

IgA glomerulonephritis: which is the best treatment to offer?

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■ ABSTRACT

IgA nephropathy (IgAN) is a highly heterogeneous disease. ACE inhibitors and angiotensin II type I receptor blockers slow its progression but do not halt specific pathogenetic mechanisms. Many other therapeutic approaches have been proposed. Most have been tested in a relatively small number of patients and have not yet proven to be effective in the long term. Tonsillectomy may be a valid option, but it has only recently been tested in a small, prospective, non-randomised trial. Fish oil is used in the United States, but evidence supporting this therapy comes mainly from only one study with some important drawbacks. Steroids seem to be the best treatment for patients with proteinuria, as this class of drugs ameliorate it and protect against deterioration of renal function. Combined treatment with corticosteroids and cytotoxic drugs has yielded some results in small studies. Preliminary findings of a large, randomised trial testing the effect of azathioprine in addition to a course of steroids do not suggest a significant advantage over steroids alone.

Key-Words:

IgA nephropathy; azathioprine; fish oil; hypertension; proteinuria; steroids; tonsillectomy.

■ INTRODUCTION

IgA nephropathy (IgAN) is a highly heterogeneous disease. Clinical features range from asymptomatic haematuria to rapidly progressive glomerulonephritis,

but while it is most often associated with microscopic haematuria or recurrent macroscopic haematuria, spontaneously reversing acute renal failure can also occur. Pathologically, a spectrum of glomerular lesions can be seen, but mesangial proliferation with prominent IgA deposition is observed in almost all biopsies.

Contrary to initial reports that indicated favourable prognoses, long-term follow-up has revealed that outcomes are highly variable¹⁻⁴. Proteinuria exceeding 1 g/day, arterial hypertension, impaired renal function at the time of renal biopsy, glomerular sclerosis and tubulo-interstitial scarring are the most powerful predictors for adverse outcome¹⁻⁴. It remains difficult to predict long-term renal outcomes in individual patients, however. Many patients with only minor changes at the time of biopsy eventually progress to ESRD^{1,5,6} while others may have spontaneous remission⁴.

The unpredictable clinical outcomes might be partially explained by the fact that our understanding of the pathogenesis of this disease is far from comprehensive. Moreover, it is likely that more than one mechanism may contribute to susceptibility and progression of IgAN⁷⁻⁹.

The extreme heterogeneity of IgAN may partially explain why, despite the fact that this disease was first described nearly 40 years ago, we are still far from a definition of the optimal treatment for preventing progression towards ESRD in all patients without important side effects. The list of potential treatments has been expanding proportionally to criticism of their effectiveness. Treatments that aim to

influence some of the putative pathogenetic processes of IgAN development and perpetuation have been tested, but mostly in a relatively small number of patients and have not yet proven to be effective in the long term.

In this review we will try to shed some light on proposed treatments for IgAN, hopefully helping physicians choose the best available therapy according to patient characteristics.

■ TONSILLECTOMY

As part of the systemic IgA production system, the tonsils primarily produce IgA1 and may act as activators or effectors of IgA deregulation. Tonsillitis and upper respiratory infections frequently precede IgAN, and tonsillectomy has been proposed as a means of preventing its progression.

This therapeutic approach is quite popular in the far East, but data from randomised, controlled trials are still lacking. The studies performed so far have been retrospective¹⁰⁻¹³, suffering inevitably from selection biases. Moreover, patients submitted to tonsillectomy were often treated with immunosuppressive drugs, complicating data interpretation¹².

Other studies have no control group to compare data with¹⁴.

Recently, the Japanese Multicenter Study Group on Treatment of IgA Nephropathy (JST-IgAN) reported their experience of tonsillectomy combined with corticosteroids in a prospective cohort study of 101 patients, who were observed for 5 years¹⁵. They found a higher remission rate of urinary abnormalities in patients receiving tonsillectomy plus steroids compared to those treated with steroids alone, but again the study was not randomised and the control group was much smaller than the study group.

Given also that severe pain follows tonsillectomy in adults and the risk of postoperative haemorrhage is not negligible¹⁶, in our opinion, this therapeutic approach cannot at present be recommended for widespread use. The recently proposed subcapsular tonsillectomy may be of interest in reducing morbidity related to the surgical procedure¹⁷.

