Management of IgA nephropathy: contemporary views

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Ever since its first description in 1968 by the French pathologist, J. Berger, IgA nephropathy (IgAN) has remained the commonest primary glomerulonephritis worldwide. In Hong Kong, the commonest renal manifestation is microscopic haematuria which is often synpharyngitic. The disease is unique among glomerulopathies in being defined by immunohistochemical findings of mesangial deposition of IgA (Figure 1), rather than by light microscopy in which mesangial cell proliferation is the commonest feature (Figure 2). Another hallmark of the disease is its indolent progressive nature. Between 15% and 40% of adults and children will eventually progress to end stage renal disease. Approximately 15 to 20% develop ESRD within 10 years, and 30 to 35% develop ESRD within 20 years of onset. Proteinuria, elevated serum creatinine, and hypertension predict progression, as does renal biopsy demonstrating focal proliferative glomerulonephritis with crescents, diffuse proliferative glomerulonephritis, or advanced, chronic lesions of tubulointerstitial fibrosis. Until recently, there was no effective treatment available for patients with IgAN. Although there remains no cure, treatment options that slow disease progression are becoming available. In this update I will review the current armamentarium in the management of IgAN.

Conservative treatment

For patients with normal renal function, normotension and only minor urinary abnormalities, such as isolated microhaematuria, and/or low grade proteinuria, the general consensus is not to offer specific treatment but to keep such patients under review. Up to 23% of patients will have a spontaneous complete remission.

Blockers of the renin-angiotensin system

Reduction in proteinuria is considered to be the hallmark of effective treatment in preserving renal function in nondiabetic renal diseases. Angiotensin-converting enzyme inhibitors (ACEI), and more recently angiotensin II type 1 receptor blockers (ARB), are widely used to control blood pressure and proteinuria, both of which are considered modifiable risk factors for progressive disease, in IgAN subjects with significant proteinuria with or without hypertension. They are superior to other antihypertensives in lowering proteinuria by virtue of their capacity to reduce intraglomerular pressure. Response to ACEi in IgAN has been reported to be related to the ACE genotype, with more favourable outcome in subjects with the DD genotype over those with ID or II genotypes. Limited data are available on the effects on proteinuria of combination therapy with ACEi/ARB. In a small trial, the combination of losartan and enalapril appeared to have an additive effect on the reduction of urinary protein excretion, whereas doubling the dose of monotherapy had no effect. In the COOPERATE study in which half of the subjects had IgAN, combination treatment safely retarded progression of non-diabetic renal disease compared with monotherapy. One of the precautions in prescribing monotherapy or dual therapy is refractory hyperkalaemia particularly in subjects with significant renal impairment. Another precaution is the precipitation of acute renal failure in subjects with bilateral renovascular disease.

Corticosteroids

Corticosteroids have been used for over 20 years in the treatment of IgAN because of their antiinflammatory and immunosuppressive properties, and are usually confined to patients considered at risk of progressive renal failure. A meta-analysis of six available trials of sufficient quality suggested that corticosteroid therapy may be effective in reducing proteinuria, although the impact on protecting renal function is less clear. In an RCT from Italy, treatment with steroids (1 g/d of intravenous methylprednisolone for 3 d at the beginning of months 1, 3, and 5, plus 0.5 mg of oral prednisone/kg BW on alternate days for 6 m) was shown to lower proteinuria by 50% after 6 months and to reduce the risk of a 50% increase in the serum creatinine level by 36% after five years. The long-term follow-up data from this study showed impressive benefits of corticosteroid treatment in reducing proteinuria and preventing ESRD. Although several
other studies have shown beneficial results in small numbers of patients treated with daily or alternate-day steroid early in their illness, long-term efficacy in controlling disease progression has not been validated in Chinese patients, and therapy is only beneficial to selected groups of patients with IgAN and nephrotic syndrome\(^{14}\). Another recent RCT of corticosteroids showed only a modest reduction in proteinuria with no protection of GFR amongst Japanese patients\(^{15}\).

At this juncture, steroid does not appear to consistently offer any beneficial effect other than modest amelioration of proteinuria. The only exception is found in children with IgA deposition in the setting of minimal change nephrotic syndrome. Such patients respond to corticosteroid promptly\(^{16}\). In adults, in view of the toxicities associated with steroid therapy, it should be considered only when proteinuria persists $>1\,g/24\,h$ despite optimal BP control and maximum RAS blockade.

### Fish oil (n-3 Polyunsaturated Fatty Acids) supplementation

The first landmark report on the efficacy of dietary fish-oil supplements was published in 1994 from the Mayo Clinic\(^{17}\). The rationale of using fish oil in IgAN is based on the premise that ω-3 polyunsaturated fatty acids alter the production or action of cytokines and eicosanoids evoked by the initial or by repeated immunological renal injury, thereby alleviating ongoing renal inflammation and glomerulosclerosis, both being hallmarks of progressive renal disease. However, a meta-analysis of 5 controlled trials failed to substantiate the efficacy of fish oil in IgAN\(^{18}\). The mean effect to indicate that treatment was superior to control was not statistically significant. Despite this, the Mayo investigators published their long-term data in 1999 to conclude that early and prolonged treatment with fish oil slows renal progression for high-risk patients with IgAN\(^{19}\). Locally, a study performed in the late 1980s on 11 patients with IgAN given dietary fish oil supplement showed either no demonstrable or an unpredictable effect\(^{20}\). The preliminary report of a more recent RCT showed no benefit of 2 years of treatment with fish oil compared with corticosteroids and placebo\(^{21}\). Hence, the clinical benefit of fish oil supplementation in IgAN cannot be established at this point, and primary treatment of IgAN with fish oil is not recommended.

