

To Treat or Not to Treat IgA Nephropathy? That Is the Question!

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IgA nephropathy (IgAN) remains one of the most common forms of idiopathic glomerulonephritis in many populations worldwide (1,2). It also is a potentially serious condition in which from 4 to 38% of patients progress to ESRD by 10 yr (2). Given its frequency and significance, there should be a consensus on which treatment strategy is optimal for patients with IgAN (1,3,4). For those who work with patients with IgAN, the reasons for a lack of consensus are obvious. First, despite progress in understanding the mechanisms that are involved in IgAN, ranging from abnormalities of galactosylation of the hinge region of the IgA molecule to altered mesangial cell binding and incitement of inflammatory mediators, the pathogenesis of the disease remains unknown (1,5). Hence, specific treatment cannot be directed at the cause of the disease, and we are forced to use less specific disease modifiers. A second problem in dealing with the treatment of IgAN is the variability of glomerular manifestations and their severity. Some patients seem to show no progression of disease over many years, whereas others present with crescentic glomerulonephritis and progress to renal failure in weeks to months. How can one treatment be effective in such a diverse disease population? A third problem is the long duration of disease progression in many patients who ultimately do experience a progressive course. All treatments with medications must include an assessment of risk *versus* benefit by the prescribing clinician. The longer and slower the course of disease progression, the more that potential toxicities of treatment become a factor in this cost–benefit analysis.

Despite these limitations, numerous studies have examined the treatment of IgAN. Many include data on trials that are retrospective, nonrandomized, uncontrolled, or insufficient in number to reach statistically significant conclusions (6). Many patients who are unable to judge these data critically form opinions about treatment options from less-than-optimal sources. There are more data on the potential benefits of tonsillectomy in IgAN on the Internet than in the medical literature! Some therapies have little risk, have been shown to be effective in almost all studies regardless of flaws in design, and have been proved effective in randomized, controlled trials so that there is consensus. The use of angiotensin-converting en-

zyme inhibitors or angiotensin II receptor antagonists in patients with proteinuric or hypertensive IgAN is regarded as routine standard therapy by many clinicians (7). Likewise statin use in hyperlipidemic patients with IgAN is not a source of much controversy. However, there is no such consensus on therapy with fish oils or corticosteroids or other immunosuppressive agents for patients with IgAN, despite numerous studies. Some of these studies are very well designed, have been published in the very best medical journals, and would seem to provide a conclusive answer on therapy (8–10); yet they are counterbalanced by other studies that have failed to show positive results. If there were clear, confirmatory data from a well-performed large, randomized, blinded, controlled trial, then the answer would be clear. This is the intent of the manuscript by Hogg *et al.* in this issue of *CJASN* (11), which describes the much-awaited results of a large, multicenter, randomized, double-blind, placebo-controlled trial that evaluated the role of prednisone and omega 3 fatty acids (O3FA) in slowing the progression of renal disease in patients with IgAN. Approximately 100 patients with biopsy-proven IgAN and a GFR >50 ml/min per 1.73 m² were randomly assigned to receive either 2 yr of a tapering dose of prednisone every other day, 4 g/d O3FA, or placebo. Hypertensive patients were treated with an angiotensin-converting enzyme inhibitor, and the primary outcome was clearly defined as a fall in GFR to <60% of baseline. The results are disappointing for treatment enthusiasts. Neither the prednisone nor the O3FA showed benefit over the placebo group in time to renal failure. Indeed, of the 14 patients who experienced progressive renal failure, two were in the prednisone group, four were in the placebo group, and eight were in the O3FA group.

Does this study provide a definitive answer on therapy of IgAN? The bad news is, unfortunately, no. The authors state that definitive conclusions cannot be made from this study. The most significant factor in predicting progressive renal failure in this patient population was initial urine protein-to-creatinine ratio (UP/C). Those with a higher ratio had more progressive disease. Many other studies have noted that the degree of proteinuria at baseline or follow-up is of major prognostic influence in patients with IgAN (12,13). Unfortunately, the randomization process in this study did not stratify patients equally for urine UP/C. The O3FA group had significantly higher UP/C than the placebo group. Even with appropriate randomization for degree of proteinuria, the short follow-up

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even to 3 yr may not be long enough to show effects of treatment on the course of many patients.

There is good news in this study. This was a multicenter, randomized, blinded, and placebo-controlled trial. This is the way in which future treatment studies in IgAN must be designed. Small, retrospective, uncontrolled trials just will not give the answers that clinicians want and that their patients deserve. This study also calls attention to the fact that risk factor stratification, including UP/C, will be crucial in future studies. It points out the need for large numbers of patients with adequate follow-up periods. This clearly will require multicenter, national trials. Such a study of the use of mycophenolate mofetil in progressive IgAN now is under way in the United States. However, until definitive results are provided, the clinician still is served best by considering the risks and benefits of O3FA, prednisone, and other immunosuppressive agents on an individual basis.

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See related article, “Clinical Trial to Evaluate Omega-3 Fatty Acids and Alternate Day Prednisone in Patients with IgA Nephropathy: Report from the Southwest Pediatric Nephrology Study Group,” on pages 467–474.