Drugs 1998 Jan; 55 (1): 73-83
0012-6667/98/0001-0073/$11.00/0

Recognition and Management of IgA Nephropathy

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Summary

IgA (immunoglobulin A) nephropathy is the most common form of primary glomerulonephritis worldwide. It generally has a good prognosis, with 15-year rates of kidney survival from the apparent onset of disease usually well in excess of 70%. Progression, when it occurs, is usually a slow, indolent process, and spontaneous remission of disease activity occurs in 7% of patients.

It is possible to predict, from the initial presenting features and laboratory findings, renal biopsy and clinical course during follow-up, which patients are likely to have progressive renal disease. Identification of the factors likely to be associated with progression is of importance in helping to establish which patients will benefit from specific therapeutic intervention.

For all patients, attention should be directed toward general health issues in an endeavour to reverse factors that are likely to have an adverse impact on renal function. This should include early detection and tight control of hypertension (present in 50% of all patients with IgA nephropathy during the course of their disease), along with utilisation of antihypertensive agents that have specific renoprotective effects, namely ACE inhibitors or calcium antagonists. Such therapy should also be considered in normotensive patients with heavy proteinuria, as a reduction of proteinuria is often achieved by this means.

Other aims should include maintenance of desirable bodyweight, correction of hyperlipidaemia, cessation of smoking, participation in an active exercise programme, avoidance of exposure to nephrotoxins and maintenance of a high fluid intake. A low protein/low phosphate diet together with phosphate binder therapy should be commenced early in the course of renal impairment. Corticosteroid and/or cytotoxic drug therapy should be considered in the small percentage of patients with heavy proteinuria or a rapid decline in renal function. Such therapeutic endeavours are likely to delay the onset of renal failure in patients with progressive IgA nephropathy.

The syndrome of IgA nephropathy was first reported nearly 30 years ago in a study of 25 patients with proteinuria, microscopic haematuria and, in half of the patients, single or recurrent episodes of macroscopic haematuria.[1] It is now recognised that IgA nephropathy is the most common form of glomerulonephritis, accounting for 25 to 50% of patients with primary glomerulonephritis, the reported prevalence being higher in countries such as Singapore and Japan, where community-based screening tests for haematuria are performed.[2]

The major clinical implication of IgA nephropathy is its potential to progress to end-stage renal failure, of which it is a leading cause. In Australia, in 1995, it accounted for 9% of patients presenting for renal replacement therapy from all causes and for 31% of patients with renal failure secondary to primary glomerulonephritis.[3] Similarly, in Asia and Europe (including the UK), it accounts for approximately 10% of patients with end-stage renal failure.[2]

This article reviews the prognosis, diagnosis and management of patients with IgA nephropathy.

1. Prognosis

In view of the fact that IgA nephropathy is the most common form of glomerulonephritis and will therefore affect larger numbers of patients than other causes of end-stage renal failure, the statistics quoted above unfairly suggest a poor prognosis for patients with IgA nephropathy.

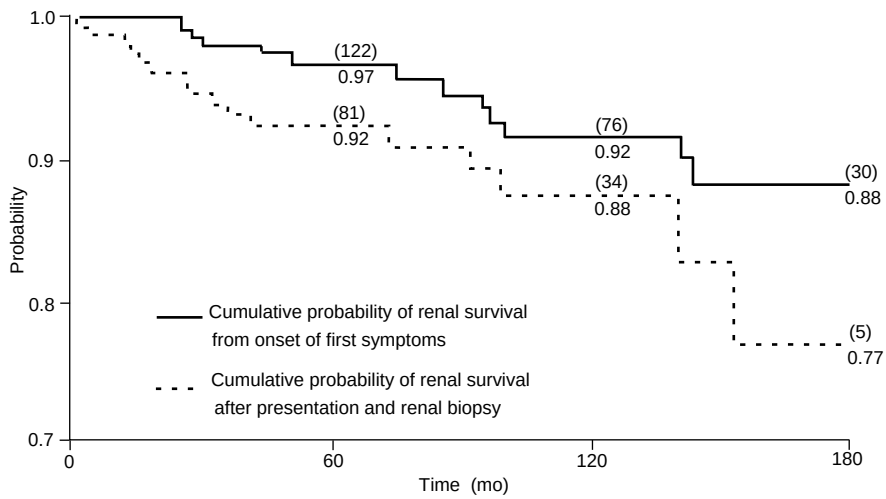

Fig. 1. Cumulative probability of renal survival from onset of symptoms, and from presentation and renal biopsy.[4] Figures in parentheses indicate the number of patients remaining in the study at each time interval.

