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Key Points:

Abstract:

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

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Drug-induced acute interstitial nephritis (DI-AIN) has been a neglected area in kidney disease; neither frequent or (usually) severe enough to drive the research that would take the field forward, yet common enough to be part of many differential diagnoses in acute kidney injury. In addition, the inclusion of a number of new drug classes to the list of causative agents, including proton pump inhibitors and immune check point inhibitors, in the last two decades would suggest it is likely to grow as a clinical problem into the future. Whilst the use of corticosteroids for DI-AIN is common, understanding their true effect is challenging as the condition often improves with removal of the causative agent and supportive treatment, and the current evidence base serves us poorly in this regard.

In arguing that corticosteroids do not have proven utility in treating DI-AIN, one must first have an understanding of the term “proven utility”. The common definition of “utility” is the state or quality of being useful but, when prefixed with the term “proven” in a medical context, it implies that the treatment must be more than useful, it must be effective in treating the condition. This then brings in the need for the balance of benefits and risks of treatment to be in favour of benefits in the intended treatment population.

The evidence:

Unfortunately, the existing literature to guide corticosteroid use in DI-AIN is conspicuous for its absence of prospective patient recruitment, control groups and randomized evidence. A systematic review of the literature from our group, including studies to November of 2017, found no randomized trials and 8 retrospective studies that compared corticosteroid treatment with non-corticosteroid treatment for drug induced acute interstitial nephritis. We weren’t able to meta-analyse these studies because of their considerable heterogeneity and low quality of evidence, but it is noteworthy that they included a total of just 430 patients, 300 treated with corticosteroids and 130 with other, poorly-defined treatments (Table 1). The literature since the systematic review is notable for one randomized trial (which compared oral with intravenous corticosteroid therapy), two retrospective analyses which added a further 295 patients to the literature, with 274 patients receiving corticosteroids.

The epidemiological features lacking in the literature; prospective patient recruitment, control groups and randomization, are critical in the setting of DI-AIN. The prospective definition of the study population is a fundamental element of clinical research, as it ensures that features of the patient and the treatment they receive are fixed at a point in time, and that inclusion in the study cohort is not influenced by events following that time point. The selection of patients on the basis of characteristics observed later in their disease course, such as the results of a late kidney biopsy, can result in a selected study population that is quite different to that which a clinician faces in their daily practice. This means that the findings, on the benefit or otherwise of corticosteroids in DI-AIN, are difficult or impossible to apply to real-time clinical decision making.

Control groups are a key element of clinical research, and their absence in the DI-AIN literature greatly limits the clinical utility of the findings. The patients reported in this literature have, by definition, abnormal renal function which is known to improve with time, or “regress to the mean” in statistical terms. Renal function is the most frequently reported outcome, and a continuous measure such as serum creatinine which is undergoing large changes may deliver numerically large and clinically relevant differences, but the existing literature gives us no ability to distinguish between artefactual and corticosteroid treatment related effects. The only way to understand the size of the effect of regression to the mean is by using comparable control groups who do not receive the treatment being studied.
The third epidemiological gap in the literature, the absence of randomized comparisons, is perhaps more readily understood. Randomization is the means by which we can derive comparative groups that are balanced in both measured and un-measured characteristics, giving reassurance that any difference of effect between the study groups is due to the studied treatment rather than differences in patients or their selection and follow up. The total absence of this feature from the literature on corticosteroids in treating DI-AIN is glaring, but such studies do present some challenges in this field.

It is also important to appreciate that these design flaws impact upon the veracity of all the reported outcomes, including any harms from the studied treatment, which is an important element in ascertaining the proven utility of any treatment. Whilst the total exposure to corticosteroids when used to treat DI-AIN is low compared to that used in other renal settings (e.g.: transplantation and other immune suppression regimens), the quality of evidence for the harms is more limited than that for the putative benefits (see Table 1). As the results of the Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study illustrated, the harms from long-used and widely accepted corticosteroid dosages in kidney disease may only come to light when robustly studied.

Is randomized evidence feasible?

A feature of randomized studies is their standardization of the other elements of care outside of the treatment of interest. This would pose a challenge in DI-AIN, as there is likely to be wide variation in the willingness to perform kidney biopsy, and the timing thereof, to confirm the diagnosis, as seen in the UpToDate recommendations. Similarly, there is likely to be variation in physician equipoise as to the timing, dosage and duration of corticosteroids in any treatment arm(s), which would pose a challenge for study protocol design.

The randomized trial from Saudi Arabia comparing oral with intravenous corticosteroids showed that such studies are feasible in this group of patients. That said, the study population in this study had very severe kidney dysfunction at randomization (mean estimated GFR of 11 ml/min/1.73m²), so constitute a group in whom many clinicians would be keen to give ‘active’ treatment to all participants. It is pleasing to see the recent publication of a protocol for a Danish randomized trial comparing prednisolone with placebo for AIN which, although open-label, would represent an important advance in the field.

Clearly, given the limitations outlined above, better designed and reported observational studies would be a meaningful step forward, if only in defining the extent of regression to the mean seen in patients not treated with corticosteroids. This alone would allow some, albeit un-controlled, comparison to those treated with corticosteroids, as well as impose a structure that would permit clinicians to better relate their patients to studied populations.

In addition, systematically surveying the views of nephrologists and their practice would also be valuable. It would allow us to understand the strength of opinion, the willingness to entertain doubt about the diagnosis and treatment, and to explore where physician equipoise sits regarding corticosteroid efficacy in DI-AIN. Such an approach could also be a means of building a team of investigators that might drive the case, and momentum, for a large-scale randomized trial comparing corticosteroids and placebo.

Many nephrologists may take the view that they already “know” that corticosteroids are effective in DI-AIN, and may point to articles with declarative titles such as “Early steroid treatment improves recovery of renal function in patients with DI-AIN” to support such a view. In such a situation, those unconvinced by the current literature may run the risk of being labelled epidemiological
fundamentalists if insisting on the need for randomized evidence. However, we would argue that not only do we now know that corticosteroids work in this setting, we have no inkling of the size of any effect and little idea of potential harms. In addition, it always worth remembering that the collective view of the nephrologists has been proven wrong before, and will be proven wrong again if we don’t embrace the best science to guide our treatment10.

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Author Contributions:

Martin Gallagher: Conceptualization; Writing – original. draft Sradha Kotwal: Validation; Writing - review and editing.

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**Table 1:** Assessment of the quality of evidence for corticosteroid use in drug-induced acute interstitial nephritis using the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) approach (from reference 1)

| Quality assessment | Overall quality of evidence |
|-------------------|-----------------------------|
| Number of participants (studies) | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias |
| Change in serum creatinine or eGFR after intervention | High | Serious: variable time points selected for comparison; some studies did not provide a time point | Direct | No important imprecision | None | Very low |
| Adverse drug reaction | High | Serious: incompletely recorded, inadequate length of follow-up | Direct | No important imprecision | None | Very low |
| Need for renal replacement therapy | High | Serious: variable time points selected for comparison, with no time point provided in two studies | Direct | No important imprecision | None | Very low |
| Mortality | High | Serious: Exclusion of data due to exposure not being linked to outcome | Direct | No important imprecision | None | Very low |

Based on the Grading of Recommendation Assessment, Development and Evaluation (GRADE) system (High-quality level = We are very confident that the true effect lies close to that of the estimate of the effect; Moderate-quality level = We are moderately confident in the effect estimate; The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low-quality level = Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; Very low-quality level = We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect) retrospective cohort studies.

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