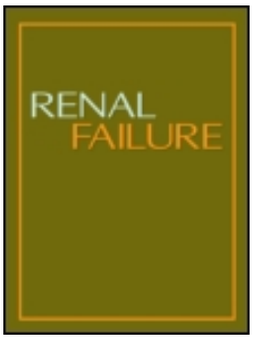

Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: informahealthcare.com/journals/irnf20

Therapeutic Approach of Patients with IgA Nephropathy

Dr. Dimitrios S. Goumenos & Dr. Colin B. Brown

To cite this article: Dr. Dimitrios S. Goumenos & Dr. Colin B. Brown (2004) Therapeutic Approach of Patients with IgA Nephropathy, Renal Failure, 26:2, 171-177, DOI: 10.1081/JDI-120038514

To link to this article: https://doi.org/10.1081/JDI-120038514

RENAL FAILURE
Vol. 26, No. 2, pp. 171–177, 2004

CLINICAL STUDY

Therapeutic Approach of Patients with IgA Nephropathy

Dimitrios S. Goumenos[1,*] and Colin B. Brown[2]

[1]Department of Internal Medicine—Nephrology, University Hospital, Patras, Greece
[2]Sheffield Kidney Institute, Northern General Hospital NHS, Sheffield, UK

ABSTRACT

Immunoglobulin A nephropathy (IgAN) is the most commonly encountered primary glomerulonephritis and it usually follows an indolent clinical course. However, hypertensive patients with proteinuria and renal insufficiency at presentation and patients with severe histological involvement are at high risk to develop end stage renal failure. There is no consensus for the treatment of patients with IgA nephropathy. In general, patients with normal renal function, mild proteinuria (<1 g/24 h) and mild histopathological involvement need only observation, whereas patients with heavy proteinuria, impaired renal function and moderate to severe histopathological involvement are candidates for specific treatment. Angiotensin converting enzyme (ACE) inhibitors are used in patients with arterial hypertension and/or proteinuria 1–2 g/24 h. Corticosteroids are indicated in patients with heavy proteinuria (>3 g/24 h) and in progressive disease despite treatment with ACE inhibitors. Fish oil might be an alternative to corticosteroids in cases with renal insufficiency and chronic histological lesions. Combinations of corticosteroids and cytotoxic drugs are saved for patients with IgA nephropathy and a rapidly progressive course.

Key Words: IgA nephropathy; Treatment; Immunosuppressive drugs; Fish oil; ACE inhibitors.

INTRODUCTION

IgA nephropathy is the most common primary glomerulonephritis (GN) in many developed countries around the world.[1] Although the clinical course is usually benign, some patients develop progressive renal disease. The 10-year renal survival rate is between 80% and 87% and about 25% of patients reach end stage renal failure (ESRF) over 20 years.[1] Various parameters, such as male gender, older age, hypertension,

*Correspondence: Dr. Dimitrios S. Goumenos, Department of Internal Medicine—Nephrology, University Hospital, Patras 26500, Greece; Fax: 003-2610-994424; E-mail: dgoumenos@med.upatras.gr.

DOI: 10.1081/JDI-120038514
0886-022X (Print); 1525-6049 (Online)

Table 1. Therapeutic regimens used in patients with IgA nephropathy.

Study	Inclusion criteria	Treatment	Follow-up (months)	Results/comments
Lai et al.,[3] RCPT	Nephrotic syndrome Mean Clcr: 68 ml/min (n=34)	Oral prednisolone daily vs. no steroid treatment	38	*Steroid treated:* – Remission of proteinuria in 80% of patients with mild lesions – Side effects in 40%
Kobayashi et al.,[4] NRCT	Proteinuria 1–2 g/24 h, Clcr >70 ml/min Moderate histological involvement (n=46)	Oral prednisolone daily for 18 months vs. no steroid treatment	120	*Steroid treated:* – Better renal survival rate
Pozzi et al.,[5] RCPT	Scr <1.5 mg/dl Urinary protein: 1–3.5 g/24 h (n=86)	Methylprednisolone 1 g IV for 3 days every other month Oral prednisolone 0.5 mg/kgBW every other day for 6 months vs. no steroid treatment	60	*Steroid treated:* – Better renal survival rate – Reduction of proteinuria – No important side effects
Ballardie et al.,[8] RCPT	Scr between 1.4 and 2.8 mg/dl (rising by at least 15%) for 1 year Proteinuria (n=38)	Oral prednisolone and cyclophosphamide initially followed by azathioprine daily for 24 months vs. no immunosuppressive drugs	60	*Treated with immunosuppressive drugs:* – Better renal survival rate – Remission of proteinuria – No serious side effects
Goumenos et al.,[9] NRCT Retro	Proteinuria >1 g/24 h and mild to moderate histological involvement (n=74)	Oral prednisolone and azathioprine daily for 24 months vs. no immunosuppressive drugs	120	*Treated with immunosuppressive drugs:* – Better preservation of renal function in patients with proteinuria >3 g/24 h – Important side effects

