IgA Nephritis with Declining Renal Function: Treatment with Corticosteroids May Be Worthwhile

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Primary IgA nephropathy (IgAN) is an autoimmune GN characterized by the presence of diffuse mesangial deposits of IgA associated with mesangial proliferation and expansion of the mesangial matrix. In patients with IgAN, circulating IgA1 molecules have an aberrant structure of O-glycans, and this can provoke the formation of autoantibodies and circulating immune complexes. These immune complexes can localize in the glomerular mesangium, with activation of mesangial cells, proliferation of extracellular matrix, and release of cytokines and chemokines acting to initiate and perpetuate glomerular injury.1 Genetic factors are likely to influence the pathogenesis of IgAN. Genes at the HLA region may predispose to the development of IgAN.2 Independent loci showing genome-wide significant association with IgAN are directly associated with either risk of inflammatory bowel disease or maintenance of the intestinal epithelial barrier,3 supporting the pathogenetic role of intestinal abnormality abnormalities in IgAN.

The clinical presentation of IgAN is highly variable. In many patients, the disease may be asymptomatic and detected by the presence of microscopic hematuria or mild proteinuria at screening or routine check-up visits. In a substantial number of patients, the disease progresses silently and is discovered late, when impaired renal function has already developed. Because progressive loss of renal function is usually slow, early studies concluded that IgAN was a benign disease. However, this concept is erroneous, because up to 50% of patients may ultimately progress to ESRD over 25–30 years from clinical discovery.4 Among the factors predicting such a progressive course are increased serum creatinine level at discovery, persistent arterial hypertension, and magnitude and duration of proteinuria.5 A contribution of renal pathology for better profiling the outcome of the disease was provided by the Oxford Classification of IgAN. In a retrospective analysis of adults and children with biopsy-proven IgAN followed for a median of 5 years, renal biopsies were scored independently by expert pathologists. Four histologic predictors of outcome were identified: (1) the mesangial hypercellularity score (M), (2) endocapillary hypercellularity (E), (3) segmental glomerulosclerosis (S), and (4) tubular atrophy/interstitial fibrosis (T)—collectively called the MEST criteria.6 To validate these data, the Validation Study of the Oxford Classification of IgAN (VALIGA) examined a large number of mostly Caucasian individuals from 13 European countries. These patients encompassed the whole clinical and pathologic spectrum of IgAN and were subjected to different treatment regimens. The study concluded that the addition of M, S, and T to clinical variables significantly enhanced the ability to predict progression, at least among untreated patients.7 A decline in predictive power of the Oxford MEST schema in treated patients suggested a possible benefit of one or more of the treatment regimen used.

Treatment of individuals with IgAN is still on the basis of empirical strategies and remains the main issue of uncertainty for clinical nephrologists. A number of immunosuppressive agents has been tested for efficacy in IgAN, including calcineurin inhibitors, azathioprine, mycophenolate salts, cyclophosphamide, and high-dose Igs. However, most of these treatments failed to show a consistent substantial benefit or even manifested augmented toxicity, and therefore, they have not been adopted in mainstream clinical practice. Also inconclusive are the results with fish oil and tonsillectomy. Four randomized clinical trials that tested the efficacy of fish oil in IgAN reported contrasting results. However, a trial with longer follow-up reported that taking daily fish oil for 2 years can attenuate the progression of renal disease with few side effects.8 Tonsillectomy combined with pulses or methylprednisolone is largely used in Asian countries. A systematic review and meta-analysis of 14 studies, most of which were observational in design, reported that tonsillectomy might induce clinical remission and reduce the rates of ESRD in patients with IgAN.9 However, a multicenter controlled trial showed that tonsillectomy combined with steroid pulse therapy has no material beneficial effect over steroid pulses alone to attenuate hematuria and increase the incidence of clinical remission.10 Inhibitors of renin-angiotensin system (RAS) are routinely used in patients with IgAN and proteinuria, regardless of the presence or absence of hypertension. This is on the basis of evidence from controlled trials identifying that these agents can obtain a significant reduction in proteinuria, but their effects on major renal and/or cardiovascular end points or long-term mortality risk may largely be caused by improved control of BP in patients with IgAN.11 Promising results have also been reported.
with use of corticosteroids in IgAN. In a long-term, open–label, randomized, controlled trial, a 6-month regimen of corticosteroids was compared with a symptomatic treatment. The steroid regimen consisted of alternate day oral prednisone for 6 months plus three intravenous methylprednisolone pulses at the beginning of months 1, 3, and 5. The 10-year renal survival was significantly better in patients who received corticosteroids compared with an untreated control group. Median proteinuria significantly decreased in treated patients. Additional randomized and observational trials have largely supported the potential benefit of corticosteroids in IgAN. A meta-analysis of nine trials in patients with proteinuria >1 g/d and normal renal function reported that steroid therapy was associated with a lower risk for kidney failure and a reduction in proteinuria. Relatively high-dose steroids and therapy with duration ≤1 year produced significant renal protection, whereas low-dose, long-term steroid use did not. Of great importance, corticosteroid therapy was associated with a 55% higher risk for adverse events. The use of corticosteroids in patients with IgAN who have persisting proteinuria >1.0 g/d after an adequate trial of RAS inhibition and an eGFR of >50 ml/min per 1.73 m² is now common and was suggested by the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines in 2012. However, the schedules are variable, and corticosteroids are seldom used in patients with lower eGFR, because they are considered ineffec
tive and potentially dangerous in the presence of renal failure.