### Cyclophosphamide

Only one study suggested efficacy of cyclophosphamide followed by azathioprine in conjunction with high-dose prednisolone in patients who are at very high risk for progression (ESRD predicted in all cases within 5 yr)\(^{22}\). However, these are only a small minority of patients encountered in clinical practice. Thus, there is insufficient evidence to justify the use of such cytotoxic agent in IgAN except in crescentic IgAN with rapidly progressive renal failure.

### Mycophenolate mofetil (MMF)

The rationale for employing MMF to treat IgAN stems from its selective suppressive effects on lymphocyte proliferation and antibody formation\(^{23}\). Four clinical trials have been published so far which together gave no conclusion. We provided evidence that a 6-month course of MMF (0.75 to 1 g b.d.) can induce lasting remission (up to 72 weeks of follow up thus far) of proteinuria in at-risk patients (i.e. those with persistent proteinuria $>1\,g/\text{day}$ despite full RAS inhibition and normal BP, but had histology that did not reveal advanced sclerosis)\(^{24}\). Similarly, another report from Beijing suggested that MMF is more effective than prednisone in reducing proteinuria in patients with urine protein $>2\,g/\text{d}$\(^{25}\). Conversely, lack of efficacy was reported from Belgium (MMF for 3 years in 21 patients with histologic unfavourable criteria, arterial hypertension, and inulin clearance between 21 and 69 ml/min)\(^{26}\) and North America (MMF for 1 year as a “salvage” therapy in 16 patients with advanced renal insufficiency)\(^{27}\). Such discrepancies likely arise from a difference in race, and our selection of patients with less advanced disease. It would be reasonable at this point to recommend MMF to at-risk patients without advanced sclerosis who can afford this expensive drug.

### Kidney transplantation

Kidney transplantation offers the best potential for full rehabilitation in ESRD from IgAN. Disease recurrence in the allograft typically is slowly progressive. Available evidence indicates at 5 years a 5% risk for graft failure due to recurrence, a 13% risk for significant graft dysfunction, and at least 50% risk for IgA deposition. Local data suggest that around 20% of patients developed recurrence by 5 years after transplantation\(^{28}\). The risk for graft loss increases markedly to 25% when a first graft was lost to recurrence. There is no consistent evidence that these risks differ between living and cadaveric donors\(^{29}\).

### Into the future

Short of an effective cure of IgAN, future therapeutic attempts should target the prevention of mesangial IgA deposition and the amelioration of the ensuing downstream inflammatory injury induced by infiltrating neutrophils and the released cytokines\(^{30}\). Based on pathogenetic insights derived from experimental studies, antagonism of platelet-derived growth factor and transforming growth factor provides an attractive and possibly more specific therapeutic alternative to immunosuppression. At present, the development of other novel therapeutic approaches is greatly hampered by the lack of animal models that resemble human IgAN.


3. Lai KN, Mac-Moune LF, Li PK, Chan KW, Au TC, Tong KL: The clinicopathological characteristics of IgA nephropathy in Hong Kong. Pathology 20:15-19, 1988


MCHK CME Programme Self-assessment Questions

Please read the article entitled "Management of IgA nephropathy: contemporary views" by Dr. Sydney CW Tang and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheet via fax (2865 0345) or by mail to the Federation Secretariat on or before 31 May 2006. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please choose the best answer.

1. What investigation is needed to make a definitive diagnosis of IgAN?
a. Serum IgA level
b. Urine RBC
c. Renal biopsy
d. 24-hour Urine protein

2. What is the confirmatory histologic feature in IgAN?
a. Mesangial proliferation
b. Concomitant IgA deposition
c. Double contouring of glomerular basement membrane
d. Predominant or codominant mesangial IgA deposit

3. What is the commonest mode of presentation?
a. Microscopic haematuria (often incidentally found)
b. Hypertension
c. Nephrotic syndrome
d. Gross haematuria

4. Which is not a modifiable risk factor for progression to ESRD in IgAN
a. Proteinuria
b. Haematuria
c. Hypertension

5. Which is the drug of first choice for patients with significant proteinuria regardless of blood pressure?
a. Ca channel blocker
b. MMF
c. ACEi and/or ARB
d. Corticosteroid

6. Which of the following is not a potential adverse effect of RAS blockade
a. Hyponatraemia
b. Hyperkalaemia in patients with CRF
c. Acute renal failure in subjects with bilateral renal artery stenoses
d. Dry cough

7. Is corticosteroid a standard form of treatment for IgAN?
a. No
b. Yes

8. When should corticosteroid be considered in IgAN?
a. In gross haematuria
b. In proteinuria
c. In microscopic haematuria
d. In crescentic IgAN

9. When should mycophenolate be considered in IgAN?
a. Advanced renal insufficiency
b. Refractory proteinuria despite full RAS blockade in the absence of significant kidney fibrosis
c. Before renal transplantation
d. Recurrent synpharyngitic haematuria

10. What may be a peculiar feature in patients who undergo renal transplantation due to ESRD resulting from IgAN?
a. Acute allograft rejection
b. Recurrent IgAN
c. Graft thrombosis
d. Polycythaemia
Please return the completed answer sheet to the Federation Secretariat on or before 31 May 2006 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

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Answers to April 2006 issue

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