For the majority of patients, IgA nephropathy is an indolent disease process, usually carrying a good prognosis. Of 174 patients we followed for a mean of 69 months, 8.6% progressed to end-stage renal failure, as did 10.5% of patients reported in the world literature.[2,4] In our experience, the cumulative probability of not progressing to end-stage renal failure is, from the onset of symptoms, 0.97 at 5 years, 0.92 at 10 years and 0.88 at 15 years, and from presentation and renal biopsy, 0.92 at 5 years, 0.88 at 10 years and 0.77 at 15 years (fig. 1).[4] Other studies have reported 15-year rates of kidney survival of 0.67 to 0.88 from the onset of symptoms and 0.67 to 0.82 from presentation and renal biopsy.[2,4-9]

In addition to this overall good prognosis, a complete remission of disease activity, with normal renal function, may be seen in approximately 7% of patients with IgA nephropathy,[2,4] although clinical remission is usually associated with persistence of IgA deposition on renal biopsy.[2,10] Most patients with microscopic haematuria, normal blood pressure and renal function never undergo renal biopsy and this must include a proportion of patients with IgA nephropathy with an excellent prognosis. On the other hand, in approximately 8% of patients who reach end-stage renal failure: (i) the cause of renal failure is unknown; (ii) renal biopsy has shown an unclassifiable glomerulonephritis (end-stage kidney); or (iii) immunofluorescence has not been performed.[3] Assuming IgA nephropathy would have accounted for approximately 9.8% of such patients, a further small number of patients would have reached end-stage renal failure as a consequence of IgA nephropathy. However, in 1996 this would have accounted for only 10 of the 1358 patients reaching end-stage renal failure in Australia.[3]

As there are a number of potentially beneficial therapeutic options available to patients with IgA nephropathy, early referral, investigation and biopsy should be encouraged.

2. Clinical and Laboratory Features

The major clinical and laboratory features of IgA nephropathy as described in the world literature, together with other features drawn specifically from our experience (urine microscopy findings, degrees of renal impairment, prevalence of hyperlipidaemia),[2,4] are summarised in table I. IgA nephropathy has a male sex predominance, and patients usually present at a relatively young age (although any age group may be affected), often with a family history of nephritis. They have frequently experienced symptoms over a long period before a definitive diagnosis is made.

Table I. Clinical features and laboratory findings in patients with IgA (immunoglobulin A) nephropathy

Feature	Mean
Male : female ratio	2.16 : 1
Age at presentation	30.4y
Duration of symptoms	50mo
Proportion (%) of patients with	
family history of IgA or other nephritis	11
recurrent macroscopic haematuria	43
persistent microscopic haematuria	88
infection-related exacerbations of disease activity	41
recurrent loin pain	31
persistent proteinuria	67
raised serum creatinine level (>0.12 mmol/L)	21
hypertension	
at presentation	25
developed during follow-up	25
centrifuged-urine microscopic evidence of	
increased number of red blood cells	94
increased number of white blood cells	46
increased number of total casts	64
hyaline	52
granular	27
hyalogranular	22
red blood cell	15
creatinine clearance <4.8 L/h (<80 ml/min)	35
serum creatinine level >0.24 mmol/L	6
24h urinary protein loss	
>1g	47
>3g	11
serum cholesterol level >5.5 mmol/L	42
serum triglyceride level >2 mmol/L	38
raised serum IgA level	41

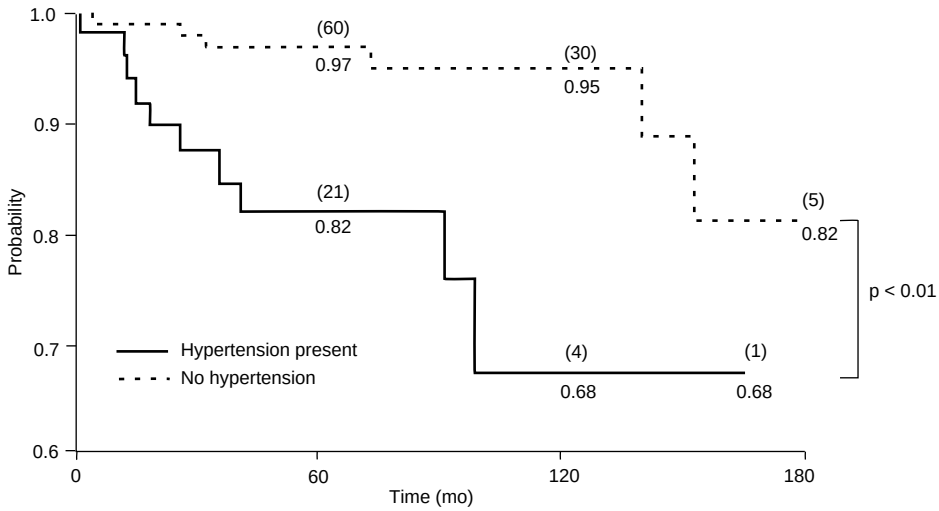

Fig. 2. Cumulative probability of renal survival in patients with, and those without, hypertension at presentation.[4] Figures in parentheses indicate the number of patients remaining in the study at each time interval. Where the number of patients in each case has tapered to 1 before 180 months of follow-up, the relevant line of the graph ends at the point of survival for the last patient.

