

Treatments Options for IgA Nephropathy

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INTRODUCTION

IgA nephropathy [IgAN] is the commonest pattern of glomerulonephritis in all countries where renal biopsy is widely practiced. It is an important cause of end-stage renal disease [ESRD] at all ages, and therefore treatment strategies to reduce the risk of IgAN progressing to ESRD would have substantial health benefit. It is disappointing that there are still few well-designed randomised controlled trials [RCTs] to inform the treatment of this condition. In this review, I will critically evaluate the available evidence on the treatment of IgAN, especially focussing on recently published RCTs; I have reviewed earlier available data elsewhere¹. I will provide recommendations for the common clinical

situations that confront the nephrologist treating patients with IgAN.

CLINICAL PRESENTATIONS AND DIAGNOSIS

The typical presentation of recurrent macroscopic haematuria coinciding with mucosal [usually upper respiratory] infection is most common in the second and third decades of life and is almost never the presenting symptom after the age of 40 years. Asymptomatic urine abnormalities are a common presentation, microscopic haematuria with or without proteinuria, and with increasing age these features are more likely to be accompanied by renal impairment and hypertension when first seen. Nephrotic syndrome occurs in around 5% of cases. Acute renal failure is seen during the course of the disease in <5% of cases; it may result from acute tubular necrosis as a consequence of macro-

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copic hematuria or superimposed crescentic nephritis.

Renal biopsy confirms the diagnostic feature of diffuse mesangial IgA deposition with a wide range of light microscopic appearances, although diffuse or segmental mesangial proliferation is the most common.

NATURAL HISTORY AND PROGNOSIS

Fewer than 10 % of all patients with IgAN have complete resolution of urinary abnormalities during follow up. IgAN has the potential for slowly progressive chronic renal impairment leading eventually to ESRD. Approximately 25-30% of any published cohort will require renal replacement therapy within 20-25 years of presentation. The perceived overall cohort risk will of course be influenced by the diagnostic approach, since centres having a low threshold for renal biopsy in patients with minor urinary abnormality will diagnose IgAN in a larger number of patients with mild disease and good prognosis, thus favourably influencing the overall outcome of the cohort.

Adverse clinical features at presentation include proteinuria, hypertension and reduced GFR, adverse histopathologic features include glomerular sclerosis, tubular atrophy, and interstitial fibrosis². None of these features which mark a poor prognosis are specific to IgAN, and would be applicable to any form of chronic proteinuric glomerular disease. They are informative for populations of patients but as yet do not have the specificity to identify an individual prognosis with complete confidence. An approach incorporating sequential information on blood pressure and proteinuria can further refine the prediction of progression risk³⁻⁵, although it has been said this will still only account 30% of overall risk³. Although prognostic formulae

using simple clinical and laboratory data have been proposed^{3,6} there is not yet sufficient consensus to recommend they are used in clinical practice for the prediction of individual progression risk. It also remains uncertain whether pathological classification adds to predictive power in the individual patient; progress in defining the answer has been limited by the lack of an international consensus on pathological classification of IgAN. Further refinement of prognostic prediction will inform recruitment criteria for future interventional treatment trials.

RECURRENCE AFTER RENAL TRANSPLANTATION

Recurrence of IgAN after renal transplantation is assuming increasing importance as a cause of graft failure as control of rejection improves. The diagnosis and management of recurrence have recently been reviewed in detail⁷ and I will not here consider this further.

TREATMENT STRATEGIES

There is still no treatment known to modify mesangial deposition of IgA, the initiating event in IgAN. Available treatment options are mostly directed at downstream immune and inflammatory events in the glomerulus and the tubulo-interstitium which may lead on to renal scarring. It is therefore likely that they are generic treatments with potential benefit in other chronic glomerular diseases.

Here I will review the available treatments from the perspective of each clinical presentation encountered in IgAN; treatment recommendations are summarised in Table 2.

Table 1: Treatment of IgAN: achieved blood pressure and use of renin-angiotensin blockade in recently published randomised controlled trials

Note that optimum BP with renin-angiotensin blockade is achieved in few trials, and in those trials there is less reported benefit for the tested intervention

Treatment ^{reference}	Benefit	Mean achieved BP	ACE inhibitor or ARB
ACE inhibitor + ARB ¹⁹	Reduction in proteinuria and preserved GFR; best with ACE inhibitor plus ARB	125/70	ACE inhibitor or ARB or combination
Corticosteroids ²¹	Reduction in proteinuria and reduced ESRD at 10 years	134/84	43% - used equally in both study groups
Corticosteroids ²²	Small reduction in proteinuria; no effect on GFR	125/80	8% - most used in responders
Corticosteroids + Cyclophosphamide ²³	Renoprotection in very high risk patients	145/85	Unclear
Mycophenolate ²⁴	None	125/73	100%
Mycophenolate ²⁵	Reduction in proteinuria; no effect on GFR	Uncertain	None

