Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers for IgA Nephropathy

By John J. Dillon

The lengthy course of IgA nephropathy and the possibility of good outcomes without therapy suggest nontoxic therapies such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

Among patients with IgA nephropathy, both ACE inhibitors and ARBs reduce the transglomerular passage of large, but not small, molecules, reducing proteinuria. The antiproteinuric effects of ACE inhibitors and ARBs are probably equivalent. Dual ACE inhibitor–ARB therapy reduces proteinuria by 54% to 73% and is more effective than either agent alone. To determine whether ACE inhibitors or ARBs preserve renal function long-term, one must rely on trials studying nondiabetic, proteinuric renal diseases rather than on trials specific to IgA nephropathy. Among this group of patients, several randomized, controlled trials, including the AIPRI trial, the REIN trial, and a metaanalysis of 11 randomized, controlled trials, have established clearly that the ACE inhibitors preserve renal function. There is no reason to believe that this information is not applicable to IgA nephropathy. The COOPERATE trial, in which 50% of the subjects had IgA nephropathy, established that ACE inhibitors and ARBs preserve renal function equally, and that dual ACE inhibitor–ARB therapy preserves renal function more effectively than either therapy alone. These data suggest that most individuals with proteinuric renal diseases, including IgA nephropathy, should be treated with ACE inhibitors and ARBs, ideally in combination. Polymorphisms of the angiotensinogen gene, the ACE gene, and the angiotensin II type I receptor gene have, so far, failed to predict either susceptibility to or progression of IgA nephropathy. However, the D allele of the ID polymorphism, particularly the DD genotype, could predict a favorable response to renin–angiotensin blockade.

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IgA nephropathy has a variable course. Many patients do very well, but 10% to 20% develop end-stage renal disease (ESRD) by 10 years. Proteinuria, an elevated serum creatinine concentration, hypertension, and severe histologic changes predict poor outcomes, but predicting the course in individuals is often difficult. The long course of IgA nephropathy, perhaps necessitating prolonged therapy, and the possibility of a good outcome without therapy suggest that treatments should be relatively nontoxic.

Inhibiting the renin–angiotensin system is one nontoxic approach. In the mid-1980s, Anderson et al. demonstrated that angiotensin-converting enzyme (ACE) inhibitors, but not other antihypertensive agents, reduced glomerular capillary hypertension and prevented proteinuria and glomerular lesions among 5 of 6 nephrectomized, hypertensive rats. Among patients with IgA nephropathy, both ACE inhibitors and angiotensin receptor blockers (ARBs) reduced the transglomerular passage of large molecules, but not small molecules, reducing proteinuria.

Proteinuria could, itself, be nephrotoxic. Reducing proteinuria seems to be a key mechanism by which inhibiting the renin–angiotensin system limits progression in human glomerular diseases.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Proteinuria fell 21% to 61% in five short-term trials of ACE inhibitor therapy in IgA nephropathy. The fall in proteinuria has been shown to be dose-dependent, at least among patients with nondiabetic, proteinuric renal diseases in general.

There is less data, specific to IgA nephropathy, regarding the effect of ACE inhibitors on renal function. Short-term trials provide little useful information, both because of the chronic nature of the disease and because ACE inhibitors tend to reduce the glomerular filtration rate (GFR) acutely. The first publication, reporting a beneficial effect on renal function, was that of Feriozzi et al. in 1989. This study was small, with only 10 patients, and was not randomized, but the mean observation period was relatively long: 21 months on conventional therapy, then 23 months on ACE inhibitor therapy. In 1994, Catrzan et al., in a retrospective analysis of hypertensive, patients with IgA nephropathy with at least 1 g per day of urinary protein, found that creatinine clearances fell 0.4 mL/min per month among 27 ACE inhibitor-treated patients versus 1.0 mL/min per month among 55 similar patients treated with other agents.
(P = 0.007). Bannister et al. published the only randomized, controlled trial in 1995. Twenty-three hypertensive patients with IgA nephropathy were randomized to either enalapril or nifedipine and followed for 1 year. There was no significant difference between the two groups in the rate at which the GFR changed. However, the statistical power to detect clinically significant differences was low and 1 year was probably not sufficient follow up.

Although the GFR data is limited for IgA nephropathy, large, well-designed, randomized, placebo-controlled trials have established clearly that ACE inhibitor therapy preserves renal function in nondiabetic, proteinuric renal diseases in general. The largest trials were the AIPRI, and the REIN. Moreover, a meta-analysis of 11 randomized, controlled trials found a significant benefit.

