IgA nephropathy treatment 25 years on: can we halt progression? The evidence base

Francis W. Ballardie

Department of Nephrology, Manchester Royal Infirmary, Manchester, UK

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Introduction

Berger’s disease, considered benign in the classic descriptions and for a decade, is perhaps the most challenging primary glomerulonephritis in which to evaluate pathogenesis, its impact on renal services and to discover effective treatments for progressive forms, yet these remain inchoate 25 years after the first trial constructs [1]. A wide variety of treatments has been attempted [2] and most facets of immune perturbations, blood rheology, glomerular inflammation and haemodynamics addressed. Three reasons suggest why we remain perplexed: (i) the timescale of progression of commoner forms (a decade or more) means studies have addressed parameters, notably proteinuria, rather than loss of glomerular filtration rate (GFR) using ‘soft’ end-points (those subject to haemodynamic variables modifying residual function); (ii) studies in a disease as heterogeneous merit careful design, incorporating probability modelling to address pivotal questions, most importantly, retarding progression ‘primum non nocere’ [3]; and (iii) broad concepts of pathogenesis encompass a failure in immune system competence, to, in contrast, one analogous to systemic lupus erythematosus – these disparate views or perceptions that disease immune mechanisms resist abrogation, have broadened the approach to treatments.

Trial strategies and evidence-base standards

Treatment decisions critically depend on whether data have been evaluated for comparable patient groups and whether benefit–risk analyses justify drug use. Evidence-base standardization [4–6] is an increasingly important framework, with scrutiny of the literature showing that only 13 trials of IgA nephropathy (Table 1) meet the criteria of grades 3b–1a [4–6]. For a prevalent disease with such impact, this might be considered extraordinary, but it reflects frustrations presented by the disease. Recent trials have improved our understanding. These and others meeting minimum criteria are examined in this precis.

Trial design in IgA nephropathy: small can be beautiful

Often undervalued is the clinical importance of a tested therapy, the delta effect (δ) [7], which is additional to standard criteria of α = 0.05 (probability control/treatment groups are dissimilar) and β = 0.2 (80% power). The risks of a treatment and its potential benefits in preserving renal function are embedded in the δ-value of a trial. Ideally, δ equates to one-third or more patients treated benefiting when there might be side effects. A δ-value of one in 10 (one-tenth of patients benefiting from a given treatment) is hardly acceptable if that treatment conveys significant side effects, but one-tenth is ethical when side effects are minimal. Likewise, short-term use of potentially higher side-effect treatments might be accepted where δ is one-tenth, but not when long-term use of such drugs is intended.

Implicit in trial design, and hence numbers to achieve satisfactory outcome analysis using these α, β and δ parameters, is homogeneity of data within patient cohorts. These parameters are related for the foregoing, widely accepted α- and β-values, by the equation:

\[ m = \frac{15.7}{\Delta^2} \]

where \( m \) is the number of patients required in each arm of the controlled trial and \( \Delta \) is the standardized difference between groups [the difference of mean values (of, for example, serum creatinines or GFRs) ÷ SDs of the data values in the two groups].

Correspondence and offprint requests to: F. W. Ballardie, Consultant Physician and Nephrologist, Department of Nephrology, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK. Email: francis.ballardie@cmmc.nhs.uk

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In practice, what this means is the number required in each arm of the trial to achieve a statistically significant answer increases with the reciprocal of the squared spread of patients' data. Data spread of a narrow range (30%), e.g. patients at entry having impaired GFRs between 90 and 60 ml/min or, alternatively, the reciprocal of serum creatinine (a function closely related to calculated clearances), gives total trial numbers of only 40 to demonstrate a clinically important do of one-third of patients benefiting. If groups are heterogeneous with 100% spread, then some 400 patients are needed to realise the same outcome analysis. Furthermore, many patients in the latter scenario might have received the treatment in question unnecessarily.

Small carefully designed trials with homogeneous cohorts of patient or disease characteristics can, thus, provide powerful tools to address a treatment issue. Heterogeneity in IgA nephropathy has not lessened the task of providing clarity in patient treatment trials.

