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Abstract:

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

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Corticosteroid treatment in drug-induced acute interstitial nephritis (DI-AIN) is a topic of growing clinical importance, given the increasing frequency of this cause of acute kidney disease\(^1\). Donati and Krishnan, in the debate in this Kidney 360 issue, defend the use of corticosteroids arguing, on the one hand, the pathophysiological rationale that justify its use in DI-AIN. Glucocorticoids block several proinflammatory pathways crucial in the recruitment of macrophages, T lymphocytes, eosinophils and plasma cells that compose the characteristic diffuse interstitial infiltrates found in kidney biopsies of DI-AIN patients. By suppressing or mitigating this interstitial inflammation, corticosteroids can prevent the development of interstitial fibrosis that follows resolution of such infiltrates. These glucocorticoid actions are nicely illustrated in a Figure. However, it should be emphasized that basic and experimental investigation on the pathogenic mechanisms of DI-AIN (research that could pave the way for the finding of new therapeutic alternatives) is scarce, especially when considering the clinical importance and the socioeconomic repercussions of this disease. The reasons why only a minority of subjects develop this type-B, cell-mediated immunological response, as well as the underlying mechanisms involved in the recruitment of the diverse cell populations that infiltrate kidney interstitium are largely unknown. Another important unmet need in this field is the availability of reliable, validated biomarkers that could help in the differential diagnosis of the disease, since the diagnosis is currently established by the finding in a kidney biopsy of the typical interstitial infiltrates\(^2\). Considering that DI-AIN is being observed with increasing frequency in elderly subjects\(^3\) whose frailty makes it difficult or contraindicates the performance of a kidney biopsy, the search for noninvasive diagnostic biomarkers is of crucial importance. In this regard, recent investigations suggest that the levels of urine tumor necrosis factor-\(\alpha\) and interleukin-9 can discriminate AIN from acute tubular injury and other kidney lesions\(^4\).

Donati and Krishnan review the studies that support the efficacy of glucocorticoids in the recovery of kidney function in DI-AIN. All of them are retrospective, with all the limitations inherent to this type of studies. However, it is important to remark that all of them concur in a common observation: the delay in the administration of corticosteroids is absolutely crucial to determine their favorable effect or condition their failure. The time interval after the diagnosis of DI-AIN in which the onset of glucocorticoids is effective varies from one study to another, but as Donati and Krishnan rightly point out,
such interval should not exceed 7-10 days. As they also point out, a delayed introduction of glucocorticoids or the presence of significant interstitial fibrosis at the time of treatment onset (that theoretically could have been prevented by an earlier initiation of corticosteroids) could be the main reasons for glucocorticoid failure in those studies that have shown negative results of corticosteroid treatment in DI-AIN. This concordance in the finding that glucocorticoids are effective in DI-AIN but only when administered in the first days after diagnosis, further reinforces the need for a greater awareness of the disease among physicians, more precise diagnostic criteria and validated noninvasive biomarkers, particularly in patients in whom a kidney biopsy cannot be performed. The increasing implication of drugs such as PPIs or NSAIDs in the etiology of DI-AIN, with a difficult to determine temporal relationship between the start of treatment and the appearance of kidney dysfunction, the increasing prevalence of oligosymptomatic forms of the disease, or the significant proportion of polymedicated elderly patients in whom it is difficult to identify the causative drug, further complicate the diagnosis of DI-AIN and the rapid onset of corticosteroid treatment.

On the con side of the debate, Gallagher and Kotwal rightly emphasize the limitations and weaknesses of the studies that showed positive results for the use of corticosteroids in DI-AIN. Particularly important limitations of these studies are the absence of prospective patient recruitment, as well as the lack of non-treated control groups and patients randomization. His group published a systematic review of the literature, which included 430 patients, 300 of whom had been treated with corticosteroids. The authors were unable to perform a meta-analysis of these studies, due to their heterogeneity and low quality of evidence. Since this publication, other studies have added 295 patients, 274 of them receiving corticosteroids. One of them is the only prospective randomized study published to date, but it compared two forms of corticosteroid treatment, without an untreated control group.

