs have been implicated, antibiotics and Non-steroidal Anti-inflammatory Drugs (NSAID) continue to be the drugs most involved.[4] The etio-pathogenesis of the histological injury is well known and is produced by a mechanism of hypersensitivity to the drug. Even though this concept is well established, there is still some controversy as to the role of steroids in DIAIN treatment. While some studies have shown a positive steroid response in terms of a quicker and more complete renal function recovery in patients treated,[5-7] other studies have not confirmed this steroid's favorable outcome.[8-11] The lack of factual information regarding therapeutic management of DIAIN is the result of limited data published to date: clinical cases and series which included very few patients.

The recent publication of a multicentre retrospective study, in which 10 Nephrology Departments in Madrid[12] collaborated, has allowed not only the collection of the largest series published to date of biopsy proven DIAIN cases (61 patients), but also the publication of interesting findings on the influence of steroid treatment in this entity. As reflected in previous editorial comments,[13] this collaborative study in Madrid has made an important contribution to the treatment of DIAIN.

Correspondence: Ester González Monte
Servicio de Nefrología.
Hospital 12 de Octubre. Madrid.
montego_12@yahoo.es

NATURAL HISTORY OF DIAIN

The mechanism by which the kidney injury occurs is due to hypersensitivity to the drug which elicits a cellular immune response. This reaction causes an interstitial infiltration of T lymphocytes, monocytes, plasma cells, and eosinophils, and at the systemic level, the appearance of cutaneous rash, arthralgia fever, eosinophilia, and occasionally, an increase in hepatic enzymes. In addition to this, in the sediment eosinophiluria can appear as a result of the tubulo-interstitial inflammatory injury. In most of the cases, this kidney injury leads to acute renal failure, and although it is generally non-oliguric, it can be serious and require replacement therapy with haemodialysis.

Obviously, the first therapeutic step for a patient diagnosed with DIAIN should be identification of the causative agent and its immediate withdrawal. However, even though this first step seems evident, it is not that simple in clinical practice as in a great number of cases, particularly in elderly patients receiving multiple medications, identifying the drug responsible for DIAIN can be difficult and even impossible. It should be taken into account that, even though antibiotics and NSAIDs represent the majority of responsible drugs, any medication can cause DIAIN. Often the identification of the drug is based on an inquiry into the drug(s) more

[2] **Members of the Interstitial Nephritis Group of Madrid:**
E. González[1], E. Gutiérrez Solís[1], C. Galeano[2], C. Hevia[3], P. de Sequera[4], C. Bernis[5], E.G. Parra[6], R. Delgado[7], M. Sanz[8], M. Ortiz[9], M. Goicoechea[10], C. Quereda[11], T. Olea[3], H. Bouarich[4], Y. Hernández[5], B. Segovia[1], E. Hernández[1], M. Praga[1].
[1] 12 de Octubre Hospital; [2] Ramón y Cajal Hospital; [3] La Paz Hospital; [4] Príncipe de Asturias Hospital; [5] La Princesa Hospital; [6] Aire Hospital; [7] Ruber Clinic; [8] Getafe Hospital; [9] Severo Ochoa Hospital; [10] Gregorio Marañón Hospital.

chronologically related to the appearance of DIAIN. We are often confronted with unreliable patients, particularly the elderly receiving multiple medicines, and the lack of clinical studies related to the interval between the start of treatment with a drug and the development of DIAIN. A good example of the difficulty encountered in the identification of the causal medicine is found in many cases of DIAIN secondary to NSAID intake. The consumption of these drugs by the general public is very widespread and these are often taken or prescribed in an intermittent way. They are found in many different presentations and a lot of patients are reluctant to admit their consumption.

Once the causal agent has been identified and withdrawn, if possible, there are unresolved issues for which we have very little information: What occurs to the characteristic interstitial infiltrate of DIAIN? How long does it take to be resolved? Does the parenchyma return to its original integrity or is it transformed into fibrotic scars? All of these questions are of considerable clinical importance, but there are no studies to clarify them.

EARLY STEROID TREATMENT CHANGES THE NATURAL COURSE OF DIAIN

The role of steroid treatment for DIAIN has caused controversy. Diverse clinical cases and series of patients (with a small number of patients) suggested that steroids are favourable, and renal function recovery is accelerated.[5-7] Based on published reports, most authors have recommended steroid use with DIAIN only in patients with no evidence of renal function recovery after a 7-15 days observation period since suspension of the involved drug. However, there are many studies showing that a significant proportion of patients who suffer from a DIAIN do not completely recover their baseline renal function, remaining with different degrees of chronic renal failure after the acute injury.[8-10]