The AIPRI trial randomized 583 patients with chronic renal diseases of various etiologies and creatinine clearances of 30 to 60 mL/min to 3 years of treatment with conventional antihypertensive therapy plus either 10 mg benazepril per day or placebo. The relative risk for either doubling the serum creatinine concentration or reaching ESRD was reduced by 48% in the benazepril group (P < 0.007). Blood pressures were similar in the two groups. A greater decline in serotonin excretion at 3 months correlated with better long-term outcomes, suggesting that proteinuria is nephrotoxic. All of the ACE inhibitor benefit for progression occurred among individuals with initial urinary protein excretions of at least 2 g per day.

Twenty-one percent of the REIN subjects had IgA nephropathy. Among these patients, the mean GFR fell 0.36 mL/min/1.73 m² per month in the ramipril group versus 0.55 mL/min/1.73 m² per month in the placebo group. The relative risk for ESRD was reduced by 28% in the ramipril group. The outcomes for the IgA nephropathy subgroup were similar to those for the study as a whole but were not statistically significant. This is probably because the trial was not powered to study IgA nephropathy.

Jafar et al. published a metaanalysis combining patient-level data from 11 randomized trials in which regimens containing ACE inhibitors were compared with regimens not containing ACE inhibitors among patients with nondiabetic renal diseases. Data from 1860 patients were analyzed. The mean follow up was 2.2 years. ESRD developed in 7.4% of the ACE inhibitor-treated patients and in 11.6% of the control subjects (relative risk = 0.63, P = 0.002). A combined end point of doubling the serum creatinine concentration or developing ESRD was reached in 13.2% of the ACE inhibitor-treated patients and in 20.5% of the control subjects (relative risk = 0.64, P = 0.001). The mean systolic blood pressure fell 4.5 mm Hg more among ACE inhibitor-treated patients than among control patients. This blood pressure difference had little clinical significance. Adjusting for differences in baseline characteristics and for the difference in the decrease in systolic blood pressure changed the relative risk for ESRD among ACE inhibitor-treated patients little, to 0.66, and did not change the relative risk of 0.64 for the combined end point. Mean urinary protein excretion decreased by 26% (P < 0.001) among ACE inhibitor-treated patients. Less initial proteinuria and greater declines in urinary protein excretion with therapy were advantageous, predicting less risk for the combined outcome. Individuals with more proteinuria benefited more from ACE inhibitor therapy, but the benefit extended down to daily urinary protein excretions of 0.5 g per day. This figure was lower than that seen in the individual trials, probably because the metaanalysis had greater statistical power.
These studies indicate that virtually all patients with nondiabetic, proteinuric renal diseases should be treated with ACE inhibitors. (Similar data exists for diabetic nephropathy.23) Currently, there is no reason to believe that the response to ACE inhibitor therapy in IgA nephropathy differs significantly from that of other proteinuric renal diseases.

**ANGIOTENSIN RECEPTOR BLOCKERS**

ARBs reduced the transglomerular passage of large molecules, but not small molecules, among patients with IgA nephropathy. Quantitatively, this effect is virtually identical for ACE inhibitors and ARBs.4 ACE inhibitors and ARBs reduce proteinuria equally in IgA nephropathy,11,12,24 in nondiabetic, proteinuric renal diseases,13,25 and in diabetic nephropathy resulting from both type I26 and type II diabetes.27,28 Randomized trials comparing the long-term effects of ACE inhibitor versus ARB therapy on renal function in IgA nephropathy alone have not been performed. However, the COOPERATE randomized 336 patients with nondiabetic renal diseases, creatinine clearances of 20 to 70 mL/min/1.73 m², and urinary protein excretions exceeding 0.3 g per day to 3 years of therapy with conventional antihypertensive therapy plus an ACE inhibitor (trandolapril), an ARB (losartan), or dual ACE inhibitor–ARB therapy.25 One-half of the participants in this Japanese study had IgA nephropathy. Blood pressures were similar in all groups. The effect on renal function was identical in the ACE inhibitor-treated and ARB-treated patients, with 23% of the subjects in each group reaching a combined end point of either doubling the serum creatinine concentration or developing ESRD.

These studies indicate that ACE inhibitors and ARBs have equivalent effects on proteinuria in IgA nephropathy. The COOPERATE trial indicates that they have equivalent effects on long-term renal function in nondiabetic, proteinuric renal diseases. With 50% of the COOPERATE participants having IgA nephropathy, this finding is most applicable to IgA nephropathy.