### Treatments: immunomodulatory

**Corticosteroids**

Glucocorticoids, the widest studied immunmodulatory drugs, not only have anti-inflammatory properties and modify inflammatory cell function, but are also vasoactive compounds influencing glomerular microdynamics. They induce renal blood flow consistent with nitrous oxide and prostaglandin, but not angiotensin-II receptor block-dependent efferent arteriolar dilatation [8]. Study end-points, such as 50% or doubling of serum creatinine or other GFR measures, are placed in doubt as reliable parameters of whether corticosteroids genuinely preserve renal function by means of lessening morphological deterioration or if the short-term benefit merely reflects haemodynamics. Data examination in several studies, cited as follows, suggests a characteristic profile of short-term improvements (< 1 year) in GFR-related measurements may be influenced by these transient changes. Trials unaffected by these ambiguities employ ‘hard’ end-points [end-stage renal failure (ESRF)] or use repeat biopsy data.

In one study, 86 patients entered into a 5-year randomized controlled trial (RCT) [9] in a detailed analysis of partial and optimal reductions in proteinuria. The most likely achievable end-point from the trial design used showed improvement on average, with all entrants having either normal or marginally impaired (serum creatinine <132 µmol/l) renal function. At 10-year follow-up [10], improvements in proteinuria on average were sustained. Those with resistant proteinuria progressed. Proteinuria relapsed in 13, withdrawn, violating protocol. Hypertension

### Table 1. IgA nephropathy trials employing controls

<table>
<thead>
<tr>
<th>Rx</th>
<th>Reference</th>
<th>Disease form</th>
<th>Outcome Progression (evidence grade)</th>
<th>Proteinuria (Prot)/haematuria (Haem)</th>
<th>Distinguishing features</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>[9]</td>
<td>M/S</td>
<td>1b–</td>
<td>(Prot) 1a</td>
<td>6 month Rx; 5 year benefit; entry GFR normal; 0/43 ESRF Rx vs 3/43; 13% ACE</td>
</tr>
<tr>
<td>P</td>
<td>[10]</td>
<td>M/S</td>
<td>1b–</td>
<td>(Prot) 1a</td>
<td>10 year follow-up [10]; benefit sustained 1/43 Rx vs 13/43 double SeCr; ACE increased to 50%</td>
</tr>
<tr>
<td>P</td>
<td>[11]</td>
<td>M/S</td>
<td>1c</td>
<td>(Prot) 1a</td>
<td>Steroids low dose; trial not powered to detect ’δ’ (q.v.) GFR effect</td>
</tr>
<tr>
<td>P</td>
<td>[17]</td>
<td>(S)</td>
<td>N/A</td>
<td>1a</td>
<td>Repeat biopsy data (1a)</td>
</tr>
<tr>
<td>P + C</td>
<td>[19]</td>
<td>M</td>
<td>3a</td>
<td>3a</td>
<td>Retrospective; low dose; 31% ACE inhibitors</td>
</tr>
<tr>
<td>P + Az</td>
<td>[20]</td>
<td>(S)</td>
<td>3a</td>
<td>1a</td>
<td>Repeat biopsy data (1a); all H + W + D</td>
</tr>
<tr>
<td>P + C, Az</td>
<td>[21]</td>
<td>M–M/R</td>
<td>1a–</td>
<td>(Prot) and (Haem) 1a</td>
<td>RCT study addressed Rx efficacy to ESRF; BP data; 20% ACE; for SeCr &lt;250 µmol/l</td>
</tr>
<tr>
<td>P + C</td>
<td>[22]</td>
<td>M/R</td>
<td>2b–</td>
<td>N/A</td>
<td>Small short-term Rx; end-point double SeCr; non-RCT; few normal entry GFR; no ACE</td>
</tr>
<tr>
<td>C + P</td>
<td>[23]</td>
<td>M/R</td>
<td>2b–</td>
<td>N/A</td>
<td>‘Controls’ are pre-Rx patients</td>
</tr>
<tr>
<td>MMF</td>
<td>[24,25]</td>
<td>M</td>
<td>1c</td>
<td>1a</td>
<td>RCT; controls steroid Rx; not powered for GFR</td>
</tr>
<tr>
<td>P + T</td>
<td>[26]</td>
<td>N/A</td>
<td>3b–</td>
<td>(Prot) 3b–</td>
<td>Tonsillectomy subjective; not randomized; 13/118 received P + C/Az</td>
</tr>
<tr>
<td>T</td>
<td>[30]</td>
<td>S</td>
<td>3b–</td>
<td>N/A</td>
<td>RCT of CRF; 131/336 had IgA nephropathy; end-point doubling SeCr</td>
</tr>
<tr>
<td>ACE</td>
<td>[31]</td>
<td>S</td>
<td>1b</td>
<td>(Prot) 1a</td>
<td>RCT; end-point 50% SeCr rise</td>
</tr>
<tr>
<td>ACE/AII</td>
<td>[32]</td>
<td>S</td>
<td>2a/b</td>
<td>(Prot) 1c–/2a</td>
<td>RCT of CRF; 131/336 had IgA nephropathy; end-point doubling SeCr</td>
</tr>
</tbody>
</table>