Recurrent macroscopic haematuria

Such episodes are self-limiting, and provoked by a range of mucosal, most commonly respiratory, infections. There is no role for prophylactic antibiotics, even in the minority of patients in whom recurrent episodes are provoked by bacterial tonsillitis. Tonsillectomy is still favoured in some regions of the world, notably Japan. Tonsillectomy may help to prevent episodic macroscopic haematuria in the short term, and proponents of tonsillectomy argue that it also gives long term renal protection. Two large 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^{8,9}; a retrospective study from Germany suggests no benefit of tonsillectomy¹⁰. An RCT of tonsillectomy in IgAN would be valuable, and such a study is now being planned in Japan.

Acute renal failure

Acute renal failure is an uncommon event in IgAN and most commonly occurs with macroscopic haematuria. Even if the diagnosis of IgAN has previously been established, evaluation

Table 2. Treatment recommendations for IgA nephropathy according to clinical features

Clinical presentation		Recommended treatment
Recurrent macroscopic haematuria with preserved renal function		No specific treatment – no role for antibiotics of tonsillectomy
Macroscopic haematuria with acute renal failure	Acute tubular necrosis	Supportive measures
	Crescentic IgAN [with little or no chronic damage]	<u>Induction</u> [~8 weeks] Prednisolone 0.5-1mg/kg/day Cyclophosphamide 2mg/kg/day <u>Maintenance</u> Prednisolone in reducing dosage Azathioprine 2.5mg/kg/day
Proteinuria <1g/24hr ± microscopic haematuria		No specific treatment
Proteinuria >1g/24hr ± microscopic haematuria		Combined renin-angiotensin blockade with ACE inhibitor and ARB
Nephrotic syndrome	With minimal change on light microscopy	Prednisolone 0.5-1mg/kg/day for up to 8 weeks
	With structural glomerular changes	No specific treatment
Hypertension		Target BP 125/75 if proteinuria > 1g/24hr ACE inhibitors/ARB first choice agents

should include renal biopsy to distinguish between ARF due to acute tubular necrosis, which should be self-limiting with supportive treatment; and crescentic IgAN which may be amenable to intensive immunosuppression.

other hand it is not uncommon to see crescentic change on a background of chronic glomerular and tubulo-interstitial injury; such chronicity usually predicts a poor response to intensive immunosuppression. Immunosuppressive treat-

Crescentic IgAN

Crescentic IgAN has a less good prognosis despite immunosuppressive therapy than other forms of crescentic glomerulonephritis, for example that associated with ANCA-positive small vessel vasculitis; cumulative published cases suggest that renal survival in crescentic IgAN is only 50% at 1 year, and 20% at 5 years. A number of optimistic case series have recently been published indicating good preservation of renal function using treatment regimens similar to those recommended for renal vasculitis, usually with high dose corticosteroids and cyclophosphamide, and in some cases plasma exchange^{reviewed in ref 11}. However there has still been no RCT of these treatments in crescentic IgAN, and response to treatment is not uniform. There is lack of clarity because published reports use varying definitions of crescentic IgAN, for example some include cases where crescents are seen, but other acute injury to the glomerular tuft is not intense and renal function is not deteriorating. One report indicates that there is a subset of crescentic IgAN with circulating ANCA antibodies which respond well to immunosuppression¹². Crescentic IgAN may occur as the first presentation of IgAN with little preceding renal insult; on the

ment is therefore only recommended in the presence of crescents, active glomerular inflammation and deteriorating renal function in the absence significant chronic damage.

Isolated microscopic haematuria and little or no proteinuria

The consensus remains that there is no specific treatment required for such patients although prolonged surveillance is indicated. A threshold for proteinuria of 1g/24hr is usually recommended to identify those at higher risk, although this is an arbitrary value, and the risk attributable to proteinuria is almost certainly a continuum.

Nephrotic syndrome in IgA nephropathy

In many patients with IgAN and nephrotic syndrome the heavy proteinuria is a manifestation of significant structural glomerular damage and progressive renal dysfunction. However a small minority, both adults and children, have nephrosis with minimal glomerular change on renal biopsy, although there are also IgA deposits, and proteinuria remits promptly in response to corticosteroids. In these patients, two common glomerular diseases may coincide: minimal-change nephrotic syndrome and IgAN^{13,14}. This observation justifies a trial of high-dose corticosteroids using a regimen appropriate for minimal-change disease in IgAN with nephrotic syndrome and preserved renal function when light microscopy shows minimal glomerular injury. However, there is no evidence to support prolonged exposure to corticosteroids if there is not a prompt response, nor their use in nephrotic syndrome in the presence of structural glomerular damage. The only RCT of corticos-

teroids in nephrotic IgAN confirms this approach since there was a remission of proteinuria only in patients with minimal glomerular change on light microscopy¹⁵. More recent RCTs of corticosteroids in IgAN have excluded those with nephrotic-range proteinuria, so there is little evidence to inform treatment choices for nephrotic IgAN with significant histologic glomerular injury.

