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Aspects of IgA Nephropathy

Clinical Issues and Treatment

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Abstract

IgA nephropathy (IgAN is the commonest chronic glomerular disease .It is a mesangial proliferative glomerulonephritis (GN) characterised by the predominant deposition of IgA in the glomerular mesangium with very variable histopathological injury and clinical presentations. A substantial minority of patients will however develop progressive chronic kidney disease and eventually require renal replacement therapy. Treatment of progressive IgAN requires tight blood pressure control with renin-angiotensin blockade to minimise proteinuria. The role of immunosuppressive treatment remains unproven.

Epidemiology & clinical features

The diagnosis of IgAN always requires renal biopsy. No clinical presentation is diagnostic, not even the typical young male with episodic macroscopic haematuria following an upper respiratory tract infection, which is the presenting feature in 30-40% of cases. Most patients only have a few episodes of frank haematuria and such episodes usually recur for a few years at most.

Asymptomatic urine testing identifies 30-40% of patients with IgAN; it is very rare for proteinuria to occur without microscopic haematuria. Nephrotic syndrome is uncommon, occurring in only 5% of all patients, but is more common in children and adolescents. Patients may develop nephrotic-range proteinuria when there is mild glomerular injury and when there is advanced glomerulosclerosis.

Acute renal failure is very uncommon (<5% of all cases) and develops by two distinct mechanisms. There may be acute, severe immune and inflammatory injury producing crescent formation – crescentic IgA nephropathy; this may be the first presentation of the disease or can occur superimposed on known milder IgAN. Alternatively, acute renal failure can occasionally occur with mild glomerular injury when heavy glomerular haematuria leads to tubular occlusion by red cells. This is a reversible phenomenon and recovery of renal function occurs with supportive measures.

The remainder of patients with IgAN, typically older at presentation, already have proteinuria, renal impairment and hypertension when first diagnosed. It is usually presumed that they have longstanding IgAN which was not detected earlier because the patient did not have frank haematuria or undergo routine urinalysis.

There is no certain explanation for the very wide range of presenting clinical features and the variable tempo of disease after diagnosis. Data from Japan suggest that the prevalence of subclinical IgAN may be even higher than already suspected, based on renal biopsies in living kidney donors, in which 16% were found to have previously unknown mesangial IgA. IgAN is more common in Asia and Southern Europe than in North America and Northern Europe, but a genetic basis for these variations has not yet emerged

Pathology

Mesangial IgA deposits are diffuse and global, even if light microscopic change is focal or segmental. IgA is the sole immunoglobulin present in only 15% of biopsies; IgG and IgM accompany IgA in the majority of cases. C3 deposition is usual and has the same distribution as IgA.

Light microscopic abnormalities may be minimal, but the commonest appearance is mesangial hypercellularity, most commonly diffuse and global but focal segmental hypercellularity is also seen. Crescentic change may be superimposed on diffuse mesangial proliferative GN with or without associated segmental necrosis. With progressive disease there is accumulation of mesangial matrix, with tubulointerstitial changes which do not differ from those seen in other forms of progressive GN.

A proportion of patients with IgAN have diffuse uniform global thinning of the GBM indistinguishable from that seen in thin membrane nephropathy; it is not clear whether this group of patients have any defining clinical or prognostic characteristics.

Do these various clinical presentations and pathological features of IgAN all arise from the same disease process? It is common to describe IgAN as a single disease, but our present limited understanding of the aetiology and pathogenesis of IgAN does not yet provide strong support for such a view. Mesangial IgA deposition and subsequent injury may eventually turn out to represent a final common path of glomerular response to a wide range of etiologic and pathogenic processes [1].

Natural History & Prognosis

Fewer than 10 % of patients with IgAN have complete resolution of urinary abnormalities. Slowly progressive chronic renal impairment leading eventually to end stage renal disease [ESRD], is common, 25-30% of most published cohorts will require renal replacement therapy within 20-25 years of presentation. From first symptoms, 1.5% of patients with IgAN have been calculated to reach ESRD per year.

