**Is There a Role for More Intense Immunosuppression in IgA Nephropathy?**

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In this issue of *Kidney360*, Beck et al. try and expand upon the controversial topic regarding the use of immunosuppressive agents for the treatment of IgA nephropathy (IgAN) (1). They do this via chart review of 119 patients treated at their institution between 2000 and 2020 for biopsy-proven IgAN. Fifty-three patients who received intravenous cyclophosphamide (Cyc) and glucocorticoids are compared with 66 patients who did not receive any immunosuppressive therapy (including glucocorticoids) with a follow-up time of 5 years.

The immunosuppressive regimen was defined as follows: intravenous Cyc 0.75 g/m² every 4 weeks for 3–6 months along with glucocorticoids dosed at 1-mg/kg body wt (maximum 60 mg/day) followed by a 10 mg/week taper to a dose of 20 mg.

It is important to note that given the retrospective nature of this study, there was no defined “standard of care” for the comparison group. There was no difference between mean systolic or diastolic blood pressure or use of angiotensin-converting enzyme inhibitors (ACE-i)/angiotensin II receptor blockers (ARB) between groups. However, patients who received immunosuppressive therapy had higher baseline creatinine (3.0 ± 0.4 mg/dl versus 1.0 ± 0.2 mg/dl; P = 0.02), proteinuria (3.0 ± 0.7 g/g creatinine versus 1.9 ± 0.2 g/g creatinine; P = 0.02), and inflammatory activity on biopsy on the basis of MEST-C score.

Due to higher baseline creatinine and proteinuria in the immunosuppressive therapy group, results were presented as a fold change compared with the patients’ baseline value. Interestingly, despite this higher baseline, there was no significant difference between eGFR and proteinuria between groups at 1 year due to the significant, early reduction in proteinuria and creatinine in patients who received immunosuppression.

At first glance, this study may suggest that patient’s with IgAN with elevated creatinine and proteinuria could stand to benefit from immunosuppressive therapy. However, a brief review of the literature regarding immunosuppressive therapy for the treatment of IgAN will reveal that the answer is not so simple.

IgAN is the most common glomerular disease worldwide, caused in part by autoantibodies directed toward galactose-deficient IgA1 leading to nephritogenic immune complex deposition in the glomerulus and complement activation (2). Due to the immune and inflammatory pathogenesis suggested by biopsy findings, it is not surprising that immunosuppression has been an attractive framework for therapeutic strategies in IgAN, although its implementation remains controversial (3).

In 2002, Ballarde et al. conducted a randomized controlled trial (RCT) comparing prednisolone alone with prednisolone plus CYC followed by azathioprine in 38 patients with IgAN. This trial demonstrated significant improvement in renal survival in patients who received CYC at 5 years compared with those who received prednisolone alone (72% versus 6%) (4). A major criticism of this trial is that the subjects’ blood pressures were significantly elevated compared with today’s standards (<160/90 mm Hg), and only 26% of patients were on ACE-I, suggesting that any benefit from cytotoxic therapy may be obliterated by modern supportive care with adequate blood pressure control and renin-angiotensin-aldosterone system (RAAS) blockade.

In 2009, two RCTs investigated the addition of ACE-i to prednisone for the treatment of IgAN and demonstrated benefit (5,6). Importantly, mean systolic and diastolic blood pressure was more consistent with today’s standard of care in both studies. Given the known side effects of systemic glucocorticoid exposure, the two arguably most important studies in IgAN, TESTING (7) and STOP-IgAN (8), were performed, comparing the addition of steroids on the background of RAAS blockade with ACE-i/ARB. In the TESTING trial, no benefit was seen in renal outcomes in patients who received steroids compared with control, although more adverse events, specifically infections, were seen in the steroid group. STOP-IgAN was ended early due to adverse events, again, mostly driven by infections, although a trend toward benefit was seen in patients who received immunosuppression. However, a 10-year follow-up study of the original STOP-IgAN cohort demonstrated no benefit in patients who received immunosuppression (9). STOP-IgAN is unique in that it required a 6-month run-in period for a patient’s antihypertensive regimen to be optimized, with titration up to the maximally tolerated dose of ACE-i/ARB. In doing so, 34% of

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patients had their proteinuria reduced to <0.75 g/day and thus were excluded from the study.