Recurrent macroscopic haematuria, often accompanied by loin pain and constitutional symptoms, and occurring within 48 hours of an upper respiratory tract, or other, infection, is a classic feature of IgA nephropathy and is seen in over 40% of patients. Persistent microscopic haematuria is present in the majority of patients, often accompanied by proteinuria and, when specifically looked for,[2,4,11,12] increased numbers of white blood cells and casts on centrifuged urine microscopy. Proteinuria in excess of 1 g/day is present in nearly 50% of patients, and exceeds 3 g/day in 11%. Renal function is impaired (serum creatinine >0.12 mmol/L) at presentation in over one-third of patients, and is severely impaired (serum creatinine >0.24 mmol/L) in 6%. Hyperlipidaemia is present in over a third of patients, while 41% have a raised serum IgA level. In the authors' series hypertension was present in about 25% of patients at presentation and developed in a further 25% over the mean 69 months of follow-up (table I). Transient decreases in renal function of greater than 10% are seen in over 70% of patients during follow-up, and of greater than 20% in 45% of patients.[2,4]

3. Factors of Importance in Prognosis

A number of factors have been shown to be associated with progressive renal impairment in patients with IgA nephropathy. Identification of patients who are potentially at higher risk should be of value in deciding on the use of therapeutic interventions that are likely to retard the progression of renal disease. Nevertheless, there remains some controversy as to which factors are of importance, so we have emphasised those on which there is majority agreement.

3.1 Clinical Features

Clinical features at presentation that are associated with poor renal survival rates include hypertension,[2,4,7-10,13-18] an older age,[2,13-17,19] a family history of glomerulonephritis,[2] and a longer duration of symptoms in some studies,[2,19] but not in all.[9,15,18] In our series,[4] patients with hypertension at presentation had a 10-year cumulative probability of renal survival of 0.68, significantly worse than those without hypertension, in whom it was 0.95 ($p < 0.01$) [fig. 2]. Hypertension is also unduly

prevalent, being present in about 50% of patients during follow-up.

Many studies have shown a favourable prognosis in patients presenting with recurrent macroscopic haematuria,[2,4,5,9,14,15] or with infection-related exacerbations of disease activity.[2] We have found that patients who present with recurrent macroscopic haematuria had a 15-year cumulative probability of renal survival of 0.95,[4] significantly different from those without recurrent macroscopic haematuria, whose probability of renal survival was 0.68 ($p < 0.05$) [fig. 3].

3.2 Laboratory Findings

Laboratory findings associated with an adverse renal outcome are the severity of both proteinuria and renal impairment at presentation.[2,4,8-10,13-19] Nephrotic-range proteinuria (urinary protein excretion >3 g/day) and severe renal impairment are both indicative of a poor prognosis in patients with IgA nephropathy.[2,4,8,10,17,19]

Our group[4] found that the cumulative probability of renal survival from the time of presentation and renal biopsy in patients with proteinuria >3 g/day was only 0.36 at 15 years (fig. 4), while in patients with a serum creatinine level of >0.24 mmol/L, the cumulative survival at 5 years was only 0.12 (fig. 5). Moreover, if this degree of renal impairment was accompanied by a urinary protein loss of >1 g/day, no patient had functioning kidneys 3.3 years after presentation and renal biopsy. On the other hand, we and others[4,10,15-17] have observed an excellent prognosis if the urinary protein loss is normal or only increased up to 1 g/day, with cumulative renal survival rates of 0.90 to 1.00 at 10 years. In addition, moderate degrees of renal impairment do not appear adversely to affect the prognosis of patients with IgA nephropathy.[4,19] Our group[4] has also reported that in patients with a serum creatinine level of 0.12 to 0.24 mmol/L, the cumulative renal survival at 10 years was 0.97, not significantly different from that in patients with a normal serum creatinine level, whose 10-year survival was 0.92 (fig. 5). In patients with a normal urinary protein loss, and a normal or mildly to moderately raised (0.12 to 0.24 mmol/L) serum creatinine level, the 15-year cumulative survival was 1.00.

Microscopy of a centrifuged urine specimen provides a valuable indication of the severity of

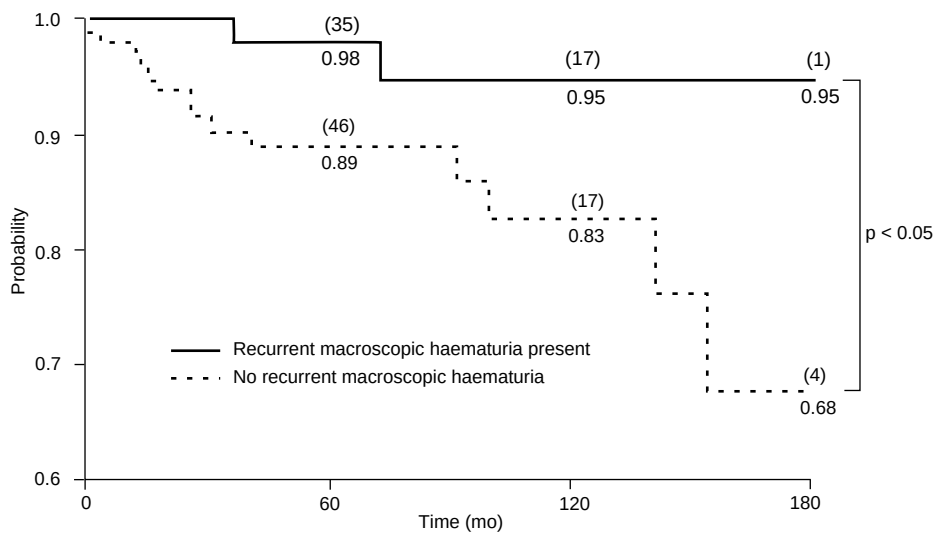

Fig. 3. Cumulative probability of renal survival in patients presenting with, and those presenting without, recurrent macroscopic haematuria.[4] Figures in parentheses indicate the number of patients remaining in the study at each time interval.

