Treatment options for IgA nephropathy in adults: a proposal for evidence-based strategy

Maurice Laville1 and Eric Alamartine2

1Service de Néphrologie, Université Claude-Bernard Lyon 1, Hôpital Edouard-Herriot, Lyon, France and 2Service de Néphrologie, Dialyse et Transplantation Rénale, Université Jean-Monnet, Hôpital Nord, Saint-Etienne, France

Treatment of patients with IgA nephropathy (IgAN) remains a matter of debate. Why, given that IgAN is the most prevalent glomerulonephritis in several countries, does it cause end-stage renal disease (ESRD) in 15–20% of patients within 10 years of the apparent onset of disease, and account for 10% of incident ESRD patients?

At a first look, this results from the heterogeneity of patients referred for IgAN. In fact, there are important differences in renal biopsy policy between centres and countries, leading to very dissimilar patient populations at inclusion in treatment protocols. Most of the patients have only a far potential diagnosis lacking histological documentation, and some are seen only at late stages of renal disease, precluding accurate treatment evaluation and inclusion in controlled studies. Finally, patients have different lengths of disease course, associated with distinct evolution potentials as assessed by the severity of either clinical presentation or histological lesions.

Risk factors

The decision of treatment relies on accurate identification of a handful of risk factors. Ultimately end-stage renal failure is the relevant endpoint of progression. An extreme variability of the clinical course characterizes IgAN, which makes it still difficult at present to predict outcome for an individual patient.

D’Amico extensively reviewed the numerous studies on prognostic factors [1]. He retained an elevated serum creatinine at presentation, a severe proteinuria at presentation or during follow-up, and severe renal tissue damage at light microscopy examination as the strongest predictors of an unfavourable outcome.

Arterial hypertension at presentation and marked extracapillary proliferation were predictors of an intermediate power.

Although morphological lesions are undoubtedly of great importance, they may be difficult to use for a treatment decision analysis. The first reason is that too many different grading systems have been used in the prognostic studies to allow an easy comparison. The second reason is that histopathological damage has rarely been used as inclusion criterion for the prospective trials we rely upon. Extracapillary proliferation might be seen as a peculiar lesion. It failed to be a significant predictor in nine out of ten multivariate analyses reviewed by D’Amico, although it must not be discarded when considering risk factors in an individual patient. The presence of marked extracapillary proliferation should lead to the specific treatments of this lesion.

Surprisingly, the presence of arterial hypertension will not change the decision process. The influence of high blood pressure on the outcome of nephropathies, and in particular its role in accelerating the progression rate of chronic renal failure, have been so strongly documented that there is no more room for discussion. Not only should arterial hypertension be treated, but recommended blood pressure targets should be attained. If we add the compelling evidence that ACEI are renoprotective, even in normotensive patients, the strict control of blood pressure and the use of ACEI must be first-line therapies, as soon as proteinuria or renal function decline are present.

All studies retained proteinuria as one of the strongest prognostic factors. It may be expressed in different ways but the higher the amount of proteinuria, the worse the prognosis. We demonstrated a continuous effect of proteinuria [2]. A level of proteinuria >1.0 g/24 h was already predictive of ESRD [3]. If high levels have been shown to be very harmful, there is no evidence of a lower threshold at which treatment initiation could be recommended although it has been shown that disease progression was possible.
even in patients with minimal proteinuria [4]. Proteinuria can either be taken into account at presentation or during follow-up. A sustained level >1.0 g/24 h is considered to be an important predictor. Donadio et al. reported that proteinuria at a 1 year visit was strongly associated with subsequent ESRD: if proteinuria was <0.5, <1.5, <3.0 or >3.0 g/24 h, the actuarial 5-year rates of ESRD were 0, 10, 15 and 60%, respectively [5]. Therefore, we propose to reconsider the degree of proteinuria after 1 year of any specific therapy.

Considering the degree of renal function impairment in establishing the renal prognosis may appear as a tautology. Nevertheless, a high serum creatinine level at presentation was also a strong predictor of unfavourable outcome in all studies reviewed by D’Amico. Serum creatinine was constantly taken into account in the quoted prospective clinical trials, although this might seem inappropriate since our preference should go for more reliable estimates of GFR [6].

Treatment efficacy

Persisting uncertainties mainly result from the limited number of patients included in the few controlled randomized studies performed to date, which hardly produce statistically significant evidence regarding the heterogeneity of IgAN patients, the diversity of study treatment protocols, and the length of follow-up. The initial meta-analysis by Schena et al. [7] identified only 196 patients among a total of eight studies, and even the most recent analysis from the same group, 13 years later, identified only 551 patients in 10 eligible trials [8]. However, considering the long-term prognosis of IgAN, the percentage of those patients who could benefit from an aggressive treatment was relatively high. Surprisingly, even in comparable intervention groups, there was a large heterogeneity between study populations regarding the risk of progressive renal disease, as the most aggressive treatment schedules were not systematically applied to the patients at highest risk (Figure 1).