■ FISH OIL

Fish and marine oils are the most abundant sources of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the two major n-3 fatty acids that are substrates for cyclooxygenase and lipoxygenase pathways, leading to less potent inflammatory mediators than those produced through the n-6 PUFA substrate, arachidonic acid. N-3 PUFA can also suppress inflammatory and/or immunologic responses through eicosanoid-independent mechanisms¹⁸. A number of experimental studies have indicated dose-dependent positive effects of EPA and DHA^{19,20}. However, conflicting results have been reported in IgAN patients²¹⁻²⁴. Earlier studies were small, had little statistical power, and enrolled patients with varying degrees of renal insufficiency and proteinuria²¹⁻²³. More than ten years ago the Mayo Nephrology Collaborative Group²⁴ conducted a double-blind, placebo-controlled, randomised trial of fish oil in 106 IgAN patients with proteinuria >1 g/day. After nearly two years, less patients in the fish oil than in the placebo group (6% vs. 33%, respectively) reached the primary endpoint of the 50% increase in serum creatinine from baseline. This positive effect was evident also after four years of follow-up. However, interpretation of results is complicated by the fact that patients in the control group had higher baseline proteinuria levels and an atypically severe outcome. This might have falsely amplified the benefit of fish oil. Fish oil was more effective in patients with impaired renal function, but this analysis is influenced by a low event rate in the patients with normal renal function. Strangely, fish oil was not effective in reducing proteinuria. The long-term results of this study confirmed better rates of renal survival in patients treated with fish oil²⁵. The same group also compared two different doses of fatty acids (EPA 3.76 g and DHA 2.94 in a randomised trial of 73 IgAN patients²⁶. Unfortunately, the effects of the two dose regimens were equivalent. A meta-analysis of these trials, which was dominated by the study of Donadio *et al*²⁴, concluded that fish oil has a positive, but not statistically significant, effect in reducing the risk of intermediate renal end-points (equal to serum creatinine over time or the creatinine clearance rate)²⁷.

Recently, Hogg *et al*²⁸ published the results of a placebo-controlled, double-blind trial evaluating the role played by omega 3 fatty acids in comparison to prednisone or no treatment (placebo) in 96 IgAN

patients with estimated GFR ≥ 50 ml/min per 1.73 m^2 and moderate to severe proteinuria. Neither treatment group showed benefit over the placebo group with respect to time to primary end-point (estimated GFR $< 60\%$ of baseline). However, interpretation of these findings is affected by the fact that patients receiving placebo had a lower level of proteinuria than those receiving fish oil or steroids. Moreover, the sample size was less than foreseen and the study follow-up was probably too short to adequately study progression rate.

Despite its favourable adverse effects profile, fish oil is an expensive treatment. In our opinion available evidence does not support an indiscriminate and extensive use of this therapy in IgAN.

■ LEFLUNOMIDE

Leflunomide is an immunomodulatory drug that may exert its effects by inhibiting the mitochondrial enzyme dihydro-orotate dehydrogenase (DHO-DH), which plays a key role in the *de novo* synthesis of the pyrimidine ribonucleotide uridine monophosphate (rUMP). It is currently used to treat rheumatoid arthritis. Lou *et al*²⁹ tested this agent in 60 IgAN patients who were randomised to receive either leflunomide or foscipril for six months. Both agents were able to significantly reduce proteinuria during follow-up. These preliminary results are encouraging, but further larger, long-term, randomised studies are required before leflunomide can be recommended for the treatment of IgA nephropathy.

■ ACE INHIBITORS AND/OR ANGIOTENSIN II RECEPTOR BLOCKERS

Once renal damage occurs, other mechanisms contribute to disease progression, independent of the underlying nephropathy. Activation of the renin-angiotensin system (RAS) plays a key role, promoting intraglomerular and systemic hypertension and inducing proliferation of mesangial and tubular cells, by both direct and indirect mechanisms. It has been clearly demonstrated that RAS blockade effectively slows the progression of chronic nephropathies, especially when proteinuric³⁰.

ACE inhibitors (ACEI) induce a significant reduction in proteinuria also in IgAN³¹⁻³³; retrospective studies have shown a slower rate of glomerular filtration rate decline in ACEI-treated IgAN patients^{34,35}. Conversely, secondary analyses of the two largest studies examining the use of ACEI in patients with non-diabetic renal diseases did not show a specific beneficial influence on the evolution of the disease in IgAN patients^{36,37}, with the only exception a trend towards slower progression rates among ramipril-treated patients in the REIN study³⁸. Probably, the mean follow-up (less than 3 years) of the patients included in the AIPRI and REIN studies was too short to detect pharmacological effects in a nephropathy characterised by a slow progression rate in the majority of patients. Moreover, the sample size of these subgroups was quite small.

Praga *et al*³⁹ studied 44 IgAN patients with plasma creatinine ≤ 1.5 mg/dl and proteinuria ≥ 0.5 g/day, randomised to receive enalapril (beginning with a dose of 5 mg/day, and then increasing it to achieve and keep blood pressure $\leq 140/90$ mmHg, up to a maximal dose of 40 mg/day) or no treatment. After a mean follow-up of 75 months, the proportion of patients reaching the primary endpoint (50% increase of baseline plasma creatinine) was significantly lower in the treated group than in the control group (12% vs. 57%, respectively). Proteinuria showed a significant decrease in the treated group, whereas it did not show significant changes in the control group. At multivariate analysis, treatment with enalapril was the only predictor of renal survival (OR, 0.18; 95% CI, 0.03 to 0.87; $P=0.04$). However, the sample size of this study was quite small and heterogeneous.

