Quantitative Appraisal of Treatment Options for IgA Nephropathy

Francis W. Ballardie

Department of Nephrology, Manchester Royal Infirmary, Manchester, United Kingdom

ABSTRACT

IgA nephropathy has an impact on renal health care costs worldwide. The paucity of good clinical trials highlights the uncertainty in determining best treatment and for how long. Ongoing debate still raises questions on why opinions vary but may suggest that current data are not fully understood. The scale of benefit of immunosuppressive drugs in suppressing clinical nephritis or improving outcome is unmatched by use of renin-angiotensin inhibitors alone. By minimizing the use of immunosuppressive drugs, higher risk patients may hazard more ESRD. This review addresses how disparate views have formed, quantifying existing data, to give balance to recommendations.


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\(^1\) demonstrated the value of combined immunosuppressive drugs in reducing renal failure (the most important outcome variable in progressive IgAN).\(^2\) A homogeneous cohort of 38 patients who had mean BP within 10% of current targets and estimated GFR (eGFR) \(\geq 50\)% normal but losing \(\geq 10\) GFR/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 in these patients continues.\(^3-5\)

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,\(^1\) there is need still to “find a safer approach,”\(^6\) 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.

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\(^4\) or denying\(^6-7\) use of corticosteroids when proteinuria exceeds 1 g/24 h. The quality of randomized, controlled trials is substantially influenced by design parameters,\(^8\) 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,\(^7\) to recognition of the efficacy of both, albeit with reservations.\(^3\) 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,\(^6\) as some data show the effectiveness of corticosteroids alone in reducing ESRD,\(^9\) more so with cytotoxics in severe disease.\(^1,2,8\) Logically, in this spirit, reevaluating all trials of immunosuppressive drugs for other immune-mediated nephritides would follow—lupus,\(^10\) membranous,\(^11\) 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 erythro-

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

Correspondence: Dr. Francis W. Ballardie, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK. Phone: +44-161-276-4148; Fax: +44-161-276-4129, E-mail: francis.ballardie@cmmc.nhs.uk or francisballardie@mail.com

Copyright © 2007 by the American Society of Nephrology

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 resembling treatment with ACEI could account for 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 patients11,12 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 dissimilar) 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, patients having rates of decline of renal function within a 30% range or eGFR between 90 and 60 ml/min, gives a total estimated 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 patients are needed to realize the same outcome effect. ACEI trials show an effect size δ = 0.05 to 0.1, whereas in trials using corticosteroids with cytotoxics, the δ is ≥0.33, nearly an order of
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 and immunosuppressive drugs.

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)</td>
<td>45 to 60% decrease (corticosteroids only)</td>
</tr>
<tr>
<td>Drug effect durability</td>
<td>54 to 73% decrease (ACEI + ARB)</td>
<td>80% decrease (corticosteroids + cytotoxics)</td>
</tr>
<tr>
<td>Reverses on withdrawal</td>
<td></td>
<td>Sustained (5 to 10% relapses reported &gt;2 yr; reversible remissions)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>No benefit: Treated versus controls stated as nil difference</td>
<td>Decreased 96%: 23-fold reduction in erythrocyturia</td>
</tr>
<tr>
<td>MAP achieved</td>
<td>100 mmHg</td>
<td>101 mmHg</td>
</tr>
<tr>
<td>target</td>
<td>92 mmHg</td>
<td>92 mmHg</td>
</tr>
<tr>
<td>Renal function end pointc</td>
<td>1: 4 at 6 yr</td>
<td>1:1.6 at 5 yr; 1:12 at 10 yr</td>
</tr>
<tr>
<td>fractional creatinine risesd</td>
<td>No data published using ESRD</td>
<td>1:12 at 5 yr; &gt; after 6 yr</td>
</tr>
<tr>
<td>ESRD</td>
<td>Improved at 1 yr</td>
<td></td>
</tr>
</tbody>
</table>

aProteinuria is extrapolated from mean g/24 h data, displayed as a percentage reduction from entry levels to trial completion.
bMAP from data cited12; is approximated. Current recommended target, 125/75, is MAP of 92.
cRatios of treatment versus controls quoted: Higher ratio implies greater efficacy; = (infinite) ratio: All control patients in ESRD; cohorts were selected for progressive disease.1

d“Soft” end-point data only (q.v. text).
eMaximum proteinuria reduction after >12 mo of treatment.
fIn two thirds of patients, responders, proteinuria suppressed to NS levels.
g50% rise in serum creatinine data at 5 yr cited for comparison (at 10 yr, doubling of serum creatinine was 1:12 for corticosteroids).
hCorticosteroids compared with antiplatelet agents: Significance values achieved across a range of histologic indices on repeat biopsies at 1 yr.

Table 2. Trial risk based on length

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adverse Effect Risk</th>
<th>Trial α Values</th>
<th>Spread of Variable Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short Term</td>
<td>Long Term</td>
<td>m value</td>
</tr>
<tr>
<td>Lower</td>
<td>≤0.1</td>
<td>0.1</td>
<td>30%</td>
</tr>
<tr>
<td>Higher</td>
<td>≥0.1</td>
<td>≥0.33</td>
<td>100%</td>
</tr>
</tbody>
</table>

aSuggested effect size, α, values, consistent with ethically acceptable risk-benefit. Ideally, α (0.33) equates to one third or more treated patients benefiting when there might be adverse effects, whereas a α value of 0.1 (one tenth of patients benefiting from a given treatment) is not; a value of 0.1 is, in contrast, ethical when adverse effects are minimal. Likewise, short-term use of potentially higher adverse-effect treatments might be acceptable when α is one tenth but not for long-term regimens.

Table 3. Trial cohort size and entry patient data homogeneity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Spread of Variable Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>m value</td>
<td>30% 20 100 200</td>
</tr>
</tbody>
</table>

aNumbers to achieve satisfactory outcome analysis using α (0.05), β (0.08), and α (Table 2) parameters. These parameters are related by the equation m = 15.7α², the effect of which using these widely accepted α and β values is shown. M, number of patients required in each arm of controlled trial to achieve a statistically significant outcome, Δ, the standardized difference between groups (this equals the difference of mean values of, for example, rates of eGFR loss or serum creatinines, whichever is the determining trial entry criteria or variable, divided by SD of data values in the two groups).
Figure 2. An algorithm of recommended treatment options for IgAN. **Therapy with efficacy of evidence base grade 1 data; *therapy with high a priori evidence to use but not tested independently in randomized, controlled trials; ††remission in erythrocyturia and proteinuria, follow no <6 and 12 mo, respectively, after starting immunosuppressive drugs; **there is no evidence that immunosuppressive drugs can benefit declining function in patients starting therapy with >50% loss in GFR. Broken lines denote less frequently encountered scenarios.

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—were as flawed as errors of commission, were 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,* 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.

DISCLOSURES
None.

REFERENCES