Corticosteroids Should Be Used To Treat Slowly Progressive IgA Nephropathy: PRO

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Introduction
Recent clinical trial results on the role of corticosteroids for prevention of progression of IgA nephropathy (IgAN) are challenging to reconcile, and the use of corticosteroids in the management of IgAN remains controversial. However, there is a clear mechanistic rationale to support the use of these medications, and compelling data supporting efficacy. We argue that corticosteroids are effective in slowly progressive IgAN and propose ways to optimize, personalize, and improve the safety of this approach.

Mechanistic Rationale
There is a strong biologic underpinning for corticosteroid use in addressing the underlying pathophysiology of IgAN. Glucocorticoids exert potent immunosuppressive activity via genomic and nongenomic effects on immune cells and tissue. A central mechanism includes interruption of the activity of key nuclear transcription factors (ex. NFκB), affecting genes encoding the mediators involved in the regulation of inflammation (1). Modulation of expression of cytokines, chemokines, and adhesion molecule synthesis has important downstream effects on the activity, proliferation, and survival of contributors to glomerular inflammation including monocytes, macrophages, and T cells.

Evidence derived both in vitro and in vivo support the potential for corticosteroids to interfere with several core pathophysiologic processes implicated in IgAN pathogenesis. For example, serum levels of total and galactose-deficient IgA1 are reduced after treatment of patients with IgAN with glucocorticoids, and in patients with IgAN initiating glucocorticoid-containing treatment for transplant (2,3). One potential explanation for this reduction in galactose-deficient IgA1 is the effect of glucocorticoids on the expression of cytokines such as IL6, which affect Ig production by IgA-secreting plasma cells, or may affect the activity of glycosyltransferases responsible for IgA1 glycosylation (4). On the basis of in vitro models of GN, where mesangial and tubular cells are exposed to protein and immune complexes, corticosteroids are hypothesized to affect glomerular and interstitial inflammation induced by infiltrating lymphocytes and resident kidney cells (5,6). Studies of kidney biopsy tissue from patients with IgAN support that the transcriptional changes associated with endocapillary proliferation can be reversed by methylprednisolone (7). A significant reduction in mesangial matrix expansion has also been demonstrated in patients treated with corticosteroids (8).

Clinical Evidence
Clinical trials support experimental data suggesting a role for corticosteroids in IgAN. An early trial by Pozzi et al. (9) suggested improved kidney survival in 86 patients randomized to receive to receive a 6-month course of corticosteroids or conservative therapy. In keeping with the standard of care during execution of the study, only 15% of patients were treated with blockade of the renin-angiotensin system and BP control was suboptimal. A subsequent trial by Manno et al. (10) confirmed the benefit of corticosteroids added to a new renin-angiotensin system in a randomized trial of 100 adults. A large meta-analysis including data from 488 subjects from randomized trials found that corticosteroids reduced the risk for a composite endpoint of kidney failure or halving of kidney function by 68%, (relative risk, 0.32, 95% confidence interval, 0.15 to 0.67; P=0.002) (11). These efforts set the stage for the design of two larger, more recent randomized trials.

The Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive-IgAN trial randomized 162 patients (of 337 enrolled) to supportive therapy versus one of two corticosteroid-based immunotherapy protocols after a 6-month run-in period (12).

Patients eligible for randomization had persistent proteinuria of >0.75 g/d. The primary outcome was positive; after 3 years, significantly more patients achieved complete remission of proteinuria (17% versus 5%, P=0.01). However, there was no difference in the proportion of patients with a loss of GFR of ≥15 ml/min per 1.73 m² kidney function at 3 years (28% versus 26%, P=0.75).

There are several challenges to understanding the discrepant outcomes of improved proteinuria but unchanged renal function, which can be clarified in
part by the following explanations. First, patients at high risk of progression with proteinuria >3.5 g/d at randomization were excluded. Second, there was minimal annual renal function decline overall (−1.6 ml/min per 1.73 m²), therefore, the follow-up period may have precluded demonstration of efficacy. Finally, the lack of histologic data makes it difficult to ascertain the proportion of patients with potentially steroid-responsive lesions (ex. proliferation) versus irreversible fibrosis. One could hypothesize that a patient with extensive fibrosis may have residual low-grade proteinuria, but is past the point of potential benefit from corticosteroids. Finally, although ambitious in size in terms of enrollment, the actual number of randomized patients in this study is relatively small.

A recent extended passive 10-year follow-up of this cohort showed nearly half reached the composite endpoint (40% eGFR loss, ESKD, or death), with ESKD in 25% of trial participants. Patients who received immunosuppression did not, as a whole, demonstrate more favorable disease trajectory. However, a compelling subgroup analysis of patients with GFR >60 ml/min per 1.73 m² showed those who had received immunosuppression demonstrated improved renal survival (13). Thus, a reduction in proteinuria in the primary study, and improved outcome in patients with better renal function at randomization, may provide important clues about patients most likely to respond to corticosteroid therapy.

The Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study randomized patients at high risk of disease progression (proteinuria >1 g/d and eGFR >20 ml/min per 1.73 m²) to receive methylprednisolone or placebo (14).

Unfortunately, enrollment was halted after randomization of 262 of a planned 750 patients, due to an 11% greater risk of serious adverse events in the steroid group, including two deaths from pneumonia. At the time of early analysis before transition to a modified protocol, the primary outcome (composite 40% reduction in eGFR, kidney failure, death due to ESKD) occurred significantly less frequently in the steroid group (hazard ratio, 0.37; 95% confidence interval, 0.17 to 0.85; P=0.02) strongly suggesting efficacy. Parallel favorable effects on proteinuria and eGFR were observed throughout the 25 months of follow-up. The patients in the TESTING trial had higher-grade proteinuria compared with the Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive-IgAN study, and the placebo group had a very rapid rate of renal function decline. Therefore, early analysis of the largest randomized controlled trial to date supports efficacy of corticosteroids in the patients with IgAN who are highest risk. This came at the important cost of infectious complications.

**Evolving Practice Patterns**

The evidence presented thus far strongly supports efficacy of corticosteroids in patients who are high risk; however, it must be acknowledged that this comes at a cost of significant side effects and potential toxicity. Long-term use of corticosteroids to maintain remission is also not practical given the associated toxicity. How can we apply this knowledge to clinical care and prescribe corticosteroids more safely?

A decision to use corticosteroids should be made together with the patient after a balanced discussion of the risks and benefits that recognizes both the limitations of the existing literature and our own biases regarding treatment controversies. Balanced discussion also should include estimates of the risk of progression to ESKD (15), and the attendant morbidity of RRT and transplantation. Dynamic assessment should be emphasized as recommendations and decisions may change over time.

Ideally, patients receiving corticosteroids are those at the highest risk of progression with the lowest risk of adverse events. None of the studies included patients with obesity or diabetes; the risks of corticosteroids may outweigh benefits in this population. We also lack sufficient information to determine whether there is a threshold of GFR below which risks outweigh benefits. The proportion of patients with eGFR below 30–40 ml/min per 1.73 m² may ultimately be too low in the final TESTING study analysis, and until these data are available, we must approach this population with caution. Finally, pathology data are important for understanding the characteristics of patients included in a study and their baseline risk of disease progression. For example, the degree of proliferative activity versus fibrosis could potentially influence the efficacy of corticosteroids. We do not yet have data to support whether pathology should influence treatment decisions; however, future analyses of existing and emerging clinical trial data could further help individualize recommendations and optimize risk-benefit balance.

Certainly, additional contraindications should be considered before starting any patient on corticosteroid therapy, including latent infections, psychiatric illness, and osteoporosis.

In addition to selecting the ideal target population, modifications to corticosteroid administration may also be of benefit. There will be an updated analysis of the TESTING study using a reduced-dose protocol, with prophylaxis against *Pneumocystis jiroveci*. Reduction in corticosteroid exposure may also be accomplished by concomitant use of a steroid-sparing agent.

Minimizing systemic corticosteroid absorption is another potential approach to mitigating toxicity. Targeted-release formulation (TRF) budesonide is engineered to have focused activity at the Peyers’s patches in the distal ileum, with minimal systemic absorption. The phase 2B targeted-release budesonide versus placebo in patients with IgAN study evaluated TRF-budesonide (Nefeon) versus placebo in 149 patients with progressive IgAN (eGFR >45 ml/min per 1.73 m², proteinuria >0.75 g/d) (16). The treatment groups had a significant reduction in proteinuria (24% versus 3%) with a favorable safety profile. The ongoing Efficacy and Safety of Nefeon in Patients With Primary IgA Nephropathy (NefIgArd) phase 3 trial is designed to confirm the efficacy of TRF-budesonide versus placebo, which may ultimately be an improvement over systemic exposure in terms of combined efficacy and safety.

**Summary and New Directions**

Corticosteroids are a powerful tool for treating progressive IgAN but they are not a panacea. Ongoing clinical trials evaluating alternative therapies are essential and hold promise
for more-targeted and less-toxic treatments. Our best available data from randomized studies suggest efficacy of corticosteroids, particularly in patients with proteinuria over 2 g/d, who do not have severely impaired kidney function. Reducing proteinuria and the rate of disease progression comes at a price of toxicity, and the decision to embark on corticosteroid therapy must be shared with patients. We must adjust our practice to use corticosteroids judiciously and in an optimally safe manner moving forward, while eagerly anticipating the development of novel treatments to add to our arsenal of therapies for IgAN.

Disclosures
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Author Contributions
A.M. Cunningham wrote the original draft; A.M. Cunningham and H.N. Reich conceptualized the study; and H.N. Reich provided supervision and reviewed and edited the manuscript.

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See related debate “Corticosteroids Should Be Used To Treat Slowly Progressive IgA Nephropathy: CON,” and commentary, “Corticosteroids Should Be Used To Treat Slowly Progressive IgA Nephropathy: COMMENTARY,” on pages 1081–1083 and 1084–1086, respectively.