**DUAL THERAPY**

Dual therapy, with both ACE inhibitors and ARBs, has had an additive effect on proteinuria in small studies of patients with IgA nephropathy.12,24,29 The magnitude of the reduction in urinary protein excretion is 54% to 73%.12,24 Similar reductions with dual therapy have been observed in nondiabetic, proteinuric renal diseases13,25 and in diabetic nephropathy resulting from both type I26 and type II diabetes.28 In the COOPERATE trial, dual therapy reduced the risk of doubling the serum creatinine concentration or developing ESRD from 23% with ACE inhibitor or ARB therapy to 11% with dual therapy (P = 0.02).25 A statistically significant advantage for dual therapy was present even among the subgroup of patients with initial urinary protein excretions less than 1 g per day. The similarity in blood pressures among the three groups argues for a therapeutic advantage of dual therapy over and above its blood pressure-lowering effect.

These studies indicate that dual therapy is more effective at reducing proteinuria than ACE inhibitor or ARB monotherapy. The COOPERATE trial indicates that dual therapy also preserves renal function better than monotherapy in nondiabetic, proteinuric renal diseases. Given the composition of the COOPERATE trial, this finding is most applicable to patients with IgA nephropathy.

**Adverse Effects of Dual Therapy**

Ruilope et al. examined the safety of ARB therapy versus dual ACE inhibitor–ARB therapy among 108 patients with chronic renal diseases and creatinine clearances of 20 to 45 mL/min.30 The study duration was 5 weeks. The adverse effects, as well as the most common adverse effects seen in the COOPERATE trial, are shown in Table 1. None of the between-group differences in Table 1 were statistically significant.

Overall, dual therapy was well tolerated. Hyperkalemia is common with renin–angiotensin system blockade. Diuretics are often a logical choice for managing this. Dietary potassium restriction or potassium binders are alternative therapies for hyperkalemia among patients who do not require blood pressure reduction.

**GENETIC POLYMORPHISMS AND IgA NEPHROPATHY**

Variability in the genes governing the renin–angiotensin system could modify glomerular disease susceptibility, natural history, or response to therapy. The angiotensigen gene, the ACE gene, and the angiotensin II type 1 receptor (AT1R) genes are all potentially important and have all been studied in IgA nephropathy. The best-studied
polymorphism is ID, representing insertion (I) or deletion (D) of a 287 base pair DNA fragment into intron 16 of the ACE gene on chromosome 17. The D allele confers greater serum ACE activity, with individuals having the DD genotype having the greatest activity.

In 1995, Yoshida et al. reported that the DD genotype was significantly more frequent among Japanese patients with IgA nephropathy and declining renal function than among similar patients with stable renal function. In addition, 48 weeks of ACE inhibitor therapy decreased proteinuria significantly among patients with the DD genotype, but not among patients with the ID or II genotypes. This study was small with 53 patients, only 21 of whom (9 DD, 6 ID, 6 II) were included in the ACE inhibitor, therapeutic analysis.

The results of subsequent studies of the ACE ID polymorphism have been mixed. However, a large Italian study, involving 247 patients with IgA nephropathy and 205 healthy control subjects, and an associated metaanalysis concluded that the ID polymorphism did not contribute either to the development of IgA nephropathy or to the progression of renal damage. Although the metaanalysis could not exclude an effect limited to Asians, a subsequent analysis of 527 Japanese patients with IgA nephropathy found no relationship between the ID genotype and renal disease progression.

The ID polymorphism might not be the best ACE-gene marker. Among Nigerians, ACE concentration differences were best explained by the ACE4 and ACE8 polymorphisms. The ID polymorphism had no effect independent of these other markers.

The M235T polymorphism of the angiotensinogen gene encodes either methionine or threonine. The T allele could be associated with hypertension, diabetic nephropathy, and chronic renal allograft dysfunction. Among patients with IgA nephropathy, presence of the T allele could predict more proteinuria and more-rapid loss of renal function. In addition, the C(-20) allele, a substitution in the core promoter region of the angiotensinogen gene found only among individuals with the T allele (at least among Japanese patients with IgA nephropathy), could further predict loss of renal function.

The A1161C polymorphism of the AT1R gene refers to whether adenine or cytosine is present at position 1161. It could correlate with hypertension. This polymorphism has failed to predict either proteinuria or loss of renal function among patients with IgA nephropathy.