Evidence-base grades are [4–6]: 1a, RCT, cohort homogeneity; 1b, RCT, lesser homogeneity but narrow confidence limits; 1c, non-RCT, ‘all-or-none’ case series; 2a, homogeneous cohort, may be retrospective; 2b, individual cohort study or poor adherence RCT; 3a/b, study with homogeneity/case-control study.

*Disease progression form based on estimated from normal GFR to ESRF. S, slow (>10 years); M, moderate (5–10 years); M/R, moderate/rapid (<5 years); R, rapid (<1 year). SeCr, serum creatinine; N/A, not applicable; Rx (P, prednisolone; C, cyclophosphamide; Az, azathioprine; MMF, mofetil mycophenolate; ACE, angiotensin-converting enzyme inhibitors; AII, angiotensin-receptor blockers); T, tonsillectomy; H, heparin; W, warfarin; D, dipyridamole.
(>140/90 mmHg) did not differ between groups and the use of angiotensin-converting enzyme (ACE) inhibitors was 14% initially, increasing to 50% in both groups. Only one of 43 corticosteroid-treated patients had doubled serum creatinine, compared with 13 controls. Notable is the short-term (6 months) corticosteroid treatment conferring long-term benefit in progression and proteinuria. Improved outcome is explicable only by steroid effects and the study also suggested cause and effect insight into the dependence of GFR loss on proteinuria. In contrast are one controlled study using low-dose prednisolone [11] and three earlier uncontrolled trials, where either preservation of GFR could not be shown [12,13] or short-term improvement was likely a result of vasoactive effects of glucocorticoids [14]; similar concerns apply to a recent case-control study [15]. Another 10 year trial [16] (not randomized, entry selected by proteinuria) for choice of steroids vs controls placed doubt on GFR data. Preservation in glomerular morphology was demonstrated in repeat biopsy studies of 21 patients selected from 319, randomized to receive prednisolone (tapering to 10 mg alt. dieb.) vs dipyridamole [no ACE inhibitors were permitted and blood pressure (BP) data were included] [17]. All retained normal renal function.

Cytotoxics

Combined with corticosteroids. Data published in 2002–2004 reveal firm new ground for optimism: meta-analysis, peculiarly susceptible to vagaries of interpretation in a heterogeneous disease, had earlier suggested no benefit of steroids with cytotoxics [18]. Forty-five patients with impaired function in a retrospective study may have had decline in GFR slowed after they received cyclophosphamide with prednisolone [19]. Prednisolone with azathioprine and antiplatelet agents provided no evidence of efficacy [26,27]. Efficacy of low-dose steroids with cyclophosphamide in 21 patients with more rapid progression is suggested in a recent case-control study [23]. Mycophenolate to date has proved elusive [24,25], although one RCT of 62 patients with more severe grades on biopsy showed similar benefit in proteinuria and repeat biopsy compared with steroid-treated controls, but the trial was not powered to reveal differences in progression: current trials may add to initial findings.

Cytotoxics as sole immunosuppressive. Early non-randomized studies of cyclophosphamide with antithromboproteins provide no evidence of efficacy [26,27].

Tonsillectomy

The evidence base does not exceed category 3. Patients with concurrent diabetes mellitus and borderline impaired function showed improvements when corticosteroids were combined with tonsillectomy [28]. A non-randomized study on patients with normal renal function using prednisolone and antiplatelets, repeating biopsies [29], and a retrospective study with steroids (tonsillectomy being physician-led) did not prove GFR loss could be slowed [30].