MARCEL DEKKER, INC. 270 Madison Avenue, New York, New York 10016

Petterson et al.,[10] RCT	Urinary protein >0.5 g/24 h (mean 2 g/24 h) Clcr: mean 91 ml/min (n=32)	Fish oil (6 g daily) for 6 months vs. placebo	6	*Fish oil-treated patients:* – No beneficial effect on renal function – No remission of proteinuria
Donadio et al.,[11] RCT	Urinary protein >1 g/24 h Scr <3 mg/dl but increasing by at least 25% over 6 months (n=106)	Fish oil (12 g daily) for 24 months vs. placebo	24	*Fish oil-treated patients:* – Significantly better preservation of renal function – Non significant reduction of proteinuria – No important side effects
Cattran et al.,[14] NRCT Retro	Urinary protein >1 g/24 h Clcr: mean 60 ml/min (n=115)	ACE inhibitors vs. other antihypertensive drugs	29	*Treated patients by ACE inhibitors:* – Better preservation of renal function – Higher percentage of remission of proteinuria
Ruggenenti et al.,[15] (REIN study), RCPT	Urinary protein >1 g/24 h Patients with chronic nephropathies (n=352) (IgAN n=75)	Ramipril vs. placebo or conventional treatment	30	*Ramipril-treated patients:* – Better preservation of renal function (mainly in patients with proteinuria >2 g/24 h) – Renoprotective effect of ramipril similar in patients with normotension and hypertension

RCPT: Randomized Controlled Prospective Trial, Retro: Retrospective, NRCT: Non Randomized Controlled Trial.

MARCEL DEKKER, INC. 270 Madison Avenue, New York, New York 10016

heavy proteinuria and renal impairment at presentation, have been correlated with a poor clinical outcome whereas presence of glomerulosclerosis, crescents, severe mesangial proliferation, interstitial inflammation and fibrosis has also been related to an adverse prognosis.[1]

Several therapies such as corticosteroids, cytotoxic drugs, fish oil, angiotensin converting enzyme (ACE) inhibitors and others have been used in different trials.[2] However, there is an argument for which patients require treatment and with which therapeutic regimen. In this review most randomized prospective trials and large retrospective studies are analyzed (Table 1) and some therapeutic suggestions based both on evidence and clinical practice are given.

CORTICOSTEROIDS

Corticosteroids have been tried in adult patients with IgA nephropathy on a daily or alternate day basis with variable results. In a randomized prospective trial, 34 patients with nephrotic syndrome due to IgAN were allocated to either oral prednisolone (40–60 mg daily) for 4 months or placebo treatment.[3] Both groups of patients were comparable in renal function impairment and severity of histopathological involvement. After a mean follow-up period of 38 months, although no significant difference in creatinine clearance was observed between the two groups, corticosteroid treatment resulted in remission of nephrotic syndrome in 80% of patients with mild glomerular histopathological changes. However, complications related to corticosteroids such as cushingoid, gastritis and hypertension occurred in 40% of patients.

A favorable long term outcome of IgAN patients with normal renal function and moderate proteinuria (1–2 g/24 h) treated with corticosteroids for 18 months was reported by Kobayashi et al. in their retrospective study. The 5- and 10-year renal survival rate of these patients was 100% and 80% respectively.[4]

Corticosteroids (1 g methylprednisolone intravenously for three consecutive days every other month and oral prednisolone 0.5 mg/kgBW every other day for 6 months) have been used in the recent Italian multicenter randomized trial.[5] Eighty-six patients with significant proteinuria (1–3.5 g/24 h) and well-preserved renal function (serum creatinine <1.5 mg/dL) were randomly assigned to either supportive treatment alone or to corticosteroids. A significantly better renal outcome, estimated using the end points of 50% and 100% increase of serum creatinine, was observed in steroid treated patients over a follow-up period of 5 years.[5] None of the treated patients experienced any important side effect. Although the difference in renal survival rate was particularly striking until the third year, the risk of renal function deterioration was subsequently similar in both groups of patients and proteinuria increased in some treated patients during the rest of follow-up period.[6] Whether steroids alone are enough to induce persistent remission of the disease is not known[6] and a large prospective randomized trial comparing the effect of steroids alone to that of their combination with azathioprine planned by the same authors in order to clarify this issue.[7]

CORTICOSTEROIDS AND CYTOTOXIC DRUGS

Combined therapy with corticosteroids and cyclophosphamide or azathioprine has been used in patients with severe IgA nephropathy with or without a rapidly progressive course.