Features at presentation which mark a poor prognosis do not differ from those in other chronic GN [2]. These features do not have the specificity to identify an individual prognosis with complete confidence. An approach incorporating sequential information on blood pressure and

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proteinuria can further refine the prediction of progression risk, [3], although this will still only account for 30% of overall risk.

Recurrence after renal transplantation

Recurrence of IgAN after renal transplantation is becoming increasingly important as a cause of graft failure as control of rejection improves [4]. It is typically slowly progressive although occasional patients will have a rapidly progressive course. There is a 5% risk of graft failure due to recurrence at 5 years, although a 13% risk of significant graft dysfunction, and a risk of IgA deposition of at least 50%. The risk of graft loss increases markedly to 25% if a first graft was lost to recurrence. There is no evidence that any particular immunosuppressive regimen alters the incidence of IgAN recurrence after transplantation or of the prognosis of recurrence in the short term.

Treatment of IgA Nephropathy

There is still no treatment known to modify mesangial deposition of IgA, and available treatment options are mostly directed at downstream immune and inflammatory events which may lead on to renal scarring.

Recurrent macroscopic haematuria

Such episodes are self-limiting, and provoked by a range of mucosal, most commonly respiratory, infections. In a minority of patients recurrent episodes are provoked by bacterial tonsillitis, and tonsillectomy may be advised. Although this will help to prevent episodic haematuria in the short term, the proponents of tonsillectomy argue that it also gives long term renoprotection. Retrospective studies from Japan support its efficacy although follow up of more than 10 years is required before benefit becomes apparent, and the concomitant use of other treatment modalities make these data difficult to interpret.

Slowly progressive IgAN

The main area of treatment controversy is for patients with IgAN who are at risk of slowly progressive renal dysfunction – typically those with hypertension, proteinuria >1g /24 hr, or reduced GFR at the time of diagnosis. Because progression is usually slow, large studies with prolonged follow up are necessary to determine the efficacy of any therapeutic intervention with confidence, and many recently published studies are insufficiently powered to answer these questions. Recent data have been reported on interventions intended to slow immune and inflammatory events implicated in progressive IgAN including corticosteroids, cyclophosphamide and mycophenolate, and these have recently been reviewed [1]. Because of the long duration required to identify with confidence the benefit of interventions, it is inevitable that recruitment into a number of these studies goes back ten years or more, at a time when the generic approach to progressive glomerular disease was less well defined. The modern approach to such proteinuric patients emphasises rigorous blood pressure control to a target of 125/75 mm Hg and comprehensive renin-angiotensin system blockade to minimise proteinuria [5]. Increasingly vigorous blood pressure control has been recommended over recent years for IgAN, predominantly by extrapolation from other studies of progressive proteinuric renal disease, although one randomised controlled trial [RCT] in IgAN supports the additional benefit of an ACE inhibitor by achieving additional reduction in proteinuria despite equivalent blood pressure control. Furthermore, the 'COOPERATE' study provides evidence for additive renoprotection when an angiotensin receptor blocker [ARB] is given in combination with an ACE inhibitor in non-diabetic proteinuric renal disease; additional reduction in proteinuria being achieved with no further lowering of blood pressure; 131 patients in this large study had IgAN [6].

Corticosteroids

Meta-analysis of six available trials of sufficient quality suggests that corticosteroid therapy may be effective in reducing proteinuria and reducing risk of ESRD although the impact on protecting renal function is less clear [7]. A large Italian study of corticosteroids now has 10 year follow up with impressive benefit from treatment in reducing proteinuria and preventing ESRD. However this high-dose corticosteroid regimen is regarded by many physicians as likely to carry considerable toxicity, even though none is reported by the investigators. RAS blockade was only used in a minority of patients in this study, although equally distributed among the participants, and achieved blood pressure was not in line with current recommendations. [Table 1]. Another recent RCT of corticosteroids showed only a modest reduction in proteinuria with no protection of GFR, a difference attributed by the investigators to the lower dose of corticosteroids, but blood pressure control was tight even though RAS blockade was not used [Table 1]. In my opinion corticosteroids should only be considered if proteinuria persists > 1g/24hr despite optimal blood pressure control and maximum renin-angiotensin blockade.