Modifying glomerular microdynamics

ACE inhibitors and angiotensin-II receptor blockers

Broad acceptance that ACE inhibitors or angiotensin-II receptor blockers are effective antiproteinurics and that reduction in proteinuria per se is important in minimizing glomerular injury, is tempered by the knowledge that they are unlikely to modify primary immune-mediated nephritic processes and, until recently, lack of prospective trial evidence that ACE inhibitors might retard progression. Using 50% serum creatinine rise as an end-point, a randomized study of 44 patients with slow progression disease [31] confirmed significant benefit to 7 years. Within a ACE/angiotensin-II receptor blocker study over 3 years [32], the minority of IgA nephropathy patients included are not known to have benefited, since design heterogeneity precludes scientific conclusion. In these studies, provided that ESRF ‘hard end-point’ data bear out this early analysis, and it does not simply represent the phenomenon of vasoactive compounds retarding a protean measure of a small serum creatinine rise, then ACE inhibitors will become a mainstay of treatment for most disease forms for reasons of low side-effects, as they have for diabetic nephropathy.

Fish oils

Initial optimism for this treatment with anti-inflammatory and glomerular dynamic modulation and minimal side effects is negated by meta-analysis [33].
Subsequent trials, described most recently in 2003 by the South West Paediatric Group comparing omega-3 oils with alternate-day prednisolone 60 mg and placebo in higher-risk nephrotic IgA disease patients [34] also suggested neutral effect, further analysis of these trials is excluded from this review.

**Treating cause, and consequences, of IgA nephropathy: balancing the issues**

There is no treatment panacea for progressive IgA nephropathy and deciding therapeutic options remains based on inexact science. Nevertheless, scepticism that the disease is ‘incurable’ or that small reductions (<10%) in BP [35] could explain or nullify the substantial outcome improvements – progression, proteinuria and urinary sediment – due to immunosuppressive treatments in several recent trials (Table 1) does not do justice to the quality of the evidence published. Is the evidence now available to decide therapeutic options in IgA disease inferior to that for lupus or membranous nephropathy? The current issue for our choices is which clinical disease types should receive which form of treatment?

There is a spectrum of indication to introduce therapies, according to IgA disease clinical expression and progression type (Table 1). Ethical considerations may deny the use of immunosuppressives when renal function is normal: recent repeat biopsy studies, cited, include evidence grade la that glomerular scarring can be ameliorated using corticosteroids, even in patients with normal renal function, and that long-term function was improved (grade lb); but is this justifiable? When patients have associations of poor prognosis (microscopic haematuria only, heavier proteinuria, hypertension, renal function impaired at presentation), adverse biopsy appearances are likely present; however, if the latter is not recent, the appearance may have changed. In practice, it may be simpler to suggest that all patients, even if normotensive, should receive ACE inhibitors at presentation (evidence grade la for proteinuria reduction and 1b for progression) and that addition of immunosuppressives should be considered as soon as renal function declines in the presence of good BP control.

A barrier to wider acceptance of the evidence base for immunosuppressives has been, in part, not only hesitancy in conceptualizing that IgA nephropathy has parallels in pathogenesis with lupus nephritis [2,36], but that constructing the evidence base has been problematic. Similarities within the diverse spectrum of immune system perturbations of the two diseases include evidence of systemic immune system hyperactivity, immune-complex formation (albeit with distinct profiles and immunoglobulin isotypes), autoimmunity and exuberant but restricted in profile cytokine production from monocytes and other cell sources [37,38]. In modifying broad concepts of pathogenesis together with recent clinical trials data defining benefits and morbidity of immunosuppressives in IgA nephropathy, the issue is now more clearly defined as why progressing IgA disease should not be treated as we would treat middle-grade lupus nephritis?

‘Incurable’ diseases generally have found haven and improved morbidity in treatments from multiple simultaneous avenues of therapy, which have proved to be synergistic in clinical trials. Clearly, treatment with ACE inhibitors to minimize glomerular filtration-related injury is essential, but, where justified in the context of trial data and established practice, we should treat the disease cause and not merely its consequences.

**Recommendations for progressive IgA nephropathy**

In the absence of direct benefit–risk comparisons of potentially complementary therapies (immunosuppressives and ACE inhibitors) in IgA disease types and since definitive end-point data will take time to construct in future trials, weighting the current evidence-base towards categories 1a and 1b (grade A evidence [6]), achieved in recent trials, suggests that the recommendations should be as follows.

**Moderate progressive disease**

In moderate progressive disease, loss of normal GFR progresses to ESRF in <10 years and serum creatinine rises 8–15% per annum.