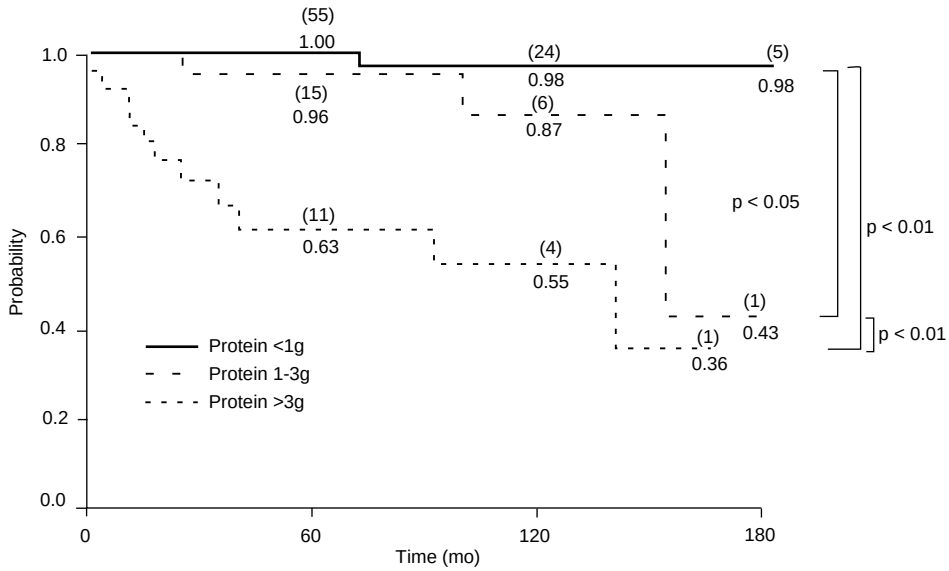

Fig. 4. Cumulative probability of renal survival in patients with 24-hour urinary protein excretion of <1g, 1 to 3g or >3g.[4] Figures in parentheses indicate the number of patients remaining in the study at each time interval. Where the number of patients in each case has tapered to 1 before 180 months of follow-up, the relevant line of the graph ends at the point of survival for the last patient.

renal pathology,[11,12,20] and should be an integral part of the assessment of all patients with renal disease. We have found the number of casts to be an important prognostic indicator in patients with IgA nephropathy.[2,4] Presumably the presence of red blood cells and granular casts is indicative of more severe renal parenchymal inflammation and fibrosis, and thus of the potential for progressive renal disease.

Although 41% of patients with IgA nephropathy have raised serum IgA levels, this has been found to have no prognostic implications in most studies,[2,4,7,10,14,16,18] but not all.[8] Our group has observed that haematuria or pyuria noted at the time of referral is associated with a favourable effect on renal outcome,[2] which may have been related to the initial presentation of a number of patients with macroscopic haematuria. However, continuing high urinary red blood cell counts, either during follow-up or when assessed 6 weeks or more after an acute exacerbation, may be associated with a poor prognosis.[2,9,10] Raised β-globulins on both serum protein electrophoresis and serum complement 4 (C4) concentrations were also associated with adverse outcomes for renal function.[2]

3.3 Renal Biopsy Findings

The major factors on renal biopsy that are associated with a poor prognosis include not only the degrees of global and segmental glomerular sclerosis[2,4,8-10,13-15,19] and epithelial cell crescent formation,[2,10,14,18] but also the degrees of chronic tubulointerstitial fibrosis, tubular atrophy and interstitial inflammation,[2,4,8,9,13-15,19] and vascular changes;[2,4,8,13-15] this emphasises the importance of tubulointerstitial and vascular pathology in the progression of IgA nephropathy. In our studies and in others, the degree of mesangial hypercellularity,[4,14-16,19] the intensity of deposition of IgA,[2,4,19] immunoglobulin M (IgM)[2,18] and C3,[2,19] the presence of mixed-site immune complex deposition,[2,4,14,15,19] and the extent of capillary wall electron-dense deposits,[2,21] were also identified as potentially poor prognostic findings.

3.4 Features During Follow-Up

Persistence of hyaline casts[2] and continuing high red blood cell counts on urine microscopy[2,10] are predictive of a progressively deteriorating course in patients with IgA nephropathy. A poor renal prognosis is also seen in association with persistence or development of heavy proteinuria,[2,4,8,19] evolution or persistence of hypertension (particularly if blood pressure is poorly controlled),[2,4,8,9,18] reduction in serum immunoglobulin G (IgG), IgA and IgM and absolute C3 levels, abnormal serum protein electrophoretic patterns,[2,4] and (not surprisingly) the degree of impairment of renal function at last follow-up.[2,4]

Transient worsening of renal function is a recognised accompaniment of IgA nephropathy,[2,4,6,10,15] and was shown in our studies[2,4] not only to be relatively common, but also to be associated with an ultimately worse prognosis. This association presumably represents exacerbations of disease activity that are sufficient to cause temporary impairment in renal function, with subsequent healing of inflammatory changes (via glomerular, tubulointerstitial and vascular sclerosis) leading to progressive renal failure. In one other study,[15] histological changes of acute renal failure accompanied by transient increases in the serum creatinine level were associated with 10-year renal survival rates of only 40.4%.