Very recently, Coppo *et al*⁴⁰ published the results of a multicentre, randomised, placebo-controlled, double-blind trial investigating the effect of benazepril in 66 children and young people with IgAN, moderate proteinuria and creatinine clearance >50 ml/min per 1.73 m^2 . Despite these inclusion criteria, the majority of the patients had normal renal function and were normotensive at baseline, consequently displaying a slow progression rate during follow-up. After a median follow-up of nearly three years, only one patient in the ACE-I group and five in the placebo group reached the primary end point of a 30% decrease in CrCl. This difference was not statistically significant, probably because of the small number of

patients reaching the endpoint. Mean proteinuria significantly decreased in patients receiving benazepril (from 1.61 ± 0.70 to 0.94 ± 0.98 g/d per 1.73 m^2 at the end of follow-up; $p=0.002$), whereas it slightly diminished in the placebo group (from 1.87 ± 0.74 g/d per 1.73 m^2 to 1.80 ± 1.34 g/d per 1.73 m^2 at the end of follow-up; $p=NS$).

Angiotensin II receptor blockers (ARB) have also been tested recently in IgAN. Li *et al*⁴¹ performed a double-blind, randomised, placebo-controlled, multicentre study on 109 patients with proteinuria greater than 1 g/day and/or chronic renal insufficiency who were randomly assigned to valsartan (80 mg/d) or placebo. Only 4 patients in the placebo group and 1 patient in the treatment group reached the primary end point of the doubling of serum creatinine from baseline or ESRD, (log-rank test, $P=0.18$), but the follow-up was again probably too short (nearly two years). Conversely, proteinuria decreased significantly in the treatment group (from 1.8 ± 1.2 to 1.2 ± 1.2 g/day; $P=0.03$), but did not change in the placebo group. Unfortunately, the interpretation of these findings is biased by the fact that patients treated with valsartan had slightly greater baseline GFR and less proteinuria than those receiving placebo. Moreover, they achieved significantly lower blood pressure values than those of the control group. This latter drawback is absent in another randomised clinical trial, performed in 263 patients mainly affected by glomerular nephropathies (nearly half of whom were affected by IgAN) that showed comparable effects of treatment with ACEI (trandolapril 3 mg/day) and ARB (losartan 100 mg/day) on renal survival and proteinuria⁴²; combination treatment markedly improved renal survival and significant reduced proteinuria compared to treatment with the single agents⁴².

Altogether, RAS blockade is an effective therapeutic approach in IgAN. However, it is not specific to this disease and it is therefore unlikely to substantially alter its natural course, as the underlying mechanisms persist and perpetuate renal damage.

■ CORTICOSTEROIDS

Corticosteroids are potent anti-inflammatory agents that have been used to treat glomerular diseases for nearly 50 years. Administered on a daily

or alternate-day basis, they have had variable success in patients with IgAN. However, the majority of the studies published in this area are of poor quality, retrospective^{43,44} non-randomised⁴⁵, have small sample sizes and short follow-up^{28,44,46-50}. Only two trials^{51,52} were prospective and randomised, with adequate sample sizes and follow-up (more than five years).

Katafuchi *et al*⁵¹ randomised 90 IgAN patients with normal renal function to steroids (oral prednisolone (20 mg/day for 1 month followed by 15 mg/day for 1 month, 10 mg/day for 1 month, 7.5 mg/day for 3 months and 5 mg/day for 18 months) plus dipyridamole (150 or 300 mg/day) or dipyridamole alone at the same dose. Steroids significantly reduced proteinuria, but were ineffective on renal survival. However, the event rate was very low (only three patients in each group progressed to ESRD during follow-up). Moreover, treatment groups were not homogeneous for IgAN activity, since the patients in the steroid group had significantly higher proteinuria and proliferation indices at baseline. Finally, as acknowledged by the authors themselves, the dose of steroids used was perhaps too low to halt nephropathy progression.

Pozzi *et al*⁵² studied the effects of steroids in 86 patients with IgAN in the early stage with relatively well preserved renal function and significant proteinuria (1-3.5 g/day). The patients received either support therapy or a six-month steroid course (1 g of methylprednisolone intravenously for three consecutive days at the beginning of the first, third and fifth months, and oral prednisone (0.5 mg/kg) every other day for 6 months). After five years' follow-up, renal survival was significantly better in the steroid-treated patient group than in the control group for both the primary endpoints of 50% and 100% increase from baseline plasma creatinine levels (respectively of 17% and 21%; log-rank test $P < 0.048$ and < 0.005). Three patients in the control group and none in the steroid group required dialysis. Evaluation of renal survival after ten years follow-up confirmed that outcomes in the steroid-treated group were better than those in the control group (97% vs. 53%, $P = 0.0003$, $NNT = 4$)⁵³.

Mean urinary protein excretion also significantly decreased in the steroid group (from 1.93 ± 0.45 g/day at baseline to 0.78 ± 0.41 g/day at one year), and this decrease persisted throughout the follow-up, whereas proteinuria remained unchanged in the control group. The positive effect of steroids was confirmed

by analysing proteinuria as a categorical variable. After 12 months, proteinuria in 31 steroid-treated patients (72%) had dropped below 1 g/day with only 13 members (30%) of the control group experiencing a similar improvement of proteinuria⁵³. None of the patients in the steroid group experienced any major side effects^{52,53}.

In our opinion, steroids seems to be the best available treatment for IgAN patients with proteinuria.

