Combined Immunosuppression in High-Risk Patients with IgA Nephropathy?

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In autopsy studies or 0-hour renal allograft biopsies, IgA nephropathy (IgAN) can be found in up to 1.5% of the normal population. Thus, the vast majority of patients seem not to need us and do well without a nephrologist. Patients who are in need of renal care and therapy are those with a proteinuria level of >0.5 to 1.0 g/d and/or a decline in GFR. A favorable outcome was noted in observational studies when proteinuria was reduced to <1 g/d in such patients. Similarly, loss of GFR can be retarded, albeit not absolutely prevented, with angiotensin-converting enzyme inhibitor (ACEI) therapy, corticosteroid therapy, or combined corticosteroid and ACEI therapy. There is uncertainty, however, whether an even more intense therapy might result in even better outcomes.

In this issue of JASN, Pozzi et al. describe the outcome of a long-awaited Italian and Swiss multicenter, randomized, controlled trial (RCT) in which they tested the hypothesis that adding a 6-month course of azathioprine to a 6-month corticosteroid regimen would further reduce the loss of GFR in high-risk, adult patients with IgAN. At inclusion, all patients exhibited a GFR of 1.0 to 3.5 g/d in medical centers in Italy and Switzerland. The primary end point was a 6-month decrease in GFR of 0.5 g/d in medical centers in Italy and Switzerland. The primary end point was a 6-month decrease in GFR of 0.5 g/d and/or a gain of 0.5 g/d or a proteinuria level of >0.5 to 1.0 g/d and/or a decline in GFR. A favorable outcome was noted in observational studies when proteinuria was reduced to <1 g/d in such patients. Similarly, loss of GFR can be retarded, albeit not absolutely prevented, with angiotensin-converting enzyme inhibitor (ACEI) therapy, corticosteroid therapy, or combined corticosteroid and ACEI therapy. There is uncertainty, however, whether an even more intense therapy might result in even better outcomes.

How does this study compare with the existing knowledge? So far, two RCTs have used azathioprine plus corticosteroids in...
adult patients with IgAN. A Turkish RCT tested combined corticosteroid and azathioprine therapy in patients who presented with isolated hematuria and an almost normal GFR; however, such patients have an excellent prognosis and there is consensus that they should not receive immunosuppression. A small British RCT used corticosteroids combined with cyclophosphamide followed by several years of azathioprine in patients with a serum creatinine level of 2 to 3 mg/dl plus a 15% rise within the previous year. The active treatment group achieved a much greater renal survival (72% 5-year survival compared with 6% in control subjects). These patients were much more advanced in the course of their renal disease as compared with the group of Pozzi et al. Despite views to the contrary, there are limitations of the British study: It studied a highly selected group of patients, there was no steroid monotherapy arm, and supportive therapy did not match today’s standards. Finally, a Japanese RCT of children with IgAN compared a 2-year combination of prednisolone, azathioprine, warfarin, and dipyridamole with prednisolone alone. There was complete remission of proteinuria in 92% of the patients who received the combination and in 74% of those who received prednisolone alone. GFR remained normal in all children. It may be difficult to justify an intense immunosuppression in children on the basis of that relatively soft end point. In view of these findings, it is clear that the study of Pozzi et al. is a major step forward because it provides an answer to an unresolved issue, has studied a comparatively large group of patients with IgAN, and targets a common clinical situation.

What are the limitations of this study? As discussed by the authors, the azathioprine dosage and duration of treatment might have been too low; however, another limitation may be more important: Fewer than half of the patients received an ACEI or an angiotensin receptor blocker (ARB) at baseline. Also, there was no run-in period in which supportive therapy was optimized and, in particular, in which an ACEI or an ARB was systematically adjusted upward. Although this approach was not that well established when the trial started in 1998, it is general practice nowadays. In fact, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on the treatment of glomerular disease, to be published in 2011, will recommend first to optimize supportive care before considering any immunosuppression unless the patient exhibits a rapidly progressive IgAN course, which is backed by a high level of evidence. In our own ongoing STOP-IgAN study, we noted that during the 6-month run-in phase, which was meant to adjust ACEIs or ARBs upward, proteinuria decreased to <0.75 g/d in most patients with IgAN (unpublished data). These responders to supportive therapy should have a very low risk for progression of renal damage and would not normally receive immunosuppressive therapy. Thus, it is conceivable that the trial of Pozzi et al. included a number of patients who would have ended up in a low-risk category by simply instituting and optimizing supportive therapy. Such patients, with a less aggressive course, might have diluted the identification of those who were truly in need of a more intense therapy.

The take-home message is, “Less is more.” Do not add azathioprine to corticosteroids in adult patients who have IgAN, are at high risk for progression, and have a GFR of >50 ml/min per d. Whether this statement also applies to other clinical situations, such as patients with more advanced disease and a GFR of <50 ml/min or those with a rapid decline in GFR, or to children remains to be seen.

Finally, although the authors must be congratulated on their important study, it is frustrating to see that it took >12 years from the start of the study to publication of the data, given a planned 4-year recruitment and a planned 5-year follow-up period. Remember: IgAN is the most common type of glomerulonephritis! Indeed, in the KDIGO guidelines on the treatment of glomerular disease, as mentioned already, very few recommendations for IgAN, in particular for less frequent types of glomerulonephritis, are based on high-level evidence. Thus, it clear that there is a pressing need for reliable short-term surrogate end points and for even larger consortia if we ever want to base our therapy on solid data.

DISCLOSURES
None.

REFERENCES


See related article, “Addition of Azathioprine to Corticosteroids Does Not Benefit Patients with IgA Nephropathy,” on pages 1783–1790.