In this issue of JASN, Tesar et al. retrospectively analyzed the data of the VALIGA mentioned above to evaluate whether the levels of proteinuria, eGFR, and/or histologic features could influence the effects of corticosteroid therapy on renal outcomes. After a median follow-up of 4.7 years, 86% of 1147 patients received RAS blockade, and 46% received immunosuppressive regimens, with corticosteroids used in 98% of these patients. Among patients with proteinuria ≥3 g/d, 64% of those receiving steroids reached a proteinuria level of <1 g/d compared with 4% of patients given only RAS blockers. A lower rate of renal function decline and greater reduction in proteinuria were observed in patients who received corticosteroids in almost all subgroups defined by pathologic features. Using a propensity scoring system, Tesar et al. were able to identify 184 patients who received corticosteroids and RAS blockers and another 184 patients with a similar risk profile who received only RAS blockers. Patients treated with steroids and RAS blockers showed significant reduction of proteinuria and renal function decline and increased renal survival. Of note, these benefits were observed in not only patients with normal or mildly subnormal renal function but also, patients with eGFR<50 ml/min per 1.73 m².

This post hoc analysis of the VALIGA generates the hypothesis that the benefits of corticosteroids in conjunction with RAS inhibition might be extended to a larger and more heterogeneous population of individuals with IgAN than suggested by the KDIGO guidelines, which limit the use of corticosteroids to those subjects with an eGFR of >50 ml/min per 1.73 m². This finding is of great clinical importance. Indeed, little information is available about which treatment regimen to use in these patients, because they are not usually included in randomized, controlled trials. Because of its retrospective nature, the study has some limitations, including the potential differences among centers in the criteria followed for enrolling patients and the long-term compliance of the patients to prescribed treatment. More importantly, no information is available about the adverse events caused by corticosteroids and the doses and the duration of steroid treatment. Thus, despite the important messages of this study, a number of questions still remain unsolved. What level of eGFR should be considered as a point of no return, where treatment with corticosteroids and/or RAS inhibition (other than for BP control) is futile? Is there any role for immunosuppressive agents other than corticosteroids? What is the steroid dosing and duration regimen with better therapeutic index in patients with renal dysfunction? Answering these questions is critical for a correct management of patients with low eGFR, and some studies in progress (e.g., Therapeutic Evaluation of Steroids in IgA Nephropathy Global Study and Supportive Versus Immunosuppressive Therapy for Progressive IgA Nephropathy) may illuminate these uncertainties. Accordingly, treatments with corticosteroids or other immunosuppressive agents should be attempted with caution in these patients, because the presence of renal impairment enhances susceptibility to potential adverse effects of these drugs. However, despite these limits, the study by Tesar et al. should be welcome news, because it may open new hopes for patients with IgAN and deteriorating renal function. This study should also encourage nephrologists to further investigate the optimal use of corticosteroids in patients with impaired renal function and continue the search for additional effective and safe drugs to use in patients with IgAN.

DISCLOSURES
None.

REFERENCES