■ CYTOTOXIC DRUGS

Data on cyclosporine are limited and quite disappointing⁵⁴. Mycophenolate mofetil (MMF) might hold more promise. This is an immunosuppressive agent that blocks purine biosynthesis by inhibiting the enzyme inosine monophosphate dehydrogenase (IMPDH). It inhibits T- and B-lymphocyte proliferation, induces apoptosis of activated T-lymphocytes, reduces synthesis of antibodies, and may decrease the migration of inflammatory cells into glomeruli after antibody deposition. However, available studies have a small sample size and conflicting results. Maes *et al*⁵⁵ tested this drug (2 g/day for three years) in 21 IgAN patients with decreased renal function, and/or proteinuria >1 g/day/1.73 m² and/or hypertension and/or histological unfavourable criteria and compared them to 13 untreated subjects. They found no difference in renal survival after three years, but the sample size was probably too small. Frisch *et al*⁵⁶ randomised 32 IgAN to treatment with MMF (1 g b.i.d for one year) vs. no treatment (all patients received ACEI, some of them also received fish oil at their own or at their physician's discretion). No differences were observed between the two groups at the end of the study in terms of progression rate or proteinuria changes, again probably because of the too-small sample size. It is worth noting that the majority of the patients had chronic renal insufficiency at baseline (mean serum creatinine of 2.4 mg/dl). Tang *et al*⁵⁷ were the only ones able to show significant positive effects of MMF on proteinuria. They randomised 40 patients with IgAN to receive MMF (1.5-2 g/day according to body weight for 24 weeks) or no treatment: after 18 months of follow up, 16 out of 20 patients from the MMF group and 6 out of 20 controls had proteinuria remission, defined as proteinuria below 0.3 g/day or a 50% reduction in 24 h proteinuria. A five-year, prospective

trial of early IgAN is ongoing comparing long-term renal survival in ACEI treated patients with or without one-year MMF immunosuppression⁵⁸. The planned sample size is of nearly 130 patients.

■ CORTICOSTEROIDS PLUS CYTOTOXIC DRUGS

Several controlled studies of combination of corticosteroids and cytotoxic drugs have been performed in patients with severe IgAN⁵⁹⁻⁶⁴. However, they differ markedly in design, type of drug, duration of treatment and follow-up, baseline renal function and histological characteristics. Moreover, the number of patients enrolled was often insufficient to formulate reliable conclusions, and important adverse effects, including severe infections, malignancies, drug-induced marrow suppression, secondary diabetes, alopecia and peptic ulcer were reported by 8-25% of treated patients⁶⁵.

Among these studies, in our opinion two trials using azathioprine are of particular interest. Ballardie and Roberts⁶² enrolled 38 patients with progressive IgAN in a controlled, prospective study comparing prednisolone, cyclophosphamide and azathioprine for a minimum of two years to no immunosuppression. After 5 years, renal survival was 72% in treated patients and only 6% in controls. However, the sample size was very small and the follow-up was too short to draw definitive conclusions. Yoshikawa *et al*⁵⁹ tested the effectiveness of prednisolone, azathioprine, heparin-warfarin and dipyridamole *versus* heparin-warfarin and dipyridamole alone for 24 months in 78 children with diffuse mesangial proliferation. The prednisolone/azathioprine regimen reduced proteinuria significantly. In addition, the mean percentage of glomeruli affected by segmental or global sclerosis at the end of treatment remained unchanged from baseline in this treatment group, whereas it increased from 3.9% to 16.4% in the control group. Although relatively few adverse effects were reported, in our opinion two years' azathioprine treatment of children with minimally progressive IgAN raises concerns about long-term safety. More recently, the same authors tested the effects of prednisolone, azathioprine, warfarin, and dipyridamole (combination) against those of prednisolone alone in 80 children with newly diagnosed IgAN with diffuse mesangial proliferation⁶⁶. After a follow-up of

two years, a higher percentage of patients receiving the combination treatment had proteinuria remission compared to patients receiving steroids alone.

Starting from the observation that steroids alone may not be sufficient to reverse proliferative lesions and prevent development of fibrosis, in 1998 we

Table 1

RCTs on IgA nephropathy with more than 50 patients and at least 6 months of follow-up