One limitation of these studies was that some subjects were taking ACE inhibitors or ARBs, possibly limiting the impact of the genetic differences. The IGARAS study, examining the impact of the ID, M235T, and A1161C polymorphisms on progression to ESRD among 274 French males with IgA nephropathy, excluded patients taking these medications. The mean follow up in this study was 6 years. Although there were weak relationships among the presence of the D, T, and A alleles and more advanced disease at presentation, none of the three genotypes predicted renal survival.

The fact that a marker fails to predict susceptibility or progression does not necessarily mean that it fails to predict the therapeutic response to ACE

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**Table 1. Adverse Effects of Monotherapy vs. Dual Angiotensin Converting Enzyme (ACE) Inhibitor–Angiotensin Receptor Blocker (ARB) Therapy**

<table>
<thead>
<tr>
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<th>ACE Inhibitor Therapy</th>
<th>ARB Therapy</th>
<th>Dual Therapy</th>
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<tbody>
<tr>
<td><strong>Ruilope et al., 2000</strong>&lt;sup&gt;30&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
<td>Serum creatinine Increase (mg/dL)</td>
<td>0.13</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Serum potassium Increase (meq/L)</td>
<td>0.28</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Serum potassium ≥ 6 meq/L no. (%)</td>
<td>1 (5%)</td>
<td>7 (8%)</td>
<td></td>
</tr>
<tr>
<td>Dizziness (no.; %)</td>
<td>1 (5%)</td>
<td>5 (6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Nakao et al., 2003 (COOPERATE Trial)</strong>&lt;sup&gt;35&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia (no.; %)</td>
<td>8 (9%)</td>
<td>4 (4%)</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>Dry cough (no.; %)</td>
<td>5 (6%)</td>
<td>1 (1%)</td>
<td>5 (6%)</td>
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inhibitor or ARB therapy. The REIN study examined this among 212 patients with proteinuric renal diseases. The ACE ID genotype did not predict progression in the entire population; however, the D allele, and especially the DD genotype, correlated with a therapeutic advantage for ACE inhibitor therapy (Table 2).

Overall, the work to date has not produced genetic markers useful for predicting susceptibility to or progression of IgA nephropathy. The presence of the D allele could predict a therapeutic response to inhibiting the renin–angiotensin system. The relationship between the M235T and A1161C polymorphisms and the response to ACE inhibitor or ARB therapy has been little studied. Surprisingly, the role of ACE activity in IgA nephropathy has also been little studied.

CONCLUSION
Inhibiting the renin–angiotensin system with ACE inhibitors or ARBs reduces proteinuria in IgA nephropathy and preserves renal function in proteinuric renal diseases. ACE inhibitors and ARBs are probably equally effective. ACE inhibitors and ARBs, used together, are more effective than either agent alone for reducing proteinuria in IgA nephropathy and for preserving renal function in proteinuric renal diseases. Therefore, most patients with proteinuric renal diseases, including IgA nephropathy, should receive these medications together if tolerated.

ACE inhibitors and ARBs are not antiinflammatory. IgA nephropathy is an inflammatory disease. Fish oil, which is probably antiinflammatory but lacks an antiproteinuric component, is, in theory, a natural complement to renin–angiotensin blockade. Immunosuppressive agents are also likely to be complementary.

ADDENDUM
After this paper was submitted, Praga et al. reported a long-term trial in which 44 patients with IgA nephropathy were randomized to receive either an ACE inhibitor or other antihypertensive therapy. The mean follow up was 76 months. The GFR declined 7% in the ACE inhibitor group versus 35% in the control group (P < 0.001). Proteinuria fell 55% in the ACE inhibitor group and increased 18% in the control group (P < 0.001). This trial confirms that the beneficial effects seen with ACE inhibitors among individuals with proteinuric renal diseases apply to those with IgA nephropathy.

REFERENCES

Table 2. Angiotensin Converting Enzyme (ACE) Inhibitors Were More Effective Than Conventional Therapy Among REIN Study Participants Possessing the ACE D Allele

<table>
<thead>
<tr>
<th>ACE Genotype</th>
<th>Reduction in Proteinuria (%)</th>
<th>Relative Risk for End-Stage Renal Disease (ACE Inhibitor/Conventional)</th>
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</thead>
<tbody>
<tr>
<td>II</td>
<td>26.7</td>
<td>0.95</td>
</tr>
<tr>
<td>ID</td>
<td>19.2</td>
<td>0.3 ( P &lt; .01 ) v ACE Inhibitor</td>
</tr>
<tr>
<td>DD</td>
<td>38.2</td>
<td>0.39 ( P = .04 ) v ACE Inhibitor</td>
</tr>
</tbody>
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