Combined Immunosuppression in High-Risk Patients with IgA Nephropathy?

Jürgen Floege and Frank Eitner
Division of Nephrology and Immunology, Rheinisch-Westfälische Technische Hochschule Aachen, Aachen, Germany

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 >50 ml/min per d and a proteinuria level of 1.5 to 3.5 g/d. Most also had advanced inflammatory and/or sclerosing histologic lesions in their baseline biopsies; however, none had a rapidly progressive course. After a median follow-up of 4.9 years, only 12% of the patients experienced a 50% increase in serum creatinine, the primary end point. There was no difference between the two treatment groups in terms of maintaining renal function or their decreases in proteinuria; however, adverse events, in particular hepatotoxicity, leukopenia, and gastrointestinal symptoms, were significantly more common in the combined corticosteroid and azathioprine group. The authors concluded that the addition of azathioprine in this particular group of patients only increased adverse effects but did not improve the outcome beyond that observed with a corticosteroid alone.

How does this study compare with the existing knowledge? So far, two RCTs have used azathioprine plus corticosteroids in...

---

See related article, “Albuminuria and Estimated Glomerular Filtration Rate Independently Associate with Acute Kidney Injury,” on pages 1757–1764.

REFERENCES


Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Jürgen Floege, Division of Nephrology, University Hospital, RWTH Aachen University, Pauwelsstrasse 30, 52057 Aachen, Germany. Phone: +49 (0)241-8089 530; Fax: +49 (0)241-8082 446; E-mail: juergen.floege@rwth-aachen.de

Copyright © 2010 by the American Society of Nephrology
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.7 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.7 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,7 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, 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.