The variety of opinion on best treatment for IgA nephropathy (IgAN) intrigues yet concerns because it suggests that the analysis of the evidence is uneven. The expectations of some observers still exceed what has been achieved in the few controlled trials. Although perfection eludes, current data are better than for most nephropathies. Opinion that discourages use of immunosuppressive drugs may deny patients subsequent relief from ESRD.

A 10-yr trial in IgAN demonstrated the value of combined immunosuppressive drugs in reducing renal failure (the most important outcome variable in progressive IgAN). A homogeneous cohort of 38 patients who had mean BP within 10% of current targets and estimated GFR (eGFR) ≥50% normal but losing ≥10% eGFR/yr were randomly assigned; no patient had crescentic disease. Renal survival improved 12-fold at 5 yr, with remission of nephritis by urinalysis. Five years later, however, mistrust of studies using immunosuppressive drugs may deny patients subsequent relief from ESRD.

The paucity of trials during the past decade contrasts with the number of recent reviews, illustrating frustrations in obtaining new, reliable long-term data. Scrutiny and evaluation of other regimens can only be good for patients, but current recommendations are polarized and sometimes changeable, supporting use of corticosteroids when proteinuria exceeds 1 g/24 h. The quality of randomized, controlled trials is substantially influenced by design parameters, so retrospective interpretation using a mathematically insufficient approach is a likely source of discrepancy between reviews. This commentary addresses how disparate opinion may have risen and quantifies existing data to balance recommendations.

Current views range from excluding corticosteroids with or without cytotoxics, even for more progressive IgA disease, to recognition of the efficacy of both, albeit with reservations. One hypothesis even suggests that the benefit of angiotensin-converting enzyme inhibitors (ACEI) might reproduce or surpass those of immunosuppressive drugs. This approach was cited as nihilism, as some data show the effectiveness of corticosteroids alone in reducing ESRD, more so with cytotoxics in severe disease. Logically, in this spirit, reevaluating all trials of immunosuppressive drugs for other immune-mediated nephritides would follow—lupus, membranous, and the vasculitides—because accepted data in these diseases could similarly be suspect, but such data do show that addition of cytotoxics to corticosteroids often improves outcomes.

The issue, perhaps, is scale: the magnitude of avoidance of ESRD and normalization of proteinuria and erythrocytopenia.

The magnitude of primary and secondary benefit using immunosuppressive drugs further begs notice that there are no parallel data using agents modifying glomerular hemodynamics. Even a proponent of immunosuppressive therapy opined recently that in our study, there is need still to “find a safer approach,” yet our treatment schedule used lower total corticosteroid dosages than the previous and current Italian studies, and the only minor and reversible adverse effects were azathioprine related, a cytotoxic central to both studies.

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cyturia using immunosuppressive drugs is unmatched by data from ACEI studies (Figure 1). Only two randomized, controlled trials detailed prevalent BP: in our study of immunosuppressive drugs, mean arterial pressure (MAP), matching in both cohorts at 101 mmHg, was 135/85 or 140/80,1 remark-
ably equal to levels achieved in the ACEI study12; pressures in both were <10% above current recommendations: MAP 92 (125/75). However, the benefits of BP control, more so using ACEI and/or angiotensin receptor blockers (ARB), have an event ratio effect in preserving renal function in IgAN an order of magnitude lower than those of a combined immunosuppressive regimen (Table 1).2 Event ratios have not been a consideration of critics, who claim that minor changes in MAP or effects on glomerular hemodynamic with ACEI could account for trial outcomes, but there is no additional evidence to support that notion.

Long-term remission of proteinuria, 6-fold reduction with combined immunosuppressive drugs, normalizing in those avoiding ESRD, was mirrored by a sustained 20-fold fall in erythrocyturia, compared to controls, to near normal Addis count. ACEI do not improve erythrocyturia,12 and, typically, proteinuria is reduced only 50 to 70% with ACEI or combined ACEI/ARB,13 reversing on withdrawal (Table 1). This striking contrast seems powerful confirmation that only immunosuppressive drugs can induce clinical remission in IgAN.3