RCT	Year	N	Drug	Follow-up (months)	Primary end-point	Secondary end-point
Coppo ⁴⁰	2007	66	Benazepril vs. placebo	38	>30% decrease of CrCl, no significant effect	1) >30% decrease of CrCl or proteinuria ≥ 3.5 g/d/1.73m ² ; one (3.1%) with ACEI and 9 (26.5%) with placebo, p= 0.034 2) proteinuria partial remission (<0.5 g/d/1.73m ²); 13 (40.6%) with ACEI and 3 (8.8%) with placebo group, p = 0.0002 3) total remission (<160 mg/d/1.73m ² for >6 mo; 4 (12.5%) with ACEI and 0 with placebo p=0.015
Hogg ²⁸	2006	96	Fish-oil vs. steroids vs. placebo	36	GFR <60% of baseline, no significant effect	UP/C ratio changes, no effect.
Lou ²⁹	2006	60	Leflunomide + fosinopril vs. fosinopril	6	24h proteinuria, from 1.66 \pm 0.42 g to 0.87 \pm 0.80 g with leflunomide (P < 0.05) and from 2.04 \pm 0.64 g to 1.63 \pm 0.52 g in the control group (P < 0.05).	GFR changes, no significant effect.
Lj ⁴¹	2006	109	Valsartan vs. placebo	26	Doubling of serum creatinine or ESRD, no significant effect	Change in proteinuria, from 1.8 \pm 1.2 to 1.2 \pm 1.2 g/dl with valsartan; P=0.03, unchanged with placebo; decrease in GFR, with valsartan -5.62 \pm 6.79 mL/min/y, with placebo -6.98 \pm 6.17 mL/min/y after adjustment for proteinuria and blood pressure.
Chen ⁶⁸	2004	71	Urokinase + benazepril vs. benazepril	12	Decrease in 24h proteinuria $\geq 50\%$, 25 (71.4%) in the UK + BZ group and 16 (44.4%) in the BZ-alone group, p<0.05	Proteinuria decrease: significantly more with UK + BZ than BZ alone (P<0.05 at 6 and 12 months); endogenous CrCl changes: stable in the UK + BZ group, while CrCl declined significantly at 6 and 12 months in the BZ-alone group compared with baseline (P<0.05).
Chan ⁶⁹	2003	55	Vitamin E vs. placebo	24	GFR changes, no significant effect	Significant decrease in proteinuria, but different proteinuria at baseline.
Katafuchi ⁵¹	2003	90	Prednisolone vs. control	~ 65	Changes in UP-UCR: (steroid group, -0.84 \pm 1.78; controls, 0.26 \pm 1.65; P = 0.0034)	Kidney survival (ESRD) similar in both groups.
Donadio ²⁶	2001	73	EPA 3.76 g and DHA 2.94 g vs. EPA 1.88 g and DHA 1.47 g	24	Change in SCR, no effect	ESRD, no difference.
Pozzi ⁵²	1999	86	Steroids vs. no treatment	60	50% increase in SCR: 9 (21%) in the steroid group vs. 14 (32%) in the control group, p<0.048. 100% increase in SCR: 1 (2%) in the steroid group and 9 (21%) in the control group, p=0.005	Proteinuria changes: median protein excretion decreased in the steroid group, but remained unchanged in the control group.
Yoshikawa ⁵⁹	1999	78	Prednisolone, azathioprine, heparin-warfarin, and dipyridamole vs. heparin-warfarin and dipyridamole	24	Mean urinary protein excretion fell in group 1 (P<0.0001), but remained unchanged in group 2	The percentage of glomeruli showing sclerosis was unchanged in group 1, but increased in group 2 (P=0.006).
Donadio ²⁴	1994	106	Fish-oil vs. placebo	106	50% increase in SCR: 3 (6%) in the fish-oil group and 14 (33%) in the placebo group, P=0.002.	No change in proteinuria.
Walker ⁷⁰	1990	52	Cyclophosphamide (6 months), and dipyridamole and warfarin (2 years) vs. no treatment	24	Creatinine changes: mean \pm SEM from 0.12 \pm 0.01 to 0.13 \pm 0.01 mmol/l (p<0.05) in untreated patients and from 0.10 \pm 0.01 to 0.12 \pm 0.01 mmol/l (p<0.05) in treated patients.	Proteinuria from 1.67 \pm 0.35 to 1.15 \pm 0.31 g/24h (p<0.01) in treated patients, unchanged in the control group.

initiated a new, long-term, randomised, controlled, adequately-sized trial aimed at evaluating the role of low-dose azathioprine (1.5 mg/kg/day for 6 months) plus steroids (methylprednisolone 1 g i.v. for three consecutive days at the beginning of the first, third and fifth months, plus oral prednisone 0.5 mg/kg every other day for 6 months) compared with steroids alone (same dosing schedule) in adults in the early phase of IgAN. This is the largest randomised controlled study performed so far in IgAN, with 251 patients enrolled. Preliminary results were presented last year at the XLIV ERA-EDTA Congress, which was held in Barcelona, Spain⁶⁷. Both treatment regimens were equally effective in reducing proteinuria, with no differences observed in renal survival between the two groups after five years. These findings confirm the effectiveness and safety of steroid treatment in IgAN in a large sample size, but indicate that the addition of azathioprine may not significantly improve patient outcome, and may possibly increase side effects.

CONCLUSIONS

Many therapeutic approaches have been proposed to halt or slow progression of IgAN. Unfortunately, many of them have been shown to be ineffective or have not been tested in high quality trials. For this reason, there is currently considerable diversity of opinion regarding the optimal treatment for this type of nephropathy. Given our personal, positive experience with steroids, we do believe that they may be the best therapeutic options for patients with proteinuria higher than 1 g/day. However, this treatment remains aspecific. We hope that considerable efforts that are ongoing trying to better understand the complex pathogenesis of this nephropathy may open up newer and more specific therapeutic approaches. In the meanwhile, we should not forget to try to reverse all the factors likely to negatively impact on renal function. This means that we must make the effort to detect early hypertension and achieve strict blood pressure control, possibly by means of antiproteinuric and renoprotective agents such as ACE-inhibitors and ARBS and their combination⁶⁵ and eventually statins, considering that proteinuria decrease should be the primary aim of therapy in addition to blood pressure control.