The evidence cited supports that disease pathogenesis should be treated. Corticosteroids are justified short-term (6 months) or medium-term, cautiously adding cyclophosphamide (for 3 months) followed by azathioprine (both at 1.5 mg/kg/day) for projected ESRF at <7 years. Cytotoxics might also be considered or when proteinuria does not improve within 12 months after starting steroids, in the 8–10+ years to ESRF patients, but there are no data currently available on benefit and risk in that group.

Cytotoxics with steroids are only of proven value, however, in patients treated before there is loss of >40% GFR and where serum creatinine is <250 μmol/l. There are no data to answer whether concurrent ACE inhibitors further improve immunosuppression-dependent containment of glomerular inflammation. A priori, addition of ACE inhibitors is prudent, to achieve BPs ≤125/75 mmHg [39,40].

For more rapidly progressing disease [ESRF in 1–2 years and true rapidly progressive glomerulonephritis (ESRF <1 year)], intermediate category evidence (2b) suggests treatment with steroids and cytotoxics is correct, but with indeterminate outcome probability.

**Slowly progressive disease**

Where there is progression to ESRF in >10 years and serum creatinine rises up to 7% per annum, ACE
therapy is appropriate with tight BP control at <125/75 mmHg. The data [10] on corticosteroid treatment (80 mg/day reducing to nil over 6 months with long-term benefit) also support this therapy is justified: evidence grade 1a for proteinuria >1–1.5 g/day and 1b– for reducing progression.

There is no evidence base in these disease types that any treatment is effective once >50–60% of GFR is lost (approximately, serum creatinine >250 μmol/l), so patients should not be exposed to immunosuppressives beyond this degree of renal failure. Although reduction in glomerular scarring is apparent when patients receive corticosteroids where renal function is normal, there is a higher risk of progression with moderate proteinuria and, infection is present, many physicians might find it difficult to justify corticosteroid use to patients before renal function started to decline. However, progressive rises in creatinine within ‘normal range’ (e.g. 70–110 μmol/l) in the presence of BP control at ≤125/75 mmHg, with recent biopsy showing early but adverse characteristics, indicates that the corticosteroid regimen is appropriate [10]. No firm conclusions have been reached on whether early immunosuppressives (cyclophosphamide then azathioprine) with corticosteroids, introduced as soon as creatinine rises above 130 μmol/l, confers advantage in probability of success in a patient [21], but it is rational to use this combination early in the disease course once there is clear evidence of progression in a patient with good BP control and in the absence of other causes, including overt or occult infection.

Future trials: short-term therapy, long-term benefit?

There is a need for rigorous, evidence-base category 1 studies examining the role of immunosuppressives combined with modifiers of glomerular scarring mechanisms in progressive disease, with clear delineation of benefit and risk. Future trial design may allow smaller patient numbers. The intriguing but crucial issue [10,21] that immune-mediated glomerular injury might be modulated long-term with short-term immunosuppressives warrants closest scrutiny. Multiple therapeutic avenues, with trials using concurrent ACE/angiotensin-II receptor blockers, adding immunosuppressives for appropriate, homogeneous disease cohorts, are needed. Time to construct data for this indolent, intriguing disease will control our endeavours.

Conflict of interest statement. None declared.

References

Sodium, blood pressure and cardiovascular pathology: is it all volaemia?

Jeroen P. Kooman, Frank M. van der Sande and Karel M. L. Leunissen

Department of Internal Medicine/Nephrology, University Hospital Maastricht, Maastricht, The Netherlands

Keywords: dialysis; hypertension; nitric oxide; oxidative stress; renal failure; sodium

Introduction

The daily intake of salt in the western world greatly exceeds human needs, which may have adverse cardiovascular consequences, especially in patients with abnormalities in renal sodium handling. In normotensive subjects, the effects of salt intake on blood pressure appear to be relatively small [1]. However, a large subset of patients with essential hypertension responds to salt loading and restriction with pronounced changes in blood pressure, which has led to the concept of salt sensitivity [2].

Patients with end-stage renal disease are very susceptible to the adverse effects of salt, as their ability to excrete sodium is lost or greatly impaired. In these patients, sodium loading may lead to severe hypertension and left ventricular hypertrophy. It is generally accepted that in renal patients, the adverse effects of salt are predominantly due to a combined water and sodium overload due to the fact that the body tries to maintain the osmolarity of the extracellular compartment. However, in parallel to salt-sensitive patients with...