Hesitancy to use immunosuppressive drugs in patients who are at high risk for ESRD, corticosteroids with or without cytotoxicos (short-term, low-dose cyclophosphamide, a component considered essential,1 then azathioprine), is understood, as are risks and benefits to be balanced against the morbidity of uremia and renal replacement, including use of other immunosuppressive drugs at transplantation. The issue is similar to membranous and lupus regimens incorporating chlorambucil, cyclophosphamide, or azathioprine. Increasing evidence that corticosteroids are essential in the treatment of IgA disease9 may explain why trials using cytotoxics alone have proved ineffective.6,14

No one really advocates use of immunosuppressive drugs for any low-grade glomerulopathy, likewise, milder IgAN with stable function or <1 g/24 h proteinuria. Nevertheless, for patients losing 10 to 15% eGFR/yr, with ESRD in prospect in less than a decade, immunosuppressive treatment is justifiable. Long-term data to >12 yr of follow-up is under analysis from our original cohort,1 all of whom in the control group progressed to ESRD in half this time. This suggests clear outcome benefit for treated patients, and none developed cyclophosphamide-associated morbidity.

Small, randomized, controlled trials have been insightful. Trials of immunosuppressive drugs and ACEI both entered fewer than 45 patients1,12 but yielded as much information as a larger study of corticosteroids alone.9 Homogeneity within smaller cohorts is essential to achieve interpretation. In such designs, the therapeutic importance of risks and benefits is embedded in effect size or calculated delta (δ), in addition to standard criteria: α = 0.05 (probability that control and treatment groups are dissim-
ilar) and β = 0.2 (achieving 80% power).9 δ calculations also estimate prospectively for a trial under design the outcome ratios that might be expected (Figure 1).

Suggested effect size or δ values for two scenarios are shown in Table 2. When variable data spread is taken into account, the number of patients required increases with the reciprocal of the squared spread of entry data (Table 3). Thus, a narrow range, for example, pa-
tients having rates of decline of renal function within a 30% range or eGFR be-	ween 90 and 60 ml/min, gives a total esti-
mated trial number of 40 to demonstrate a clinically important effect size with one third of patients benefiting, whereas if groups are heterogeneous with 100% spread, then some 400 pa-
tients are needed to realize the same outcome effect. ACEI trials show an effect size δ ≤0.05 to 0.1, whereas in tri-
als using corticosteroids with cytotoxicos, the δ is ≥0.33, nearly an order of
Table 1. Treatment effect and event frequency avoidance ratios: Data for pivotal clinical variables within regimens—ACEI and immunosuppressive drugs

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>ACEI/ARB</th>
<th>Immunosuppressives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria**</td>
<td>50% reduction (ACEI)¹³</td>
<td>45 to 60% decrease (corticosteroids only)⁹,¹⁵e</td>
</tr>
<tr>
<td>Drug effect durability</td>
<td>54 to 73% decrease (ACEI + ARB)¹³</td>
<td>80% decrease (corticosteroids + cytotoxics)¹⁵e</td>
</tr>
<tr>
<td>Hematuria</td>
<td>No benefit: Treated versus controls stated as nil difference¹⁵</td>
<td>Decreased 96%: 23-fold reduction in erythrocyturia¹</td>
</tr>
<tr>
<td>MAP achieved⁶</td>
<td>100 mmHg¹²</td>
<td>101 mmHg¹</td>
</tr>
<tr>
<td>target</td>
<td>92 mmHg</td>
<td>92 mmHg</td>
</tr>
<tr>
<td>Renal function end point³</td>
<td>fractional creatinine rise³</td>
<td>1: 4 at 6 yr¹²</td>
</tr>
<tr>
<td></td>
<td>ESRD</td>
<td>1:1.6 at 5 yr; 1:12 at 10 yr⁶,g</td>
</tr>
<tr>
<td>histologic indices</td>
<td>No data published using ESRD³d</td>
<td>1:12 at 5 yr; ➔ after 6 yr⁶e</td>
</tr>
</tbody>
</table>

Note: MAP from data cited¹²; is approximated. Current recommended target, 125/75, is MAP of 92 H/mHg.

Table 2. Trial risk based on length³

<table>
<thead>
<tr>
<th>Treatment Adverse Effect Risk</th>
<th>Trial δ Values</th>
<th>Spread of Variable Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short Term</td>
<td>Long Term</td>
</tr>
<tr>
<td>Lower</td>
<td>≤0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Higher</td>
<td>≥0.1</td>
<td>≥0.33</td>
</tr>
</tbody>
</table>

**Proteinuria is extrapolated from mean g/24 h data, displayed as a percentage reduction from entry levels to trial completion.