Conflict of interest statement. None declared.

References

- Koyama A, Igarashi M, Kobayashi M. Natural history and risk factors for immunoglobulin A nephropathy in Japan. Research Group on Progressive Renal Diseases. *Am J Kidney Dis* 1997;29:526-32
- D'Amico G, Imbasciati E, Barbiano Di Belgioioso G, *et al.* Idiopathic IgA mesangial nephropathy. Clinical and histological study of 374 patients. *Medicine (Baltimore)* 1985;64:49-60
- Alamartine E, Sabatier JC, Guerin C, Berliet JM, Berthoux F. Prognostic factors in mesangial IgA glomerulonephritis: an extensive study with univariate and multivariate analyses. *Am J Kidney Dis* 1991;18:12-9
- Ibels LS, Györy AZ. IgA nephropathy: analysis of the natural history, important factors in the progression of renal disease, and a review of the literature. *Medicine (Baltimore)* 1994;73:79-102
- Usui J, Yamagata K, Kai H, *et al.* Heterogeneity of prognosis in adult IgA nephropathy, especially with mild proteinuria or mild histological features. *Intern Med* 2001;40:697-702
- Szeto CC, Lai FM, To KF, *et al.* The natural history of immunoglobulin A nephropathy among patients with hematuria and minimal proteinuria. *Am J Med* 2001;110:434-7
- Xu LX, Zhao MH. Aberrantly glycosylated serum IgA1 are closely associated with pathologic phenotypes of IgA nephropathy. *Kidney Int* 2005;68:167-72
- Coppo R, Amore A. Aberrant glycosylation in IgA nephropathy (IgAN). *Kidney Int* 2004;65:1544-7
- Chow KM, Wong TY, Li PK. Genetics of common progressive renal disease. *Kidney Int Suppl* 2005;(94):S41-5
- Tomioka S, Miyoshi K, Tabata K, Hotta O, Taguma Y. Clinical study of chronic tonsillitis with IgA nephropathy treated by tonsillectomy. *Acta Otolaryngol Suppl* 1996;523:175-7
- Nishi S, Xie Y, Ueno M, *et al.* A clinicopathological study on the long-term efficacy of tonsillectomy in patients with IgA nephropathy. *Acta Otolaryngol Suppl* 2004;(555):49-53
- Hotta O, Taguma Y, Yoshizawa N, *et al.* Long-term effects of intensive therapy combined with tonsillectomy in patients with IgA nephropathy. *Acta Otolaryngol Suppl* 1996; 523:165-8
- Chen Y, Tang Z, Wang Q, *et al.* Long-term efficacy of tonsillectomy in Chinese patients with IgA nephropathy. *Am J Nephrol* 2007;27:170-5
- Suwabe T, Ubara Y, Sogawa Y, *et al.* Tonsillectomy and corticosteroid therapy with concomitant methylprednisolone pulse therapy for IgA nephropathy. *Contrib Nephrol* 2007;157:99-103
- Miyazaki M, Hotta O, Komatsuda A, *et al.* Japanese Multicenter Study Group on Treatment of IgA Nephropathy (JST-IgAN). A multicenter prospective cohort study of tonsillectomy and steroid therapy in Japanese patients with IgA nephropathy: a 5-year report. *Contrib Nephrol* 2007;157:94-8
- Windfuhr JP, Chen YS, Remmert S. Hemorrhage following tonsillectomy and adenoidectomy in 15,218 patients. *Otolaryngol Head Neck Surg* 2005;132:281-6
- Noordzij JP, Affleck BD. Coblation versus unipolar electrocautery tonsillectomy: a prospective, randomized, single-blind study in adult patients. *Laryngoscope* 2006; 116:1303-9
- Donadio JV, Grande JP. The role of fish oil/omega-3 fatty acids in the treatment of IgA nephropathy. *Semin Nephrol* 2004;24:225-43
- Jia Q, Zhou HR, Bennink M, Pestka JJ. Docosahexaenoic acid attenuates mycotoxin-induced immunoglobulin A nephropathy, interleukin-6 transcription, and mitogen-activated protein kinase phosphorylation in mice. *J Nutr* 2004;134:3343-9
- Shi Y, Pestka JJ. Attenuation of mycotoxin-induced IgA nephropathy by eicosapentaenoic acid in the mouse: dose response and relation to IL-6 expression. *J Nutr Biochem* 2006;17:697-706