In summary, none of the prognostic indices (sections 3.1 to 3.4) alone accurately predicts the outcome in an individual patient, and thus it is necessary to look at an overview of all clinical and laboratory features and renal biopsy findings in an endeavour to assess prognosis and to identify patients in whom there is a high probability of progression of disease. Identification of such patients should assist in deciding therapeutic strategies aimed at retarding the progression of renal impairment.

4. Treatment

4.1 General Measures

In all patients with IgA nephropathy, general health issues should be addressed in an endeavour

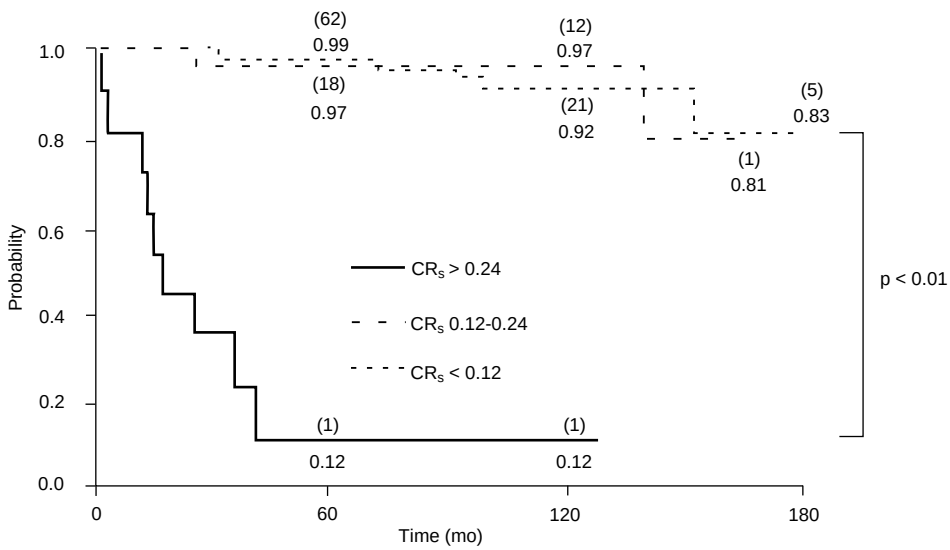

Fig. 5. Cumulative probability of renal survival in patients with serum creatinine levels (CR_s) at presentation of <0.12 mmol/L, 0.12 to 0.24 mmol/L or >0.24 mmol/L.[4] Figures in parentheses indicate the number of patients remaining in the study at each time interval. Where the number of patients in each case has tapered to 1 before 180 months of follow-up, the relevant line of the graph ends at the point of survival for the last patient.

to reverse factors that are likely to have an adverse impact on renal function. Tight blood pressure control, correction of hyperlipidaemia, maintenance of desirable bodyweight, cessation of smoking, participation in an active exercise programme, avoidance of exposure to nephrotoxins, and maintenance of a sufficiently high fluid intake to ensure an adequate urinary flow rate and thus decrease the tubulointerstitial toxicity of filtered red cells and protein, are all of value in such patients.[22-24]

A low salt, low protein (0.6 g/kg/day)/low phosphate diet, phosphate binder therapy and judicious use of 1,25-dihydroxycholecalciferol to individual patient requirements should be commenced early in the course of renal impairment. Control of calcium/phosphate homeostasis retards the development of secondary hyperparathyroidism and progression of renal disease.[22] While there is some controversy over the value of a low protein diet,[25] there is abundant evidence attesting to the value of protein and phosphate restriction in such patients.[22,26-29] Dietary and other therapeutic measures should be introduced early, as early intervention is associated with better therapeutic outcomes.[28,29]

4.2 Control of Hypertension

Systemic hypertension has a major deleterious effect on renal function in patients with intrinsic renal disease, irrespective of the cause of renal impairment. This is related in part to the transmission of raised systemic pressures to poorly autoregulated glomeruli.[30] Tight control of blood pressure can delay the progression of chronic renal disease.[22,24,26,30-36] In patients with renal impairment or proteinuria greater than 1 g/day, the target mean arterial pressure should be reduced to less than 92mm Hg (equivalent to 125/75mm Hg).[24]

Much of the recent literature on this subject has focused on the role of ACE inhibitor therapy and its beneficial effects in retarding the development or progression of both diabetic nephropathy[35,36] and nondiabetic chronic renal disease.[30,32,33] These class-specific effects result, at least in part, from reduction of intraglomerular pressure secondary to the preferential dilatation of efferent glomerular arterioles. Moreover, ACE inhibitors have a specific renoprotective effect independent of their antihypertensive properties,[30,35,37] which has also been observed in normotensive patients.[37]

There is very good evidence that calcium antagonists may be equally effective in retarding the progression of both diabetic and nondiabetic renal disease.[30,33,38,39] In view of the afferent arteriolar vasodilatation that occurs with these agents, it is essential that tight blood pressure control is achieved and that long-acting preparations are used in order to protect the glomeruli against the adverse effects of systemic hypertension.[39]

Therapy with either class of drug reduces proteinuria,[24,30,33,35,37,39] and the degree of proteinuria has a major impact on prognosis in IgA nephropathy. Thus, in patients with IgA nephropathy, hypertension – which is so prevalent – should be detected early and tightly controlled with agents such as ACE inhibitors or calcium antagonists which have a specific renoprotective effect. An agent from either class should also be trialled in normotensive patients with heavy proteinuria.