Map from data cited¹²; is approximated. Current recommended target, 125/75, is MAP of 92 H/mHg.

1Ratio of treatment versus controls quoted: Higher ratio implies greater efficacy; ➔ (infinite) ratio: All control patients in ESRD; cohorts were selected for progressive disease.
²Proteinuria is extrapolated from mean g/24 h data, displayed as a percentage reduction from entry levels to trial completion.
³Ratios of treatment versus controls quoted: Higher ratio implies greater efficacy; ➔ (infinite) ratio: All control patients in ESRD; cohorts were selected for progressive disease.
⁴Soft end-point data only (q.v. text).
⁵Maximum proteinuria reduction after 12 mo of treatment.
⁶In three fourths of patients, responders, proteinuria suppressed to NS levels.
⁷50% rise in serum creatinine data at 5 yr cited for comparison (at 10 yr, doubling of serum creatinine was 1:12 for corticosteroids).
⁸Corticosteroids compared with antithrombotic agents: Significance values achieved across a range of histologic indices on repeat biopsies at 1 yr.

magnitude more effective. Smaller trials can thus be powerful tools when entry cohorts are homogeneous, minimizing exposure to treatments with more adverse effects, although extending their findings a priori to patients with a different clinical status than those in the trial is imprudent.

“Soft” end-point data in ongoing trials suggest temporizing before firm conclusions are drawn. For example, alteration in glomerular hemodynamics, a benefit of ACEI, contrasts with vasodilator effects of glucocorticoids on microcirculation; by improving glomerular flow, the latter may induce transient improvements in serum creatinine or eGFR, probably not sustained beyond 1 yr. Thus, current trials with end points of 50% rise or doubling of serum creatinine also do not confirm preservation of renal tissue. Few trials have used incontrovertible end points of ESRD or repeat biopsy to assess glomerular or interstitial scarring, but those that have should be afforded greater appreciation, an important issue not addressed in subsequent critiques.²–⁵ Enthusiasm for ACEI is justifiable because of negligible adverse effects, but short-term benefits are not yet consolidated into “hard” end-point data. Until those are available, the only data proving renal preservation in IgAN are found in trials using immunosuppressive drugs.¹,⁹,¹⁵

Should we treat the disease, glomerular/interstitial inflammation, or only its sequelae, hypertension and disordered hemodynamics? This dichotomy epitomizes arguments surrounding use of immunosuppressive drugs versus ACEI/ARB. Accepting parallels between the pathogenesis of IgAN and other immune-mediated nephropathies enhances the case for using immunosuppressive regimens. Autoimmunity and selective, exuberant expression of inflammatory mediators are implicated in IgAN. This concept of pathogenesis is not held by some to whom IgA disease is a “mucosal serum sickness” or an immunodeficiency disease with impaired formation and clearance of immune complexes. Inertia in thinking may thus also explain resistance in accepting cytotoxic drugs for treatment of...
IgA subgroups. Future trials in IgAN might reveal that ACEI/ARB concurrent with immunosuppressive drugs in appropriate subgroups is optimal, but that design has not yet been studied in any nephropathy. The current dichotomy now argued may thus prove one that is false. An algorithm (Figure 2) summarizes treatment recommendations for different degrees of IgAN, derived from quantitative analysis of the current evidence, with a priori, low δ modification.

The transformation in outcomes using corticosteroids with cytotoxics in lupus, membranous, and also ANCA-positive small vessel vasculitis may be no different from those emerging in IgAN. Therapeutic errors of omission—avoiding immunosuppressive drugs in suitable patients—are as flawed as errors of commission, were milder disease types to be treated with more than ACEI/ARB.

IgAN? “It’s a lot like lupus” (J.V. Donadio, MD [retired, previously of the Mayo Clinic, Rochester, MN], personal communication, February 18, 2007). We should treat it as such, but primum non nocere,16 proportional to its severity, with consideration of clear risks and benefits of treatments. Otherwise, patients may be deprived of good opportunity to avoid ESRD from progressive disease.

**REFERENCES**