This point is imperative when interpreting the IgAN therapeutic literature. It has been demonstrated that proteinuria >1 g/day is associated with poor renal outcomes in patients with IgAN (10,11). Furthermore, in a review of 11 RCTs evaluating treatment interventions for IgAN, early reduction of proteinuria was associated with improved renal outcomes. Thus, early reduction of proteinuria serves as a valuable surrogate for long-term renal outcomes in this patient population (12).

We now have better context to interpret the findings of the study by Beck et al. Whereas this study does suggest renal benefit with steroids and CYC, it is not compared with a proper, modern control due to its retrospective design. Whereas blood pressure is better controlled compared with some of the previously mentioned trials, in this study, a little more than three quarters of patients were on RAAS blockade, and many were not on maximum doses.

What this study does show, however, is the effect of immunosuppression with CYC and steroids in a higher-risk patient population compared with both TESTING and STOP-IgAN. Patients in this trial had higher baseline creatinine and urinary protein compared with the earlier trials (Table 1). In fact, on the basis of proteinuria alone, many of these patients would have been excluded from STOP-IgAN. Having said this, the low GFR arm (30 ml/min/1.73 m²) in STOP-IgAN did receive CYC with azathioprine and showed no benefit compared with supportive care (13). Although limited by its retrospective design, this study shows that patients treated with immunosuppression did have a significant reduction in proteinuria—an important surrogate marker for long-term renal survival in patients with IgAN.

It is interesting that despite the higher baseline creatinine, increased proteinuria, and higher inflammatory findings on renal biopsy, the immunosuppressive therapy group was able to achieve similar creatinine, eGFR, and proteinuria levels by 1 year compared with the comparison group. Given that the immunosuppressive therapy group had worse renal parameters at baseline, this trial represents a different population of patients who may benefit from more aggressive immunosuppression fitting with data from patients with aggressive, crescentic IgAN (14). Regarding safety and tolerability, this study did not demonstrate a significant difference in infections between groups (38% versus 27%; P=0.24), although the incidence was much higher when compared with both STOP-IgAN and TESTING. Thirteen percent developed diabetes compared with 2% of controls (P=0.02), which is comparable to the findings in STOP-IgAN (11%) but not TESTING (1.5%).

We cannot say on the basis of these data that CYC should be moved toward the top of our armamentarium for all patients with IgAN. The biggest lesson for IgAN from the STOP-IgAN is that significant benefit may be obtained with intensive supportive care with the use of easily available, less toxic medications. Furthermore, recent data showing significant benefit of SGLT2 inhibitors in patients with IgAN further support this notion that there are more desirable medications to utilize in our patients with IgAN before immunosuppression is considered (15). However, if high-risk patients fail to show a response to intensive supportive care and glucocorticoids, as suggested by the recent Kidney Disease Improving Global Outcomes guidelines (16), data from this study suggest that CYC may potentially be beneficial.

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Author Contributions
A. Aron wrote the original draft of the manuscript.

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Table 1. Patient characteristics of Beck et al. (1) compared with STOP-IgAN and TESTING trials

<table>
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<tr>
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<th>STOP-IgAN (8)</th>
<th>TESTING (7)</th>
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<tbody>
<tr>
<td>Creatinine, mg/dl</td>
<td>3.0±0.4</td>
<td>1.5±0.6</td>
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<tr>
<td>Proteinuria, g/day</td>
<td>3.0±0.7</td>
<td>2.2±1.8</td>
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<tr>
<td>Mean SBP, mm Hg</td>
<td>141±3</td>
<td>131±14</td>
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<tr>
<td>Mean DBP, mm Hg</td>
<td>84±2</td>
<td>81±9.9</td>
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DBP, diastolic blood pressure; SBP, systolic blood pressure.


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