It is beyond the scope of this editorial to summarize the results of all treatment strategies, which have been used in often uncontrolled trials. Instead we shall review current evidence, which could be useful for clinicians in charge of patient management. We therefore consider the trial results only from the point of view of clinical relevance, focusing on main end points for chronic renal disease, namely renal function, proteinuria and blood pressure. Treatment modalities have been grouped according to the type of intervention, namely fish oil, steroids and immunosuppressive drugs or to a so-called ‘symptomatic’ treatment approach with ACE-inhibitors and/or angiotensin II receptor antagonists as studied in more recent trials.

Fish oil

The fish oil story began in 1984 with the report by Hamazaki et al., who described favourable results in an uncontrolled study of 20 patients. Five years later, studying 37 patients with normal to severely impaired renal function, randomly allocated to receive either fish oil or supportive treatment for 2 years, Bennett et al. did not find a significant effect on both proteinuria and creatinine clearance [9]. Similar negative results against placebo were reported by Pettersson et al. in 32 patients with non-nephrotic proteinuria and normal to moderately impaired renal function, who received higher dosages of PUFA for 6 months. Conversely,
in a larger multicentre trial Donadio et al. [11] found a significant beneficial effect of fish oil on renal function over a 2-year follow-up. There were 106 patients with normal to moderately impaired renal function, a relatively fast decline in GFR, and nephrotic range proteinuria, who were randomly allocated to fish oil or placebo. The primary endpoint of a ≥50% increase in serum creatinine was reached by 14 patients in the placebo group and by only three patients in the fish oil group, irrespective of baseline proteinuria and renal function, but there was no significant difference in proteinuria. These results were sustained in a long-term extension of the initial study, extending the follow-up to a mean of 6.4 years [12], but were not improved by the use of higher doses of fish oil [13].

However, as demonstrated by two met-analyses [8,14], the overall results of fish oil therapy in IgAN are too inconsistent to take a reliable part in patient management.

Steroids

At the beginning of the 1980s, corticosteroid treatment was first proposed for paediatric patients with IgAN and nephrotic syndrome, which was generally seen as predictive of progressive renal insufficiency. It was then extended to adult patients with severe proteinuria and minimal glomerular lesions, or conversely, to patients with crescentic, rapidly progressive glomerular lesions. Following several case reports and short uncontrolled studies, Lai et al. [15] published the first randomized trial. In 17 patients with nephrotic syndrome and mild renal insufficiency, a 4-month course of prednisolone (40–60 mg/day) resulted in a 65% decrease in mean protein excretion compared with 30% in the 17 untreated patients, and had a slight, although not significant, effect on renal function changes over a 38-month follow-up. The next trial by Pozzi et al. enrolled 86 patients with mild to moderate glomerular lesions, non-nephrotic proteinuria, and normal to moderately impaired renal function. Patients were allocated to receive either a 6-month methylprednisolone and prednisone treatment, or supportive treatment only. These authors observed a rapid decline in proteinuria in steroid-treated patients and, for the first time, a slight but significant improvement of functional prognosis in a 5-year extension study. Another controlled trial of early prednisolone treatment, as compared with anti-platelet treatment, for 1 year in 21 low-risk patients found a significant decrease in proteinuria but no change in renal function [16]. Most recently, 103 patients with similar characteristics were prospectively enrolled in a trial comparing low-dose (20 mg/day) prednisone with dipyridamole for 18 months [17]. Again, proteinuria was found to decrease, but only during the first year of a 5-year follow-up, and there was no difference in renal function impairment. Two patients in each treatment group reached ESRD later than 5 years after inclusion.

Taken together, the results from these well-designed studies and a meta-analysis [8] are consistent with a significant effect of steroid therapy even at low dose, on proteinuria in IgAN patients with non-nephrotic proteinuria and relatively well preserved renal function. This effect appears early, within the first months of treatment, and is sustained for at least 5 years except with lowest dosages. The effects of steroid treatment alone on renal function are inconsistent, and could be observed only in patients with a relatively high risk of progression. It should be noted that the risk of renal failure was higher in the patients studied by Pozzi et al. than in subsequent studies, since three patients in the control group required dialysis within the first 5 years. It was however similar to that observed in the study by Lai et al., where three control group patients experienced a deterioration of renal function over 31–48 months. The distinctive effect of steroids on renal function in the Pozzi study could thus be due to the higher number of patients, the choice of a more discriminant endpoint, better renal function and/or lower degree of proteinuria at inclusion. The important role of proteinuria as a determinant of renal function changes in IgAN has been emphasized recently by the results of the long-term follow-up study by Pozzi et al. [18].

Anti-proteinuric treatments

Following several uncontrolled reports of a beneficial effect of anti-proteinuric treatments on the course of IgAN, the recognition of proteinuria as a major determinant of renal disease progression prompted prospective studies on the effects of ACE inhibitors on renal prognosis. Praga et al. studied 44 patients with biopsy-proven IgAN, normal or slightly impaired creatinine clearance and non-nephrotic proteinuria who were randomly allocated to receive enalapril or other anti-hypertensive treatments for 29–120 months [19]. After a mean follow-up of >6 years, with similar blood pressure control between groups, proteinuria decreased significantly in enalapril-treated patients, and the endpoint of a 50% increase in serum creatinine was reached in 13 vs 57% of patients, which is a very low number-to-treat of nearly two patients to avoid one disease progression. These results compare favourably with the effects of steroid therapy, but the risk of renal deterioration was lower than in the Pozzi study, since no patient reached ESRD over such a long follow-up period. ACE-inhibitors should therefore be considered as the first-line treatment in proteinuric IgAN patients with normal or slightly impaired renal function.