4.3 Immunosuppressive Therapy

Corticosteroid and/or cytotoxic therapy may be indicated in some patients with IgA nephropathy. These agents certainly reduce proteinuria and stabilise renal function in the small group of patients with nephrotic syndrome and mild histological changes – this was seen in 3 of 190 patients (1.6%) in our experience[2,40-44] – and they are also of benefit in patients with acute renal failure and extensive crescent formation.[40] In the majority of other patients with IgA nephropathy, immunosuppressive therapy should be utilised only when a patient has been identified as being at greatest risk of progressive renal disease (heavy proteinuria or progressive renal impairment, despite use of the measures detailed in sections 4.1 and 4.2). Such therapy, however, should be undertaken only as part of a controlled clinical trial or at the direction of a renal physician.

Schena et al.[45] performed a meta-analysis of randomised controlled trials in patients with IgA nephropathy, and concluded that it is advisable to administer corticosteroids and/or cytotoxic drugs to patients with heavy proteinuria (>3 g/day). They found that two-thirds of patients had a complete remission of proteinuria, and renal function improved in all treated patients.

Over a 12-week period, we administered prednisone (initially 2 mg/kg/day rapidly decreasing to 5 to 10 mg/day), with or without cyclophosphamide (2 to 3 mg/kg/day), to the patients with IgA nephropathy who had heavy proteinuria and deteriorating renal function (10% of the group); stabilisation of, or improvement in, renal function was observed in over half of these patients. Rarely, in patients with a fulminant clinical course and heavy proteinuria (<1%), initial therapy with pulse prednisolone (1g daily for 3 days) has been used, followed by prednisone plus cyclophosphamide, resulting in reduction of proteinuria and stabilisation of deteriorating renal function.

Other immunosuppressive regimens that may be of benefit in patients with severe or rapidly progressive IgA nephropathy include:

- mycophenolate mofetil as maintenance therapy;[46]
- prednisone plus monthly intravenous pulse cyclophosphamide for 6 months;[47]
- prednisone plus azathioprine administered for more than 1 year;[48]
- high-dosage intravenous immunoglobulin (2 g/kg each month) for 3 successive months and subsequent intramuscular immunoglobulin for another 6 months;[49]
- plasma exchange, cyclophosphamide and prednisone;[50,51]
- pulse prednisolone;[52]
- prednisone, cyclophosphamide and anticoagulants for several months;[53]
- prednisone, azathioprine and cyclophosphamide or chlorambucil;[6]
- prednisone and anticoagulation;[54]
- prednisolone therapy for more than 1 year;[55]
- cyclophosphamide, dipyridamole and warfarin.[56,57]

However, therapeutic trials that convincingly show a long term beneficial effect on the progression of renal insufficiency in IgA nephropathy are wanting; such trials are difficult to carry out as IgA nephropathy progresses toward renal failure over several years in a minority of patients.[58]

4.4 Other Measures

One study[59] reported beneficial effects of fish oil therapy in retarding the rate at which renal function is lost in patients with IgA nephropathy; however, concerns over the validity of these conclusions have been expressed,[60] predominantly with regard to the observations in the control group and the duration of follow-up, and the results have not been borne out by other studies.[61,62] No consistent beneficial effects on renal function have been observed in controlled trials involving the lowering of serum IgA levels with phenytoin, tonsillectomy, nonsteroidal anti-inflammatory drugs, gluten-free diets (designed to lower dietary antigen intake), anticoagulant therapy, antiplatelet drugs or plasma exchange.[2,60]

5. Conclusion

It can be concluded that the overall prognosis of patients with IgA nephropathy is generally good. Features that are shown to be associated with a very good prognosis include recurrent macroscopic haematuria, normal or mildly to moderately impaired renal function at presentation, and proteinuria of less than 1 g/day.

In deciding therapeutic strategies, it is important to consider the clinical indicators of a poor prognosis at presentation, the renal biopsy findings and the follow-up course. Hypertension, an older age, a family history of glomerulonephritis, proteinuria in excess of 1 g/day, severe impairment of renal function and casts on centrifuged urine microscopy are adverse clinical factors. Renal biopsy findings such as tubulointerstitial and vascular changes, glomerular sclerotic and proliferative

changes, intensity of immunofluorescence, and mixed-site immune-complex deposition portend a worse prognosis. During follow-up, persistence of casts, ongoing high urinary red blood cell counts, persistence or development of heavy proteinuria or hypertension, and transient decreases or a progressive decline in renal function, all predict renal failure.

Identification of patients at high risk of progressive renal disease enables therapeutic strategies to be instituted in an endeavour to slow such progression.

Acknowledgements

The authors gratefully acknowledge the expert librarian and editorial assistance of Ms Elizabeth de Kantzow.