- 21 Hamazaki T, Tateno S, Shishido H. Eicosapentaenoic acid and IgA nephropathy. *Lancet* 1984;1(8384):1017-8
- 22 Cheng IK, Chan PC, Chan MK. The effect of fish-oil dietary supplement on the progression of mesangial IgA glomerulonephritis. *Nephrol Dial Transplant* 1990;5:241-6
- 23 Bennett WM, Walker RG, Kincaid-Smith P. Treatment of IgA nephropathy with eicosapentaenoic acid (EPA): a two-year prospective trial. *Clin Nephrol* 1989;31:128-31
- 24 Donadio JV Jr, Bergstralh EJ, Offord KP, Spencer DC, Holley KE. A controlled trial of fish oil in IgA nephropathy. Mayo Nephrology Collaborative Group. *N Engl J Med* 1994;331:1194-9
- 25 Donadio JV Jr, Grande JP, Bergstralh EJ, Dart RA, Larson TS, Spencer DC. The long-term outcome of patients with IgA nephropathy treated with fish oil in a controlled trial. Mayo Nephrology Collaborative Group. *J Am Soc Nephrol* 1999;10:1772-7
- 26 Donadio JV Jr, Larson TS, Bergstralh EJ, Grande JP. A randomized trial of high-dose compared with low-dose omega-3 fatty acids in severe IgA nephropathy. *J Am Soc Nephrol* 2001;12:791-9
- 27 Dillon JJ. Fish oil therapy for IgA nephropathy: efficacy and interstudy variability. *J Am Soc Nephrol* 1997;8:1739-44
- 28 Hogg RJ, Lee J, Nardelli N, *et al.* Southwest Pediatric Nephrology Study Group. Clinical trial to evaluate omega-3 fatty acids and alternate day prednisone in patients with IgA nephropathy: report from the Southwest Pediatric Nephrology Study Group. *Clin J Am Soc Nephrol* 2006;1:467-74
- 29 Lou T, Wang C, Chen Z, *et al.* Randomised controlled trial of leflunomide in the treatment of immunoglobulin A nephropathy. *Nephrology (Carlton)* 2006;11:113-6
- 30 Jafar TH, Schmid CH, Landa M, *et al.* Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. *Ann Intern Med* 2001;135: 73-87
- 31 Praga M, Hernandez E, Montoyo C, Andres A, Rulope LM, Rodicio JL. Long-term beneficial effects of angiotensin-converting enzyme inhibition in patients with nephrotic proteinuria. *Am J Kidney Dis* 1992;20:240-48
- 32 Maschio G, Cagnoli L, Claroni F, *et al.* ACE inhibition reduces proteinuria in normotensive patients with IgA nephropathy: a multicentre, randomized, placebo-controlled study. *Nephrol Dial Transplant* 1994;9:265-69
- 33 Remuzzi A, Perico N, Sangalli F, *et al.* ACE inhibition and ANG II receptor blockade improve glomerular size-selectivity in IgA nephropathy. *Am J Physiol* 1999;276:F457-66
- 34 Rekola S, Bergstrand A, Bucht H. Deterioration rate in hypertensive IgA nephropathy: comparison of a converting enzyme inhibitor and beta-blocking agents. *Nephron* 1991;59:57-60
- 35 Catratan DC, Greenwood C, Ritchie S. Long-term benefits of angiotensin-converting enzyme inhibitor therapy in patients with severe immunoglobulin A nephropathy: a comparison to patients receiving treatment with other antihypertensive agents and to patients receiving no therapy. *Am J Kidney Dis* 1994;23:247-54
- 36 Maschio G, Alberti D, Janin G, *et al.* Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med* 1996;334:939-45
- 37 The GISEN Group Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet* 1997;349:1857-63
- 38 Ruggenenti P, Perna A, Gherardi G, Benini R, Remuzzi G. Chronic proteinuric nephropathies: outcomes and response to treatment in a prospective cohort of 352 patients with different patterns of renal injury. *Am J Kidney Dis* 2000;35:1155-65
- 39 Praga M, Gutierrez E, Gonzalez E, Morales E, Hernandez E. Treatment of IgA nephropathy with ACE Inhibitors: a randomized and controlled trial. *J Am Soc Nephrol* 2003;14:1578-83
- 40 Coppo R, Peruzzi L, Amore A, *et al.* IgACE: a placebo-controlled, randomized trial of angiotensin-converting enzyme inhibitors in children and young people with IgA nephropathy and moderate proteinuria. *J Am Soc Nephrol* 2007;18:1880-8
- 41 Li PK, Leung CB, Chow KM, *et al.* HKVIN Study Group. Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. *Am J Kidney Dis* 2006;47:751-60
- 42 Nakao N, Yoshimura A, Morita H, *et al.* Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *Lancet* 2003;361(9352):117-24
- 43 Kobayashi Y, Fujii K, Hiki Y, Tateno S, Kurokawa A, Kamiyama M. Steroid therapy in IgA nephropathy: a retrospective study in heavy proteinuric cases. *Nephron* 1988;48:12-7
- 44 Waldo FB, Wyatt RJ, Kelly DR, Herrera GA, Benfield MR, Kohaut EC. Treatment of IgA nephropathy in children: efficacy of alternate-day oral prednisone. *Pediatr Nephrol* 1993;7:529-32
- 45 Kobayashi Y, Hiki Y, Kokubo T, Horii A, Tateno S. Steroid therapy during the early stage of progressive IgA nephropathy. A 10-year follow-up study. *Nephron* 1996;72:237-42
- 46 Lai KN, Lai FM, Ho CP, Chan KW. Corticosteroid therapy in IgA nephropathy with nephrotic syndrome: a long-term controlled trial. *Clin Nephrol* 1986;26:174-80
- 47 Welch TR, Fryer C, Shely E, Witte DP, Quinlan M. Double-blind, controlled trial of short-term prednisone therapy in immunoglobulin A glomerulonephritis. *J Pediatr* 1992;121:474-7
- 48 Nicholls K *et al.* Prednisolone decreases hematuria in IgA nephropathy (Abstract). *Kidney Int* 1994;46:929
- 49 Julian BA, Barker C. Alternate-day prednisone therapy in IgA nephropathy. Preliminary analysis of a prospective, randomized, controlled trial. *Contrib Nephrol* 1993;104:198-206
- 50 Shoji T, Nakanishi I, Suzuki A, *et al.* Early treatment with corticosteroids ameliorates proteinuria, proliferative lesions, and mesangial phenotypic modulation in adult diffuse proliferative IgA nephropathy. *Am J Kidney Dis* 2000;35:194-201
- 51 Katafuchi R, Ikeda K, Mizumasa T, *et al.* Controlled, prospective trial of steroid treatment in IgA nephropathy: a limitation of low-dose prednisolone therapy. *Am J Kidney Dis* 2003;41:972-83
- 52 Pozzi C, Bolasco PG, Fogazzi GB, *et al.* Corticosteroids in IgA nephropathy: a randomized controlled trial. *Lancet* 1999;353(9156):883-7
- 53 Pozzi C, Andrulli S, Del Vecchio L, *et al.* Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. *J Am Soc Nephrol* 2004;15:157-63
- 54 Lai KN, Lai FM, Li PK, Vallance-Owen J. Cyclosporin treatment of IgA nephropathy: a short term controlled trial. *Br Med J (Clin Res Ed)* 1987;295(6607):1165-8
- 55 Maes BD, Oyen R, Claes K, *et al.* Mycophenolate mofetil in IgA nephropathy: results of a 3-year prospective placebo-controlled randomized study. *Kidney Int* 2004;65:1842-9
- 56 Frisch G, Lin J, Rosenstock J, *et al.* Mycophenolate mofetil (MMF) vs placebo in patients with moderately advanced IgA nephropathy: a double-blind randomized controlled trial. *Nephrol Dial Transplant* 2005;20:2139-45
- 57 Tang S, Leung JC, Chan LY, *et al.* Mycophenolate mofetil alleviates persistent proteinuria in IgA nephropathy. *Kidney Int* 2005;68:802-12
- 58 The International IgA Nephropathy Network, ongoing clinical trials. Available at: <http://www.igan-world.org/ongoingtrials.htm#3>
- 59 Yoshikawa N, Ito H, Sakai T, *et al.* A controlled trial of combined therapy for newly diagnosed severe childhood IgA nephropathy. The Japanese Pediatric IgA Nephropathy Treatment Study Group. *J Am Soc Nephrol* 1999;10:101-9
- 60 Roccatello D, Ferro M, Cesano G, *et al.* Steroid and cyclophosphamide in IgA nephropathy. *Nephrol Dial Transplant* 2000;15:833-5
- 61 Tsuruya K, Harada A, Hirakata H, *et al.* Combination therapy using prednisolone and cyclophosphamide slows the progression of moderately advanced IgA nephropathy. *Clin Nephrol* 2000;53:1-9
- 62 Ballardie FW, Roberts IS. Controlled prospective trial of prednisolone and cytotoxics in progressive IgA nephropathy. *J Am Soc Nephrol* 2002;13:142-8
- 63 Goumenos DS, Davlourous P, El Nahas AM, *et al.* Prednisolone and azathioprine in IgA nephropathy - a ten-year follow-up study. *Nephron Clin Pract* 2003;93:C58-68