Most trials of corticosteroids in progressive IgAN exclude patients with nephrotic range proteinuria, since many physicians regard this as an indication for corticosteroid therapy. However the only RCT which addresses this question showed a response to corticosteroids only in patients with minimal or minor histological abnormality on light microscopy.

Table 1: Treatment of IgAN: achieved blood pressure and use of renin-angiotensin blockade in recent randomised controlled trials
See reference 1 for publication details of trials
Note that optimum BP with renin-angiotensin system [RAS] blockade is achieved in few trials, and in those trials there is less benefit for the tested intervention

Treatment	Benefit	Mean achieved BP	ACE inhibitor or ARB
ACE inhibitor + ARB - 'COOPERATE' study	Reduction in proteinuria and preserved GFR; best with ACE inhibitor plus ARB	125/70	ACE inhibitor or ARB or combination
Corticosteroids	Reduction in proteinuria and reduced ESRD at 10 years	134/84	43% - used equally in both study groups
Corticosteroids	Small reduction in proteinuria; no effect on GFR	125/80	8% - most used in responders
Corticosteroids & Cyclophosphamide	Renoprotection in very high risk patients	145/85	Unclear
Mycophenolate	None	125/73	100%
Mycophenolate	Reduction in proteinuria; no effect on GFR	Uncertain	None

Cyclophosphamide
There is evidence in one study for the efficacy of cyclophosphamide followed by azathioprine in conjunction with high dose prednisolone given to patients at very high risk of progression [ESRD predicted in all cases within five years. However, these are only a small minority of patients encountered in clinical practice. Again blood pressure control and use of RAS blockade fell outside current recommendations [Table 1], and in my view there is insufficient evidence to justify the use of cyclophosphamide in IgAN except in crescentic IgAN with rapidly progressive renal failure [see below].

Mycophenolate
Two published studies give no consistent indication of the benefit of mycophenolate and the study showing no benefit achieved rigorous blood control with use of an ACE inhibitor [Table 1]. Other larger studies of mycophenolate are in progress.

Fish Oil
Although the original study of fish oil showing outstanding benefit remains impressive, but there are still no further studies to support its role, and a meta-analysis including other published studies does not suggest efficacy.

Blood pressure and renin-angiotensin blockade
The achieved blood pressure in the 'COOPERATE' study was significantly better than is reported in most of these recent RCTs [Table 1]. The efficacy, and low adverse reaction rate, suggest that combined RAS blockade with ACE inhibitor and ARB should be the 'standard regimen' against which any additional therapeutic intervention be judged. As well as achieving a blood pressure target of 125/75 mmHg in all proteinuric patients with IgAN, I recommend dual ACE inhibitor/ARB therapy if proteinuria reduction is insufficient with a single agent.
Additional therapy with corticosteroids or other agents should only be considered if there is still sustained proteinuria >1g per 24 hours despite achieving target blood pressure of 125/75 with full renin-angiotensin blockade. There are few patients who fulfil these criteria, and corticosteroids, cyclophosphamide and mycophenolate have not been adequately evaluated in the context of such a 'standard regimen'. Data on achieved BP or RAS blockade were not available in the published meta-analysis which suggests benefit for corticosteroids and immunosuppressive agents and so the possibility that these were confounding factors was not evaluated [7].

Crescentic IgA Nephropathy
This is an uncommon clinical presentation of IgAN. There are no RCTs of immunosuppressive therapy in crescentic IgA nephropathy associated with rapidly progressive renal failure, although recent observational studies are increasingly optimistic about the value of treatment with corticosteroids usually in combination with cyclophosphamide [8]. Nevertheless overall renal survival in crescentic IgA nephropathy is inferior to that in other forms of crescentic GN, including systemic vasculitis and Goodpasture's disease. Background chronicity in IgA nephropathy is a powerful negative influence, and immunosuppressive therapy in crescentic IgAN is only recommended if there is active crescentic injury without

major background chronic damage. In such circumstances I use corticosteroids and cyclophosphamide in a regimen similar to that applied in renal vasculitis; there is insufficient evidence for the addition of plasma exchange.

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