Corticosteroids Should Be Used to Treat Slowly Progressive IgA Nephropathy: CON

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The foundation for managing slowly progressive IgA nephropathy (IgAN) is intensive, goal-directed, supportive care. This comprises rigorous BP control with a target of <125/75 mm Hg; use of maximal dose or maximal-tolerated dose of renin-angiotensin-aldosterone system inhibitors (RAASi); and, where necessary, lowering of total cholesterol <200 mg/dl and lifestyle modification that includes dietary sodium restriction (<100 mmol of sodium per day), regular exercise, smoking cessation, and weight management. Treatment may, in the future, be augmented with sodium-glucose cotransporter-2 and endothelin receptor inhibition.

The STOP-IgAN study clearly highlighted the value of a program of intensive supportive care in reducing proteinuria and slowing the rate of progressive decline in eGFR (1). One key observation from this study was that, after a 6 month run-in period of supportive care, a significant proportion of patients with IgAN remain at increased risk of progressive kidney failure, with 50% of the cohort reaching a composite end point (time to 40% in eGFR over a median follow-up of 7.4 years (2)).

The dilemma faced by nephrologists is how to treat the often young, asymptomatic patients with IgAN who remain at high risk of progression despite optimized supportive care. When considering the value of an additional therapy for such patients, it is essential that emphasis is placed on data from randomized, placebo-controlled clinical trials and that both the evidence for efficacy and for treatment-associated harm are equally evaluated.

Systemic corticosteroids have long been advocated as efficacious in slowing the rate of progression in such patients who are at high risk. On closer inspection of the clinical trial data reporting efficacy, there are, in my view, fundamental concerns over the relevance of these data to nephrology practice in 2021. Perhaps the most widely cited study supporting efficacy of corticosteroids in IgAN is that of Pozzi et al. (3), in which 86 patients were randomized to receive either a 6 month course of corticosteroids or placebo. Significantly, less than half of the randomized patients were taking a RAASi, and it is unclear whether those on RAASi had been titrated to the maximal-tolerated dose. In the later studies by Manno et al. (4) and Lv et al. (5) that reported efficacy of corticosteroids over RAASI monotherapy, both studies actually required the patients to discontinue any prior RAASI before inclusion in the study. In addition, the median maximum RAASI dose achieved in these studies was below the maximum recommended dose. A failure of prior RAASI optimization in each of these studies is likely to have resulted in a high number of patients (at least one in three on the basis of the STOP-IgAN study), who would have ended up being low risk for future progression by simply instituting and optimizing supportive therapy, being assigned to receive additional immunosuppression. This is not consistent with current international recommendations (6).

Only two studies have evaluated the efficacy of corticosteroids in patients receiving what would be regarded in 2021 as standard nephrology care. In the STOP-IgAN study, all patients underwent a 6 month run-in phase, during which supportive care was optimized. Of the 309 participants who completed the run-in phase, 162 were randomly assigned, on the basis of persistent proteinuria >0.75 g/d, to receive supportive care alone (n=80) or supportive care plus immunosuppressive therapy (n=82) for 3 years. Corticosteroids were administered either as monotherapy, in a regimen identical to that used in the Pozzi et al. (3) study (n=55), or in combination with cyclophosphamide induction and azathioprine maintenance therapy, in a regimen identical to that reported by Ballardie et al. (7) as being efficacious in IgAN (n=27). In this study, the use of corticosteroids (either as monotherapy or in combination with cytotoxics) offered no significant advantage over supportive care alone in terms of either annual decline in eGFR at 3 years or in the incidence of an adapted primary end point (time to first occurrence of a composite
of death, ESKD, or a decline of >40% in the eGFR compared with baseline at randomization into STOP-IgAN) over a median follow-up of 7.4 years (1,2,8).