On the other hand, a recent retrospective study including a significant number of cases incited serious doubts over the validity of steroids in DIAIN.[10] Out of the 60 patients with acute interstitial nephritis included in the study, 90% had DIAIN and non-steroidal anti-inflammatory drugs was the most frequent aetiology in 44% of cases. In this study, there were no differences in final creatinine levels among those patients who received steroids and those managed conservatively. However, close inspection reveals that steroid treatment began late, and although there are not significant differences between the group receiving steroids and those managed conservatively, various patients in both groups had good renal function improvement initially, but later they develop a degree of renal failure. This is an aspect which, in our opinion, has received very little attention in the literature: the majority of patients diagnosed with DIAIN show a noticeable improvement in renal function after suspending the causal drug. However, in many cases such an improvement tends to be interrupted before the patient can recover his/her baseline renal function *ad integrum*. Therefore, a considerable percentage of acute renal failure due to DIAIN develops into chronic renal failure with various degrees of severity. In the experience of the authors, it is not exceptional to find clear undiagnosed antecedents of DIAIN (such as acute deterioration of renal function accompanied by fever and eosinophilia after receiving antibiotics during hospitalization) in patients referred for chronic renal failure assessment.

Taking into account all of these unresolved issues, there is no doubt that the recently published collaborative study of the Madrid group[12] has meant a new undertaking with important implications for clinical practice in DIAIN treatment.[13] The study, which includes the most ample series published to date, is a retrospective analysis of 61 patients diagnosed with DIAIN through biopsy in 10 hospitals from the Community of Madrid during the period of 1975-2006. As in most of the series, antibiotics and NSAID were the main drugs involved, affecting 93% of patients. Although the study was retrospective, all patients had a baseline creatinine (1.1 ± 0.39mg/dl) measurement obtained 7.5 ± 4.6 months before the DIAIN diagnosis, and all patients had an extended follow-up, in such a way that the final renal function in each patient could be verified.

Analysing the small number of patients not treated with steroids (9 out of 61), a noteworthy difference stood out: at the end of the follow-up, they had significantly higher creatinine (3.71 ± 2.91 vs. 2.1 ± 2.1) and an incidence of chronic dialysis (44.4 vs. 3.8%) higher than the patients who received steroids. Additionally, the long-term follow-up of all patients and the availability of baseline creatinine allowed for a separation of the patients: those with complete baseline renal function recovery and those with chronic renal failure of variable severity. The most conclusive difference between both groups was the time interval between the withdrawal of the drug and the start of steroid treatment: 13 ± 10 days in the first group and 34 ± 17 days in the second. Furthermore, a significant correlation was found between the delay in the initiation of the steroids and final creatinine achieved. A time interval greater than seven days between the suspension of the drug and the start of steroid treatment was the only clinical factor of significant value in the multivariate analysis which increased the risk of incomplete renal function recovery.

The development of histological injuries also shows the convenience of early steroid treatment with DIAIN.[12] All cases treated with steroids were administered after doing a renal biopsy, both in those which recovered renal function *ad integrum* and those that partially recovered. Therefore, in

KEY CONCEPTS

1. Drug Associated Acute Interstitial Nephritis (DIAIN) represents a high percentage of acute renal failure in clinical practice.
2. Antibiotics and Non-steroidal Anti-inflammatory Drugs (NSAID) are the most commonly implicated drugs in the development of DIAIN, although any medication can be responsible for this condition.
3. The kidney injury mechanism is due to hypersensitivity to the drug which stimulates a cell-mediated immune response. This reaction causes an interstitial infiltration of T lymphocytes, monocytes, plasma cells, and eosinophils.
4. When the responsible drug is suspended, a significant proportion of patients diagnosed with DIAIN do not completely recover their baseline renal function, remaining with different degrees of chronic renal failure after the acute injury.
5. The histological injury is characterized by acute cellular interstitial infiltrates that can be substituted rapidly (in a few weeks) by expanding tubulo-interstitial fibrosis.
6. In DIAIN, early establishment of steroid treatment ensures complete recovery of renal function while keeping the characteristic interstitial infiltrate from transforming progressively and irreversibly into fibrotic scars, which constitute the histological basis of chronic renal failure.

this study, an influence of previous steroid treatment could be ruled out in the histological findings. It was observed that in the cases with a long interval between the withdrawal of the causal medication and the biopsy, ample zones of interstitial fibrosis appeared; in contrast with the cases biopsied shortly after the withdrawal, in which cellular infiltrates were more predominant. In three cases a second renal biopsy was performed 33 ± 7 days after the first, due to unsuccessful development of renal function. One of these cases had only received conservative treatment, and the other two had received steroids very late after the suspension of the drug. In the three cases, a clear tubulo-interstitial fibrosis could be observed, which had mostly replaced the cellular infiltrates from the first biopsy. Collectively, all of this data point to the development of rapid interstitial fibrosis (in a few weeks) following characteristic interstitial infiltrates of DIAIN. Logically, the suspension of the drug is obligatory and results in a favourable effect, avoiding the continued formation of these cellular infiltrates. However, the steroid treatment allows a quick and efficient management of progressive and irreversible interstitial fibrosis development, which constitutes the histological base of chronic renal failure, as exhibited by the majority of non-treated cases or those treated late with steroids.

