Corticosteroids should be used to treat slowly progressive IgA nephropathy?:

COMMENTARY

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IgA nephropathy is the most common primary glomerulonephritis in the world (1). With the ultimate diagnosis dependent on kidney biopsy the true prevalence is unknown. The disorder is heterogeneous with disparate clinical outcomes and a poorly understood underlying pathogenesis. Treatment options have traditionally been sparse and based on repurposed agents, primarily corticosteroids, and plagued with the risk of undesirable side effects and unclear efficacy. Significant recent attention has been placed on identifying patients at highest risk for disease progression, making use of predictors such as kidney function, blood pressure, proteinuria and histologic criteria defined in the Oxford classification. At the same time that an unprecedented number of novel therapeutic targets and clinical trials are being pursued, the debate regarding the utility of corticosteroids to treat IgAN continues to rage.

The pathogenesis of IgAN involves mucosal plasma cell production of galactose-deficient IgA1 (Gd-IgA1) by T cell-dependent and independent processes. T cell cytokines such as APRIL promote B cell class switch to IgA1-producing plasma cells with susceptible individuals producing anti-Gd-IgA1 autoantibodies. Gd-IgA1–auto-Ab immune complexes have a propensity for mesangial deposition and contribute to local complement activation inflammation, mesangial cell-podocyte crosstalk and fibrosis, all key factors in glomerular disease progression. Genetic approaches have identified candidate genes and susceptibility loci associated with IgA1 production, mesangial deposition, alternative complement pathway activation and disease progression (2).
Consistent with the complex and evolving knowledge of underlying pathogenesis is significant heterogeneity in the clinical presentation of IgAN. Patients diagnosed with IgAN can have a rapidly progressive glomerulonephritis, nephrotic syndrome or a more slowly progressive phenotype with variable levels of proteinuria, hematuria and eGFR abnormalities. With no reliable biomarker identified, the diagnosis can only be made by a kidney biopsy. This excludes patients with subclinical disease and makes a true determination of IgAN prevalence difficult. Histologically, IgAN is characterized by prominent IgA deposits in the mesangium. The Oxford classification of IgAN includes histopathologic features of the extent of mesangial proliferation, endocapillary proliferation, segmental scarring and tubular atrophy/interstitial fibrosis (3). Combining the MEST score with clinical data at the time of biopsy has been shown to have the same predictive value as monitoring clinical data for two years. Additionally, the presence and extent of crescents is associated with renal function decline. An IgAN prediction tool utilizing clinical, demographic and histologic parameters is useful for patient risk stratification and in predicting kidney disease progression (4).

RAS blockade is an essential component of the initial approach to the treatment of IgAN. ACEi and ARB agents lower both systemic and intraglomerular pressure – an effect thought to have generalizable beneficial impact on proteinuric kidney disease rather than a specific disease modifying effect in IgAN. Patients with proteinuria >0.5 g/24 hr, whether or not they are hypertensive, benefit from ACEi or ARB treatment. Such treatment slows the decline in kidney function (5), an effect not seen in patients
with <0.5 g/24hr (6). There is no real controversy here – except perhaps for some ongoing discussions around the proteinuria threshold for initiating therapy as well as the optimal blood pressure target.

More debatable is how to address the associated inflammation and the approach to patients with proteinuria >1g per 24 hr despite maximum RAS blockade. Clinical decision making is complicated by the fact that all agents currently available to treat IgAN are not targeted, were primarily developed for other unrelated medical indications and are often associated with undesirable side effects. The efficacy of agents such as mycophenolate mofetil and fish oil is unclear. The use of cyclophosphamide should be limited to the rapidly progressive form of IgAN. Rituximab, calcineurin inhibitors and azathioprine are not recommended by KDIGO due to a lack of efficacy. The data on fish oil, tonsillectomy and hydroxychloroquine are less clear, though their benefits may be limited to specific patient groups. This leaves us with steroids. Despite being the most widely used first line immunosuppressive agent for IgAN, corticosteroids are not without controversy. There is a lack of consensus regarding efficacy, dosing, duration, patient selection (based on clinical and histologic features), treatment targets and risk/benefit profiles.

As pointed out in the PRO side of this debate by Drs. Cunningham and Reich, corticosteroids have a sounds mechanistic basis for efficacy in IgAN by inhibiting the production of galactose-deficient IgA1 by mucosal B cells, reducing mesangial matrix expansion and reversing transcriptional changes associated with endocapillary proliferation. Furthermore, while the STOP-IgAN did not show a difference in GFR endpoints at 3 years, the authors rightfully point out that the primary outcome was
positive with significantly more patients in the corticosteroid-based immunotherapy protocols achieving complete remission of proteinuria (7). Similarly, though the TESTING study was terminated early due to excess adverse events in the corticosteroids treatment group, steroid treatment was associated with better renal outcomes in an early analysis (8).

On the CON side, Dr. Barratt points out the high adverse event rate (1 in 7) in the steroid treatment group in TESTING is due primarily to excess serious infections but also includes avascular necrosis, venous thrombosis and death. He details the notable metabolic complications of weight gain, glucose intolerance diabetes mellitus and infection also seen in STOP-IgAN. A key point made by Dr. Barratt is the clinical imperative to titrate RAS blockade to the maximum tolerated dose prior to contemplating additional therapy. This standard is too often unmet in both clinical practice and trial settings, causing some patients to receive immunosuppressive therapy unnecessarily.

So, where do we go from here? The answer ultimately lies in a future that looks quite promising for IgAN treatment, with more agents in development and in clinical trials than ever before. These efforts are aided by the work of the Kidney Health Initiative that has supported proteinuria reduction as a surrogate endpoint for a treatment's effect on the progression of end stage kidney disease in IgAN (9). Similar to practical clinical management, agents in clinical trials for IgAN fall into the categories of blood pressure/intraglomerular pressure lowering versus treatment of the underlying inflammatory disease. The first category includes agents like sparsentan, a dual
angiotension type 1 and endothelin A receptor inhibitor currently in a phase 3 trial. Sodium glucose co-transporter 2 inhibitors (SGLT2i) can now be added to this group. The recently concluded DAPA-CKD study included 270 patients with IgAN (more than STOP-IgAN and TESTING) and showed that in that subgroup, dapagliflozin use improved renal survival compared to placebo (10). The second category has a longer and expanding list including agents targeting the key B-cell modulating factor APRIL and a targeted release form of budesonide that seeks to disrupt mucosal IgA production. Several complement directed agents in phase 2 trials target C3, C5 and complement factor B while a monoclonal antibody targeting MASP-2 is in phase 3. All these agents could be considered steroid-sparing and important to consider, given that the upcoming KDIGO IgAN treatment guidelines will for the first time recommend that patients who remain at high risk despite maximal supportive care be given the opportunity to participate in a clinical trial. These trial opportunities may not be widely available however and the enrollment criteria can exclude many patients who would benefit from treatment. So what is the current role for corticosteroids in patients with slowly progressive IgAN at high risk for progression despite maximum supportive care? Overall, it would appear that risks outweigh benefits with higher doses, but the ongoing low dose TESTING study (max daily dose of 32 mg per day of oral methylprednisolone) should be very helpful in determining whether a safer dosing regimen can be efficacious. In the interim, if opportunities for clinical trial enrollment are limited and corticosteroids are used, it would be prudent to counsel patients on anticipated side effects.
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