In the Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study, patients were randomized 1:1 to oral methylprednisolone (0.6–0.8 mg/kg per day; maximum of 48 mg/d; n = 136) or matching placebo (n = 126) for 2 months, with subsequent weaning over 4–6 months (9). All patients had received at least 3 months of treatment with RAASi before screening. After randomization of 262 participants, recruitment was halted by the data safety monitoring committee because of an excess of serious adverse events. Notably, patients in the study were not prescribed prophylactic antibiotics or gastroprotection, which would be regarded by many as standard of care when using high-dose systemic corticosteroids, and this may explain the high rate of serious adverse events. Although the interim results of the TESTING study were consistent with potential renal benefit, definitive conclusions about the efficacy of corticosteroid monotherapy in IgAN could not be made. The TESTING Low Dose Study (NCT01560052) is evaluating the safety and efficacy of 0.4 mg/kg methylprednisolone per day in the same IgAN population and is expected to report in mid-2023.

It is widely acknowledged there was no systematic collection of adverse events in most of the early randomized studies of corticosteroids in IgAN. However, more recent studies evaluating corticosteroids in IgAN have collected data on treatment-emergent adverse events. In the TESTING study, serious events occurred in one in seven of the patients treated with methylprednisolone, mostly due to excess serious infections, including two deaths. Other notable adverse events not occurring in the placebo group included avascular necrosis (one in 67 patients) and venous thrombosis (one in 50 patients). In the STOP-IgAN study, corticosteroid use was associated with a significantly increased risk of weight gain of >5 kg, development of impaired glucose tolerance or diabetes mellitus, and a nonsignificant increase in the risk of infection (174 infection events versus 111 events in the supportive care–only group). One patient in the corticosteroid/cytotoxic group died of sepsis. In the study by Hou et al. (10), in which patients were randomized to receive either mycophenolate mofetil (1.5 g/d for 6 months and 0.4–0.6 mg/kg prednisone per day for 2 months, and then tapered by 20% per month for the next 4 months) or prednisone monotherapy (0.8–1.0 mg/kg per day for 2 months, and then tapered by 20% per month for the next 4 months), similar adverse events were reported. Two out of three patients reported an adverse event likely related to treatment during the 6 month treatment with prednisone monotherapy, which included infection (one in five patients), impaired glucose tolerance or newly diagnosed diabetes (one in five patients), Cushing syndrome (one in three patients), and avascular necrosis (one in 88 patients).

Viewed in their entirety, there are—in my opinion—no convincing data from randomized controlled clinical trials that the addition of corticosteroids to optimized supportive care, the current global standard of care for all patients with IgAN, improves renal outcomes in IgAN. There is, however, compelling evidence from the more recent studies that exposing patients to 6 months of systemic corticosteroids is associated with a significant risk of harm. Therefore, it is essential, and explicitly recommended in the upcoming update of the Kidney Disease Improving Global Outcomes Clinical Practice Guideline on Glomerular Diseases, that nephrologists wishing to use corticosteroids ensure their patients are comprehensively counseled on both the risks and benefits of corticosteroid treatment in IgAN. Furthermore, in view of the current uncertainty over the safety and efficacy of corticosteroids, a key research recommendation in the update is the evaluation of new therapeutic strategies that minimize or avoid systemic corticosteroid exposure. To enable this, the new guideline states that all patients who remain at high risk of progressive kidney disease, despite maximal supportive care, should be given the opportunity to take part in a clinical trial, if one is available, before other therapeutic options are considered. The IgAN clinical trial landscape has never been healthier, with multiple, global clinical trials open for recruitment and more trials expected to open over the next 12 months. There has never been a better time for nephrologists and patients to advance our understanding of IgAN and deliver new therapies that are both effective and safe.

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References

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See related debate “Corticosteroids Should Be Used To Treat Slowly Progressive IgA Nephropathy: PRO,” and commentary, “Corticosteroids Should Be Used To Treat Slowly Progressive IgA Nephropathy: COMMENTARY,” on pages 1078–1080 and 1084–1086, respectively.