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Quantitative Appraisal of Treatment Options for IgA Nephropathy

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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.

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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) ≥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 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.[5] 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-

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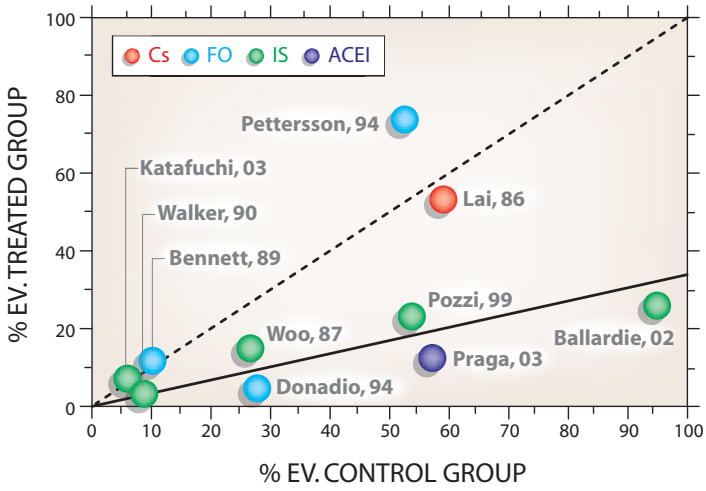

Figure 1. The relative efficacies of IgAN treatment options in randomized, controlled trials. Results are displayed as a percentage of events (renal dysfunction or failure: *q.v.* text) for treatment *versus* controls. Thus, an equal ratio, the broken line shows equivalence of events in both groups and no net effect. Below the broken line is increasing treatment effectiveness; the solid line is for reference and is not intended to suggest equivalence of ratios for therapy options. As data extend along the *x* axis to 100% of events in controls, it suggests increasing certainty of results with a higher evidence base grade, (1 (c) toward (b) or (a)).[8] Cs, cyclosporine; FO, fish oils; IS, immunosuppressives (corticosteroids with or without cytotoxics); data for IS and ACEI also displayed numerically in Table 1. Reprinted from Laville and Alamartine,[2] with permission.

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] remarkably equal to levels achieved in the ACEI study[12]; 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.[1]

Hesitancy to use immunosuppressive drugs in patients who are at high risk for ESRD, corticosteroids with or without cytotoxics (short-term, low-dosage 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 disease[9] may explain why trials using cytotoxics alone have proved ineffective.[8,14]

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 patients[1,12] 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: $\alpha = 0.05$ (probability that control and treatment groups are dissimilar) and $\beta = 0.2$ (achieving 80% power).[8] 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 $\delta \leq 0.05$ to 0.1, whereas in trials using corticosteroids with cytotoxics, 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

Outcome Variable	ACEI/ARB	Immunosuppressives
Proteinuria[a]	50% reduction (ACEI)[13]	45 to 60% decrease (corticosteroids only)[9,15e]
Drug effect durability	54 to 73% decrease (ACEI + ARB)[13]	80% decrease (corticosteroids + cytotoxics)[1e,f]
	Reverses on withdrawal	Sustained (5 to 10% relapses reported >2 yr; re-inducible remissions[9]
Hematuria	No benefit: Treated *versus* controls stated as nil difference[12]	Decreased 96%: 23-fold reduction in erythrocyturia[1]
MAP		
achieved[b]	100 mmHg[12]	101 mmHg[1]
target	92 mmHg	92 mmHg
Renal function end point[c]		
fractional creatinine rises[d]	1: 4 at 6 yr[12]	1:1.6 at 5 yr; 1:12 at 10 yr[6,g]
ESRD	No data published using ESRD[d]	1:12 at 5 yr; ∞ after 6 yr[1c]
histologic indices	–	Improved at 1 yr[15h]

[a]Proteinuria is extrapolated from mean g/24 h data, displayed as a percentage reduction from entry levels to trial completion.
[b]MAP from data cited[12]; is approximated. Current recommended target, 125/75, is MAP of 92
[c]Ratios 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).
[e]Maximum proteinuria reduction after >12 mo of treatment.
[f]In two thirds of patients, responders, proteinuria suppressed to NS levels.
[g]50% rise in serum creatinine data at 5 yr cited for comparison (at 10 yr, doubling of serum creatinine was 1:12 for corticosteroids).
[h]Corticosteroids compared with antiplatelet 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[8]; by improving glomerular flow, the latter may induce transient improvements in serum creatinine or eGFR, probably not sustained beyond 1 yr.[8] 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,[15] but those that have should be afforded greater appreciation,[8] an important issue not addressed in subsequent critiques.[3–5] 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.[8] 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