- 64 Tumlin JA, Lohavichan V, Hennigar R. Crescentic, proliferative IgA nephropathy: clinical and histological response to methylprednisolone and intravenous cyclophosphamide. *Nephrol Dial Transplant* 2003;18:1321-9
- 65 Locatelli F, Del Vecchio L, Pozzi C. IgA glomerulonephritis: beyond angiotensin-converting enzyme inhibitors. *Nat Clin Pract Nephrol* 2006;2:24-31
- 66 Yoshikawa N, Honda M, Iijima K, *et al*. Japanese Pediatric IgA Nephropathy Treatment Study Group. Steroid treatment for severe childhood IgA nephropathy: a randomized, controlled trial. *Clin J Am Soc Nephrol* 2006;1:511-7
- 67 Pozzi C, Del Vecchio L, Andrucci S, *et al*. Steroids and azathioprine vs steroids alone in IgA nephropathy. *Nephrol Dial Transplant* 2007;22(Suppl6):v10 (abstract).
- 68 Chen X, Qiu Q, Tang L, *et al*. Effects of co-administration of urokinase and benazepril on severe IgA nephropathy. *Nephrol Dial Transplant* 2004;19:852-7
- 69 Chan JC, Mahan JD, Trachtman H, *et al*. Vitamin E therapy in IgA nephropathy: a double-blind, placebo-controlled study. *Pediatr Nephrol* 2003;18:1015-9
- 70 Walker RG, Yu SH, Owen JE, Kincaid-Smith P. The treatment of mesangial IgA nephropathy with cyclophosphamide, dipyridamole and warfarin: a two-year prospective trial. *Clin Nephrol* 1990;34:103-7

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