Gallagher and Kotwal also point out the lack of data regarding the side effects of corticosteroids in the treatment of DI-AIN, and comment the example of the TESTING study which, while showing positive influence of corticosteroids in IgA nephropathy outcomes, also demonstrated a significantly higher number of serious adverse effects among treated patients. However, in a subsequent phase of the TESTING study, recently presented at ASN Kidney Week 2021, a significantly lower dose of
corticosteroids was used, with the same positive effect on the disease and fewer side effects. The untoward effects of corticosteroids (particularly common when used for a long time in adults and elderly patients) are very well known for decades and in our opinion their occurrence should be anticipated in the design of any prospective therapeutic trial. In this regard, the identification of the shortest and lowest doses of corticosteroids able to induce a beneficial effect in DI-AIN should be one the main objectives to explore in the design of future controlled studies in this disease. Another interesting issue to be investigated in such desirable randomized controlled trials (RCT) would be the use of intravenous pulses of methylprednisolone to accelerate kidney function recovery and reduce the duration of subsequent oral corticosteroids, since such scheme is currently applied in many centers without the support of scientific evidence.

A large retrospective study carried out in 182 patients, all of them treated with corticosteroids, showed that high-dose corticosteroid treatment for more than 3 weeks or prolonged treatment for more than 8 weeks were not associated with greater kidney function recovery. Notably, most of the kidney function recovery in this study occurred nearly exclusively during the first month of treatment and this early recovery was associated with kidney function at 6 months, suggesting that more intensive and shorter corticosteroid schedules could be as effective and safer as compared to longer schemes. It has been suggested that longer courses of corticosteroids (up to 6 months) could be associated with better outcomes in AIN associated with immune check-point inhibitors, but again there is a lack of prospective studies or large and solid observational studies regarding corticosteroid treatment in this increasingly important type of DI-AIN.

Despite the low quality evidence of published studies, the use of corticosteroids in DI-AIN seems to be quite widespread among nephrologists. Gallagher and Kotwal raise a very attractive idea, the performance of a large multicenter survey to know the therapeutic attitude of different centers towards the treatment of DI-AIN and the use of corticosteroids in that setting. Such a survey could provide very valuable data for the design of prospective trials. On the other hand, the open-label RCT planned by Mose et al will compare corticosteroid treatment (initiated at diagnosis) plus supportive care versus supportive care alone in DI-AIN; kidney function (eGFR) at 3 months after inclusion will be the primary endpoint of this trial. Nevertheless, another type of design, such as the one proposed in Figure 1, could better match the current therapeutic attitudes of many centers. Thus, the exclusion of patients with a degree of
tubulointerstitial fibrosis > 75% in the kidney biopsy seems reasonable, since no response to corticosteroids has been observed in this type of cases. Ideally, the definitive design of this trial should be preceded by the analysis of the multicenter survey discussed above. For example, some centers use intravenous pulses of methylprednisolone before the start of oral prednisone and it would be interesting to know the extent of this therapeutic approach.

In summary, although most of the available data support the efficacy of early administration of corticosteroids in the recovery of renal function in DI-AIN, the quality of the evidence is low. We think that this debate, with the solid and brilliantly exposed PRO and CON arguments about the use of corticosteroids in DI-AIN, updates the current situation of the topic and addresses the most important needs: the performance of well-designed RCT or large observational studies that provide high-quality evidence about the results of this treatment, the definition of the most effective and safe corticosteroid regimen, and the search for non-invasive biomarkers that can replace or complement kidney biopsy in the diagnosis of this disease and help in the implementation of early corticosteroid treatment.

Disclosures
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Author Contributions
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**Legend for Figure 1.**

Simplified proposal for a randomized controlled trial comparing conservative treatment and a short course of corticosteroids in patients with biopsy-proven DI-AIN. A short run-in period to exclude patients with an important kidney function improvement after the discontinuation of the culprit drug, and a rescue treatment with corticosteroids for those patients allocated to the conservative treatment group who do not show kidney function improvement after 3 weeks are included in this scheme.
Identification and withdrawal of culprit drug

Histologic Diagnosis (kidney biopsy)

Conservative management

If serum creatinine does not decrease at least 50% from baseline after 7 days

Corticosteroid therapy (total duration not exceeding 6 weeks)
- Oral prednisone, 1 mg/kg/day for 1 week after IV pulses (not exceeding 60 mg/day)
- Prednisone tapered down for 4 weeks

Outcomes
- Kidney function at 3 weeks
- Kidney function at 3 months
- Kidney function at 12 months

Randomization

Stratification by:
- Kidney function
- Degree of tubulointerstitial fibrosis

Exclusion criteria:
- Tubulointerstitial fibrosis >75% in kidney biopsy

Week 0 1 2 3 4 5 6
Month 3 6 9 12