Some studies have suggested that DIAIN due to NSAID could have a worse development and prognosis, and a poor response to steroid treatment. We analysed the development of patients with DIAIN due to NSAID separately. Results were similar to the rest of the patients, showing that the delay in the initiation of the steroids was once again the most determining clinical factor in the incomplete recovery of baseline renal function. In patients with DIAIN due to NSAID, who recovered renal function *ad integrum,* after receiving steroid treatment, the treatment was started 18.4 ± 16 days after suspending the NSAID, a significantly shorter time interval as compared with the group that did not completely regain their renal function (31.4 ± 15 days).

Clearly the best and most robust way to define steroid treatment indications in DIAIN would be a randomized prospective study. However, as some authors have indicated, such study would not be viable due to its inherent difficulties.[14] An important percentage of patients, in which DIAIN is suspected, are not Suitable for a biopsy due to underlying pathology or because they receive anti-platelet drugs or are anticoagulated, in which case the diagnosis is suspected by the clinical findings and by identifying the harmful drug. These cases of probable DIAIN, with a diagnosis based on clinical data, in the absence of a renal biopsy, constitute a substantial group in hospitals and often there is very little clinical information.[15] Probably, the recommendations established in this document for DIAIN demonstrated by biopsy (withdrawal of the causing medicine and early steroid treatment) could also be applicable to this group of patients, but more clinical information is needed, even if it is with retrospectively analysed series.

Another aspect to point out in the collaborative study was the rare incidence of side effects due to steroids.[12] This was probably due to the short duration of the treatment. Although the multicentre character of the study led to treatment criteria

which differed from one centre to another, the mostly used schedule was pulsed steroid therapy (250-500mg of methyl prednisolone for 3-4 consecutive days) followed by oral prednisone (initial dosage 1mg/kg/day) that was progressively decreased and discontinued after 8-12 weeks.

To conclude, as previously reported, this study confirms DIAIN natural tendency to initial renal function improvement after the suspension of the drug involved. However, this initial improvement is frequently followed by progressive chronic renal failure (slow progression with terminal renal failure, greater risk of cardiovascular complications, etc.) The data supports the use of steroids in the treatment of all DIAIN and also its early administration. The analysis carried out in this study (regarding not only the timing of steroid therapy initiation but also whether or not the patient received steroids) gives a new insight into the long-term prognosis of acute renal failure due to DIAIN, since it shows that late commencement of steroid treatment leads to incomplete recovery of renal function in many cases, and that the earlier the treatment, is more likely to lead to complete recovery.

REFERENCES

1. Rossert J. Drug-induced acute interstitial nephritis. Kidney Int 2001;60:804-17.
2. Cameron JS. Allergic interstitial nephritis: clinical features and pathogenesis. Q J Med 1998;66:97-115.
3. Haas M, Spargo BH, Wit EJ, Meehan SM. Etiologies and outcome of acute renal insufficiency in older adults: a renal biopsy study of 259 cases. Am J Kidney Dis 2000;35:433-47.
4. Baker RJ, Pusey CD. The changing profile of acute tubulointerstitial nephritis. Nephrol Dial Transplant 2004;19:8-11.
5. Galpin JE, Shinaberger JH, Stanley TM, et al. Acute interstitial nephritis due to methicillin. Am J Med 1978;65:756-65.
6. Buysen JGM, Houtholf HJ, Krediet RT, Arisz L. Acute interstitial nephritis: a clinical and morphological study in 27 patients. Nephrol Dial Transplant 1990;5:94-9.
7. Pusey CD, Saltissi D, Bloodworth L, et al. Drug associated acute interstitial nephritis: clinical and pathological features and the response to high dose seteroid therapy. Q J Med 1983;52:194-211.
8. Bhaumik SK, Kher V, Arora P, et al. Evaluation of clinical and histological prognostic markers in drug-induced acute interstitial nephritis Ren Fail 1996;18:97-104.
9. Koselj M, Kveder R, Bren AF, Rott T. Acute renal failure in patients with drug-induced acute interstitial nephritis. Ren Fail 1993;15:69-72.
10. Clarkson MR, Giblin l, O'Connell FP, et al. Acute interstitial nephritis clinical features and response to corticosteroid therapy. Nephrol Dial Transplant 2004;19:2778-83.
11. Porile JI, Bakris GL, Garella S. Acute interstitial nephritis with glomerulopathy due to nonsteroidal anti-inflammatory agents: a review of its clinical spectrum and effects of steroid therapy. J Clin Pharmacol 1990;30:468-75.
12. González E, Gutiérrez E, Galeano C, et al. Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. Kidney Int 2008;73:940-6.
13. Appel GB. The treatment of acute interstitial nephritis. More data at last. Kidney Int 2008;73:905-7.
14. Coca SG, Perazella MA. Early steroid treatment for drug-induced acute interstitial nephritis. Nat Clin Pract Nephrol 2008;4:298-9.
15. Espejo B, Herrero JC, Torres A, et al. Nefritis intersticial inmunoalérgica vs ateroembolismo de colesterol. Características diferenciales. Nefrología 2003;23:125-30.