References

1. Berger J, Hinglais N. Les dépôts intercapillaires d'IgA-IgG. J Urol Nephrol 1968; 74: 694-5
2. Ibels LS, Gyory AZ. IgA nephropathy: analysis of the natural history, important factors in the progression of renal disease, and a review of the literature. Medicine 1994; 73: 79-102
3. ANZDATA Report 1996. In: Disney APS, editor. Australia and New Zealand dialysis and transplant registry report. Adelaide, South Australia: Australia and New Zealand Dialysis and Transplant Registry, 1996
4. Ibels LS, Gyory AZ, Caterson RJ, et al. Primary IgA nephropathy: natural history and factors of importance in the progression of renal impairment. Kidney Int. In press
5. Roodnat JI, van Stiphout WAHJ, Rosendaal FR, et al. What do we really know about the long-term prognosis of IgA-nephropathy? J Nephrol 1991; 3: 145-51
6. Orlowski T, Gorski A, Rancewicz Z, et al. IgA nephropathy: a long-term progressive study. Miner Electrolyte Metab 1990; 16: 54-6
7. Kusumoto Y, Takebayashi S, Taguchi T, et al. Long-term prognosis and prognostic indices of IgA nephropathy in juvenile and in adult Japanese. Clin Nephrol 1987; 28: 118-24
8. Alamartine E, Sabatier JC, Guerin C, et al. Prognostic factors in mesangial IgA glomerulonephritis: an extensive study with univariate and multivariate analysis. Am J Kidney Dis 1991; 18: 12-9
9. Beukhof JR, Kardaun O, Schaafsma W, et al. Toward individual prognosis of IgA nephropathy. Kidney Int 1986; 29: 549-56
10. Nicholls KM, Fairley KF, Dowling JP, et al. The clinical course of mesangial IgA associated nephropathy in adults. Q J Med 1984; 53: 227-50
11. Kesson AM, Talbott JM, Gyory AZ. Microscopic examination of urine. Lancet 1978; I: 809-12
12. Gyory AZ, Hadfield C, Lauer CS. Value of urine microscopy in predicting histological changes in the kidney: double blind comparison. BMJ 1984; 288: 819-22
13. Abe S, Amagasaki Y, Iyori S, et al. Significance of tubulointerstitial lesions in biopsy specimens of glomerulonephritic patients. Am J Nephrol 1989; 9: 30-7
14. D'Amico G, Minetti L, Ponticelli C, et al. Prognostic indicators in idiopathic IgA mesangial nephropathy. Q J Med 1986; 59: 363-78
15. Bogenschutz O, Bohle A, Batz C, et al. IgA nephritis: on the importance of morphological and clinical parameters in the long-term prognosis of 239 patients. Am J Nephrol 1990; 10: 137-47
16. Johnston PA, Brown JS, Braumholtz DA, et al. Clinico-pathological correlations and long-term follow-up of 253 United Kingdom patients with IgA nephropathy: a report from the MRC glomerulonephritis registry. Q J Med 1992; 84: 619-27
17. Neelakantappa K, Gallo G, Baldwin DS. Proteinuria in IgA nephropathy. Kidney Int 1988; 33: 716-21
18. Chida Y, Tomura S, Takeuchi J. Renal survival rate of IgA nephropathy. Nephron 1985; 40: 189-94
19. Kobayashi Y, Tateno S, Hiki Y, et al. IgA nephropathy: prognostic significance of proteinuria and histological alterations. Nephron 1983; 34: 146-53
20. Pollock C, Liu P-L, Gyory AZ, et al. Dysmorphism of urinary red blood cells – value in diagnosis. Kidney Int 1989; 36: 1045-9
21. Hara M, Endo Y, Nihei H, et al. IgA nephropathy with subendothelial deposits. Virchows Arch A Pathol Anat Histol 1980; 386: 249-63
22. Ibels LS. Atherosclerosis, nephrocalcinosis and progressive renal failure: inevitable but potentially retardable complications of chronic renal disease [thesis]. Sydney: Univ of Sydney, 1991
23. Lamas S, Sanz A, Ruiz A, et al. Weight reduction in massive obesity associated with focal segmental glomerulosclerosis: another evidence for hyperfiltration? Nephron 1990; 56: 225-6
24. Jacobson HR, Striker GE. Report on a workshop to develop management recommendations for the prevention of progression in chronic renal disease. Am J Kidney Dis 1995; 25: 103-6
25. Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. N Engl J Med 1994; 330: 877-84
26. Becker GJ, Whitworth JA, Ihle BU, et al. Prevention of progression in non-diabetic chronic renal failure. Kidney Int 1994; 45 Suppl.: S-167-70
27. Pedrini MT, Levey AS, Lau J, et al. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: a metaanalysis. Ann Intern Med 1996; 124: 627-32
28. Maschio G, Oldrizzi L, Tessitore N, et al. Early dietary protein and phosphorus restriction is effective in delaying progression of chronic renal failure. Kidney Int 1983; 16 Suppl.: S-273-7
29. Maschio G, Oldrizzi L, Rugiu C. Clinical effects of long-term dietary protein and phosphorus restriction in patients with early chronic renal failure. Contrib Nephrol 1987; 55: 20-7
30. Zucchelli P, Zuccala A, Gaggi R. Comparison of the effects of ACE inhibitors and calcium channel blockers on the progression of renal failure. Nephrol Dial Transplant 1995; 10 Suppl. 9: 46-51
31. Brazy PC, Stead WW, Fitzwilliam JF. Progression of renal insufficiency: role of blood pressure. Kidney Int 1989; 35: 670-4
32. Maschio G, Alberti D, Janin G, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. N Engl J Med 1996; 334: 939-45
33. Zucchelli P, Zuccala A, Borghi M, et al. Long-term comparison between captopril and nifedipine in the progression of renal insufficiency. Kidney Int 1992; 42: 452-8