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 published studies are insufficiently powered to provide definitive answers to these questions. All such trials in IgAN use clinical entry criteria – typically the presence of hypertension and proteinuria 1-3g per 24 hours, with variable reduction in GFR. This is in contrast for example to studies in lupus nephritis where histological criteria usually dominate recruitment, and reflects the lack of international consensus on a histopathological classification of IgAN.

Blood pressure control

The recommended approach to proteinuric patients with glomerular disease emphasises rigorous blood pressure [BP] control to a target of 125/75 mm Hg and comprehensive renin-angiotensin system blockade to minimise proteinuria¹⁶. There is some specific evidence in IgAN to justify tight BP control: in one small RCT

that achieved mean blood pressure of 129/70 stabilised GFR over 3 years whereas patients with achieved BP of 136/76 showed a mean decline in GFR of 13ml/min over 3 years¹⁷. Another small RCT supports the additional benefit of an ACE inhibitor on progressive renal disease in IgAN despite equivalent blood pressure control by achieving an additional reduction in proteinuria¹⁸. 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 IgAN¹⁹.

Treatments modulating immune and inflammatory injury

Recently reported RCTs have tested interventions intended to slow immune and inflammatory events implicated in progressive IgAN including corticosteroids, cyclophosphamide and mycophenolate. 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, to a time when the generic approach to progressive glomerular disease was less well defined, so that BP targets and the use of renin-angiotensin blockade are variable in these studies.

Corticosteroids

Meta-analysis of six available trials of sufficient quality suggests that corticosteroid therapy may be effective in reducing proteinuria and reducing risk of ESRD²⁰. The large Italian study of

corticosteroids now has 10 year follow up with impressive benefit from treatment in reducing proteinuria and preventing ESRD²¹. However their high-dose corticosteroid regimen, using 'pulse' methylprednisolone and alternate day oral prednisolone for 6 months, 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 from Japan, showed only a modest reduction in proteinuria with no protection of GFR²², 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].

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]²³. However, these are only a small minority of patients encountered in clinical practice. Furthermore blood pressure control and use of RAS blockade in this trial fell outside current recommendations [Table 1]. Previous RCTs of cyclophosphamide in less severe IgAN showed no consistent benefit.^{reviewed in ref.1}

Mycophenolate

One published study gives no indication of any benefit from mycophenolate²⁴ while another points to a reduction in proteinuria²⁵, and it is

noteworthy that the study showing no benefit achieved rigorous blood control with use of an ACE inhibitor [Table 1]. Of two other preliminary reports, one suggests a transient benefit of mycophenolate on proteinuria²⁶ while another shows no benefit in more advanced disease [mean serum creatinine at entry 2.6 mg/dL]²⁷. The relatively small size of the studies so far available justifies further evaluation, and other studies are in progress²⁸.

Fish Oil

Although the original study of fish oil showing outstanding benefit remains impressive²⁹, there are still no further studies to support its role, and a meta-analysis including other published studies does not suggest efficacy³⁰. The preliminary report of a more recent RCT shows no benefit of two years treatment with fish oil compared to corticosteroids and placebo.³¹ On the available evidence I do not recommend the use of fish oil.

Coagulation modifying agents

Warfarin, urokinase, and antiplatelet agents have all been assessed for the treatment of IgAN, but in my opinion there is at the present time insufficient evidence to support their use. I have reviewed earlier trials of these agents elsewhere¹.

Choice of therapy

This remains a controversial area, but in my opinion 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. This approach is very effective so there are in clinical practice few patients who fulfil these criteria, and it should be recognised that the efficacy of corticosteroids, cyclophosphamide and mycophenolate have not been adequately evaluated by RCT in the context of such a 'standard regimen'. It should also be noted in Table 1 that those studies in which contemporary BP targets were achieved and full renin-angiotensin blockade deployed were those least likely to show benefit from the additional therapy.

Data on achieved BP or the use of renin-angiotensin blockade were not available for the published meta-analysis which suggests benefit for corticosteroids and immunosuppressive agents and so the possibility that these were confounding factors was not evaluated²⁰.

FUTURE PROGRESS

It is unfortunately becoming increasingly difficult to judge the efficacy of any proposed new therapeutic interventions. The renoprotective efficacy of the 'standard regimen' means that evaluation of any additional intervention will require increasingly large and prolonged RCTs to prove benefit for additional agents unless robust surrogate measures of outcome are developed to enable studies to be scaled down without loss of power. Information from well designed RCTs remains a pressing priority if uncertainties in the treatment of IgAN are to be resolved.

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