Treating IgA Nephropathy

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IgA nephropathy may be the most common type of glomerulonephritis, worldwide. Once thought benign, it causes end-stage renal disease in 15 to 20% of individuals within 10 yr of onset (1) and in 30 to 35% of individuals within 20 yr of onset. Proteinuria, an elevated serum creatinine concentration, and hypertension predict progression (1) as does a renal biopsy demonstrating focal proliferative glomerulonephritis with crescents, diffuse proliferative glomerulonephritis, or advanced, chronic disease (2). Despite having knowledge of these markers, predicting the course of the disease in individuals is difficult.

The chronic nature of IgA nephropathy and the possibility of a good outcome without therapy suggest that treatments should be relatively nontoxic. One nontoxic treatment is fish oil (omega-3 fatty acids), which may have an anti-inflammatory effect. Donadio et al. (3) have championed fish oil since publishing a 2-yr, 106-patient, randomized, placebo-controlled trial in 1994. The results were striking. Fish oil reduced the risk of the primary outcome—a 50% increase in serum creatinine concentrations—by 82%. It reduced the risk of death or end-stage renal disease by 67%. Creatinine clearances fell only 0.3 ml/min per 1.73 m²/yr among fish oil–treated patients versus 7.1 ml/min per 1.73 m²/yr among placebo-treated patients. No patient discontinued fish oil because of side effects. These benefits persisted after 6.4 yr of follow-up (4).

In this issue, Donadio, et al. report the results of a trial in which they randomized patients with severe IgA nephropathy to two doses of omega-3 fatty acids, one approximately equal to and one approximately double the dose used in the 1994 study. The outcomes were similar in both groups, and the authors recommend treating high-risk patients with the lower dose.

Questions remain about fish oil. Two smaller, randomized trials of fish oil for IgA nephropathy failed to demonstrated a benefit (5,6). The duration of one (5) was only 6 mo, perhaps too short. The duration of the other (6) was, like the 1994 Donadio trial, 2 yr. Using meta-analysis, I calculated that there was only a 75% probability that fish oil was beneficial (7). A dose-response effect, in the trial by Donadio et al. in this issue, would have provided strong evidence favoring fish oil; the lack of one, at least over the range studied, is weak evidence against it. Finally, neither the 1994 Donadio trial nor the trial in this issue demonstrated a significant reduction in proteinuria. Proteinuria is a key therapeutic target because it may, itself, cause renal injury (8) and because its reduction correlates with preservation of renal function (9).

What of other therapies? Proteinuria fell 21 to 61% in three short-term trials of angiotensin-converting enzyme (ACE) inhibitors in IgA nephropathy (10–12). Catran et al. (13), studying IgA nephropathy patients with at least 1 g/d urinary protein retrospectively, found that creatinine clearances fell 4.8 ml/min per yr among ACE inhibitor–treated patients versus 12 ml/min per yr among similar patients who were treated with other antihypertensive medications. We do not have prospective, randomized, controlled data demonstrating that the ACE inhibitors preserve GFR in this disease. However, the REIN trial, in which the GFR fell 4.4 ml/min per 1.73 m²/yr among ramipril-treated patients versus 6.1 ml/min per 1.73 m²/yr among patients who were treated with other antihypertensive medications, provided such evidence for chronic, proteinuric nephropathies, in general (14). The benefit increased with increasing pretreatment proteinuria; patients who excreted less than 2 g/d urinary protein did not benefit. Greater reductions in proteinuria after 3 mo of therapy led to greater long-term preservation of GFR.

The ACE inhibitors, although effective, may not accomplish enough among high-risk patients. The proteinuria reduction is modest, and patients who lose GFR at 4.4 or 4.8 ml/min eventually will develop end-stage renal disease. Adding an angiotensin receptor antagonist is one possibly effective strategy. The angiotensin receptor antagonists and ACE inhibitors have reduced proteinuria equally (11,12), but the combination has been additive, reducing proteinuria 73% (11). We do not know whether this combination preserves GFR more effectively than ACE inhibitors alone. Adding a hepatic 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor is another possibly effective strategy. In a small, randomized trial, 6 mo of fluvastatin decreased proteinuria 41% among patients with IgA nephropathy (15). There was no effect on GFR, and the long-term effects on GFR are not known.

The ACE inhibitors do not attack the inflammatory component of this disease. Potent anti-inflammatory and immunosuppressive therapy with corticosteroids is effective for IgA nephropathy. Pozzi et al. (16) conducted the largest trial, randomizing 86 IgA nephropathy patients to corticosteroids (intravenous methylprednisolone 1 g/d for 3 d at the beginning of months 1, 3, and 5, plus oral prednisone 0.5 mg/kg on alternate days for 6 mo) or supportive therapy. Proteinuria fell 50% at 6 mo and 65% at 1 yr among treated patients. With 5
yr of follow-up, corticosteroid therapy reduced the risk of a 50% increase in the serum creatinine concentration by 36%. GFR data were not provided. The authors observed no major side effects. Two smaller, randomized trials demonstrated similar reductions in proteinuria from corticosteroids (17,18). Neither demonstrated an effect on GFR, but Shoji et al. (18) observed significant improvements in renal histology after 1 yr of corticosteroid therapy. Relapses after steroid therapy and steroid dependence have been described (17). Whether the benefits outweigh the toxicities over the entire course of the disease is not known.

How should we treat our patients? Compelling evidence favors the ACE inhibitors. Patients with hypertension or with more than 1 to 2 g/d proteinuria, with or without hypertension, should receive them. Individuals who are intolerant of the ACE inhibitors probably should be treated with an angiotensin receptor antagonist. High-risk patients or those in whom ACE inhibitor therapy fails to reduce proteinuria to less than 1 to 2 g/d may require additional therapy. Individuals with inflammatory biopsy findings (especially crescentic or diffuse proliferative glomerulonephritis) may benefit from anti-inflammatory therapy with corticosteroids or, possibly, fish oil. Individuals with heavy proteinuria may benefit from corticosteroids, an angiotensin receptor antagonist, or an HMG-CoA reductase inhibitor. We do not know which of these approaches is most effective.

A placebo-controlled, randomized trial with fish oil and corticosteroid arms is under way and has completed enrollment (19). Other immunosuppressive strategies could be more effective or less toxic than corticosteroids. A trial comparing corticosteroids plus azathioprine with corticosteroids alone is in progress (20). Combining antiproteinuric and anti-inflammatory therapies is attractive theoretically and worthy of additional study. Likewise, the HMG-CoA reductase inhibitors are worthy of additional study in this and other glomerular diseases.

References