34. Gonzalo A, Gallego A, Rivera M, et al. Progression of renal failure in chronic primary glomerular diseases. Nephron 1994; 68: 32-7
35. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993; 329: 1456-62
36. Jerums G, Allen TJ, Tsalamandris C, et al. Angiotensin converting enzyme inhibition and calcium channel blockade in incipient diabetic nephropathy. Kidney Int 1992; 41: 904-11
37. Bedogna V, Valvo E, Casagrande P, et al. Effects of ACE inhibition in normotensive patients with chronic glomerular disease and normal renal function. Kidney Int 1990; 38: 101-7
38. Maki DD, Ma JZ, Louis TA, et al. Long-term effects of antihypertensive agents on proteinuria and renal function. Arch Intern Med 1995; 155: 1073-80
39. Ibels LS. Calcium channel blocker therapy and retarding the progression of chronic renal disease. Nephrology. In press
40. D'Amico G. The commonest glomerulonephritis in the world: IgA nephropathy. Q J Med 1987; 64: 709-27
41. Lai KN, Ho CP, Chan KW, et al. Nephrotic range proteinuria – a good predictive index of disease in IgA nephropathy? Q J Med 1985; 57: 677-88
42. Mustonen J, Pasternack A, Helin H. The course of disease in patients with nephrotic syndrome and IgA nephropathy. Semin Nephrol 1987; 7: 374-6
43. Fukushi K, Yamabe H, Ozawa K, et al. Clinico-pathological evaluation of IgA nephropathy associated with nephrotic syndrome. Jpn J Nephrol 1988; 30: 247-51
44. Mustonen J, Pasternack A, Rantala I. The nephrotic syndrome in IgA glomerulonephritis: response to corticosteroid therapy. Clin Nephrol 1983; 20: 172-6
45. Schena FP, Montenegro M, Scivittaro V. Meta-analysis of randomised controlled trials in patients with primary IgA nephropathy (Berger's disease). Nephrol Dial Transplant 1990; 5 Suppl. 1 : 47-52
46. Nowack R, Birck R, van der Woude FJ. Mycophenolate mofetil for systemic vasculitis and IgA nephropathy [letter]. Lancet 1997; 349: 774
47. Faedda R, Pirisi M, Satta A, et al. Immunosuppressive treatment of Berger's disease. Clin Pharmacol Ther 1996; 60: 561-7
48. Goumenos D, Ahuja M, Shortland JR, et al. Can immunosuppressive drugs slow the progression of IgA nephropathy? Nephrol Dial Transplant 1995; 10: 1173-81
49. Rostoker G, Desvaux-Belghiti D, Pilatte Y, et al. High-dose immunoglobulin therapy for severe IgA nephropathy and Henoch-Schönlein purpura. Ann Intern Med 1994; 120: 476-84
50. Boobes Y, Baz M, Durand C, et al. Early start of intensive therapy in malignant form of IgA nephropathy. Nephron 1990; 54: 351-3
51. Nicholls K, Walker RG, Dowling JP, et al. 'Malignant' IgA nephropathy. Am J Kidney Dis 1985; 5: 42-6
52. Jindal KK, Trillo A, Bishop G, et al. Crescentic IgA nephropathy as a manifestation of human immune deficiency virus infection. Am J Nephrol 1991; 11: 147-50
53. D'Amico G, Imbasciati E, Barbiano di Belgioioso G, et al. Idiopathic IgA mesangial nephropathy: clinical and histological study of 374 patients. Medicine 1985; 64: 49-60
54. Nakamura T, Ebihara I, Nagaoka I, et al. Abnormal regulation of insulin-like growth factor gene expression in peripheral blood mononuclear cells from patients with IgA nephropathy. Am J Nephrol 1992; 12: 292-302
55. Kobayashi Y, Fujii K, Hiki Y, et al. Steroid therapy in IgA nephropathy: a prospective pilot study in moderate proteinuric cases. Q J Med 1986; 61: 935-43
56. Woo KT, Lee GSL, Lau YK, et al. Effects of triple therapy in IgA nephritis: a follow-up study 5 years later. Clin Nephrol 1991; 36: 60-6
57. Walker RG, Yu SH, Owen JE, et al. The treatment of mesangial IgA nephropathy with cyclophosphamide, dipyridamole and warfarin: a two-year prospective trial. Clin Nephrol 1990; 34: 103-7
58. Galla JH. IgA nephropathy. Kidney Int 1995; 47: 377-87
59. Donadio Jr JV, Bergstrahl EJ, Offord KP, et al. A controlled trial of fish oil in IgA nephropathy. N Engl J Med 1994; 331: 1194-9
60. Van Ypersele De Strihou C. Fish oil for IgA nephropathy. N Engl J Med 1994; 331: 1227-9
61. Bennett WM, Walker RG, Kincaid-Smith P. Treatment of IgA nephropathy with eicosapentanoic acid (EPA): a two-year prospective trial. Clin Nephrol 1989; 31: 128-31
62. Cheng IKP, Chan PCK, Chan MK. The effect of fish-oil dietary supplement on the progression of mesangial IgA glomerulonephritis. Nephrol Dial Transplant 1990; 5: 241-6

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