Immunosuppressants

Prospective evaluation of the effects of immunosuppressive treatments started in the late 1980s with the randomized comparison of cyclophosphamide, dipyridamole and warfarin, vs no treatment [20,21]. The results were disappointing, showing no difference in renal function outcome in small numbers of patients
at relatively low risk (Figure 1). The most impressive results were reported by Ballardie et al., who compared a combination of cyclophosphamide, azathioprine and steroids, vs supportive treatment only, in a group of 38 patients with severe renal lesions. Patients were selected on the basis of rapidly deteriorating renal function, i.e. a serum creatinine >130 μmol/l and increasing by at least 15% within the year before entry. As expected, patients in control group had a high risk of renal deterioration, since cumulative renal survival was only 47% at 3 years and 6% at 5 years of follow-up. Corresponding figures in the treated group were 82 and 72%, respectively, a highly significant difference in renal prognosis. In the meta-analysis reported by Strippoli et al. [8], cytotoxic agents were the only treatment found to exert a protective effect on renal function. These results strongly argue for the use of immunosuppressive therapy in severe forms of IgAN. Conversely, patients at lower risk should not be exposed to the adverse effects of such a therapeutic strategy.

Decision analysis

Quantifying the risk for ultimate renal failure is necessary to predict the benefit of any therapy (Figure 1). Sophisticated models have been proposing for a long time [2,22], and again recently [23], but they are not easy to handle and not much in use. A decision tree should be as easy as possible, proteinuria and renal function being the milestones of it. We suggest that patients with proteinuria <0.5 g/24 h and normal GFR are at very low risk but they deserve a life-long follow-up. Patients with proteinuria >0.5 g/24 h and normal GFR are at an intermediate risk. If proteinuria is not controlled by symptomatic treatment, steroids should be considered. Patients with proteinuria >3 g/24 h or decline in GFR are at very high risk and will benefit greatly from cytotoxic agents.

We would therefore like to make the following proposals.

(i) The diagnosis of IgAN relies on the histological examination of a renal sample by both light microscopy and immunofluorescence.

(ii) If proteinuria is <0.5 g/24 h and GFR >60 ml/min, there is no indication for medication but propose an annual evaluation.

(iii) If proteinuria is >0.5 g/24 h and GFR >60 ml/min, propose an ACE-inhibitor, even in normotensive patients.

(a) Increase dosage of ACE-inhibitor progressively to obtain the lowest possible degree of proteinuria, reaching full dose if necessary.

(b) Aim at recommended blood pressure targets.

(c) Consider a full renoprotective strategy, especially in hypertensive patients: patients should be proposed to restrict salt intake, lose excess weight, avoid too much alcohol, and reduce or stop smoking.

Conclusions

Although still disappointingly rare, the randomized trials carried out in primary IgAN allow at present an evidence-based strategy for treatment. We know that steroids reduce proteinuria and that both ACE-inhibitors and cytotoxic agents reduce proteinuria as well and in addition protect renal function. The clue is to identify the actual risk of an individual patient to reach ESRD and to prescribe the most appropriate treatment accordingly.

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References


Restoring glutathione as a therapeutic strategy in chronic kidney disease

Francesco Santangelo1, Véronique Witko-Sarsat2, Tilman Drüeke2 and Béatrice Descamps-Latscha2

1Via Passo di Fargorida 5, Milano, Italy and 2INSERM U507, Hôpital Necker, Paris, France

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Glutathione: antioxidant and cell function regulator

The oxidation–reduction (redox) state of the pool of cellular thiols plays a central role in antioxidant defence and in the regulation of a large number of signal transduction pathways and metabolic functions [1]. The tripeptide glutathione (GSH), i.e. L-γ-glutamyl-L-cysteinyl-glycine (MW 307), represents the major low-molecular-mass thiol compound participating in cellular redox reactions and thio-ether formation. Under oxidative stress, GSH is oxidized to glutathione disulphide (GSSG) and further to other products such as sulphonates. Glutathione-cysteinyl disulphides can also be formed on proteins and such bound glutathione makes up a considerable amount of the cellular glutathione pool.

In January 2004, nearly 60 000 entries could be found under the term ‘glutathione’ in the Medline database, reflecting the importance of this biomolecule. Current knowledge concerning the regulation of mammalian glutathione synthesis is given in Griffith [2]. Briefly, GSH is synthesized from L-glutamate, L-cysteine and glycine in two consecutive steps, catalyzed, respectively, by γ-glutamyl-cysteine synthase and glutathione synthase. The redox reactions are catalyzed by GSH peroxidases (GSH-Px) and GSSG reductases...