Table 2. Trial risk based on length[a]

Treatment Adverse Effect Risk	Trial δ Values	
	Short Term	Long Term
Lower	≤0.1	0.1
Higher	≥0.1	≥0.33

[a]Suggested effect size, δ, values, consistent with ethically acceptable risk-benefit.[8] Ideally, δ (0.33) equates to one third or more treated patients benefiting when there might be adverse effects, whereas a δ value of 0.1 (one tenth of patients benefiting from a given treatment) is not; a δ 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 δ is one tenth but not for long-term regimens.

Table 3. Trial cohort size and entry patient data homogeneity[8a]

Parameter	Spread of Variable Data	
	30%	100%
m value	20	200

[a]Numbers to achieve satisfactory outcome analysis using α (0.05), β (0.8), and δ (Table 2) parameters. These parameters are related by the equation $m = 15.7/\Delta^2$, 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).

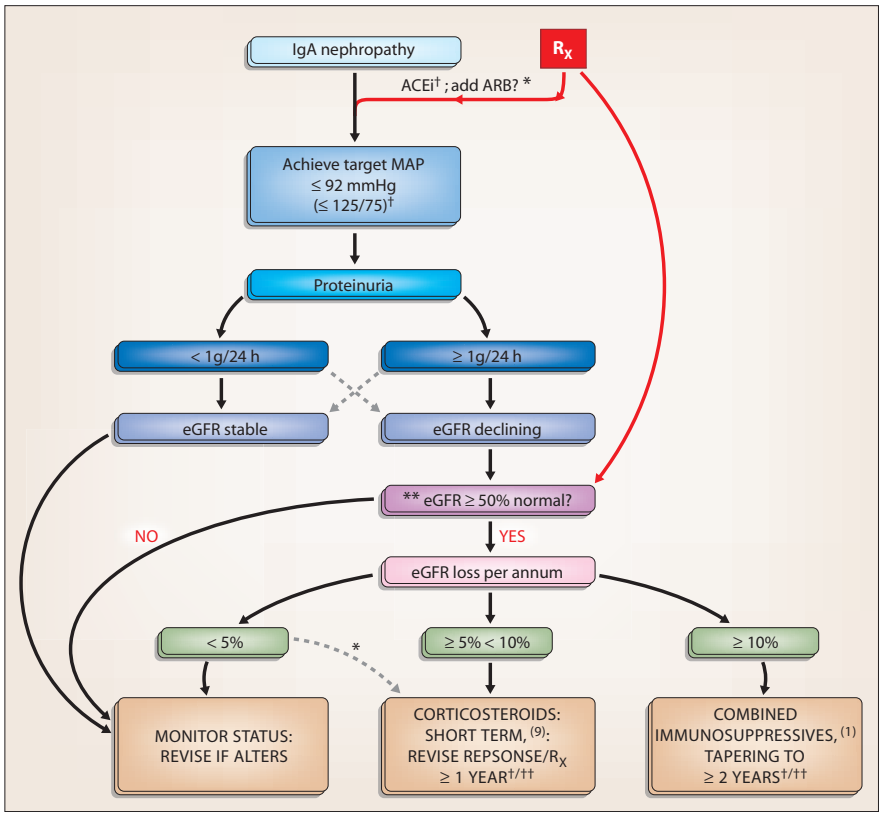

Figure 2. An algorithm of recommended treatment options for IgAN. †Therapy with efficacy of evidence base grade 1 data; *therapy with high *a priori* evidence to use but not tested independently in randomized, controlled trials; ††remission in erythrocyturia and proteinuria, follow no <6 and 12 mo, respectively, after starting immunosuppressive drugs[1]; **there is no evidence that immunosuppressive drugs can benefit declining function in patients starting therapy with >50% loss in GFR.[1] 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—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.

DISCLOSURES

None.

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