In a prospective trial, 38 patients with progressive disease were randomized to either treatment with prednisolone (initial dose 40 mg/day) and cyclophosphamide (1.5 mg/kgBW/day for 3 months), followed by azathioprine (at the same dose for 2 years) or no administration of immunosuppressive drugs.[8] All patients had deteriorating renal function (serum creatinine between 1.4 and 2.8 mg/dL, rising by at least 15% in the last year). A significantly better renal survival was observed in treated patients (82% in 3 years and 72% in 5 years of follow-up), compared to that of the control group (47% and 6% respectively). Proteinuria, present in all patients at the time of entry into the trial, was also reduced by treatment (from 4.4 g/24 h to 0.8 g/24 h). Although no morphologic variable predicted response to immunosuppressive therapy, mesangial cell proliferation and matrix score were highest in patients with a more rapidly progressive disease. Discontinuation of treatment was required in 2 patients, because of secondary diabetes mellitus and azathioprine-induced marrow suppression.

The effect of prednisolone and azathioprine over a long follow-up period of 10 years was estimated in 74 patients with IgA nephropathy in our recent retrospective study.[9] Forty-one patients were treated with prednisolone (initial dose 60 mg/day) and azathioprine (initial dose 2 mg/kgBW/day) in gradually reduced doses for 24 ± 9 months, whereas 33 patients received no immunosuppressive drugs. The clinical course was estimated using the end points of doubling of baseline serum creatinine and/or ESRF and the contribution of clinical and histological parameters in the clinical

outcome was estimated by multivariate analysis. A beneficial effect of treatment was observed only in the subgroups of patients with heavy proteinuria (>3 g/24 h) and impaired renal function at presentation (serum creatinine between 1.4 and 2.5 mg/dL). Treated patients with heavy proteinuria had a significantly better outcome compared to untreated as doubling of serum baseline creatinine and ESRF were observed in 27% and 15% vs. 70% and 50% respectively. However, no beneficial effect of treatment was found in patients with severe chronic lesions and serum baseline creatinine above 2.5 mg/dL. The presence of heavy proteinuria, arterial hypertension, renal function impairment at presentation and the presence of severe interstitial myofibroblast expression in the renal biopsy were recognized as independent risk factors related to a poor outcome. Although minor side effects were observed in 10 treated patients (24%), squamous-cell carcinoma and low-grade non-Hodgkin's lymphoma were developed in two, after discontinuation of treatment.

The results of these studies show that corticosteroids and cytotoxic agents should be restricted in patients with progressive disease such as those with deteriorating renal function or heavy proteinuria at presentation. Patients with milder forms of the disease or advanced renal failure and severe chronic histological lesions in the renal biopsy should not be treated by this regimen as no benefit is expected whereas a risk of serious side effects always exists.

FISH OIL

Fish oil is rich in omega-3-polyunsaturated fatty acids that reduce glomerular and interstitial inflammation as well as platelet aggregation during the development of renal injury. Although originally thought to be ineffective it was found to be beneficial in slowing the rate of renal function decline in some patients with IgA nephropathy.

In a prospective randomized trial by Pettersson et al., 32 patients with proteinuria >0.5 g/24 h (mean urinary protein 2 g/24 h) and mean creatinine clearance 91 mL/min were allocated to either 6 g of fish oil daily or placebo for 6 months.[10] No influence of fish oil on renal function and proteinuria was found at the end of the 6-month treatment period as renal function deteriorated (creatinine clearance ranged from 91±31 mL/min to 79±25 mL/min) and proteinuria remained unchanged.

A beneficial effect of fish oil in the preservation of renal function in patients with IgA nephropathy was reported by Donadio et al.[11] In this study, 106 patients with proteinuria >1 g/24 h and serum creatinine between 1.5 and 3 mg/dL at presentation were randomized to either fish oil (12 g/day) or placebo for at least two years. A significantly slower rate of serum creatinine increase (0.03 mg/dL vs. 0.14 mg/dL annually) and lower incidence of ESRF development (10% vs. 40% in 4 years) was observed in fish oil compared to placebo treated patients. There was only a minimal effect on proteinuria. No serious adverse reactions were observed and no patient had to stop treatment.

However, a meta-analysis of all clinical trials of fish oil in IgA nephropathy published in 1997 failed to show a conclusive benefit.[12] More recently, Donadio et al. showed that early and prolonged treatment with fish oil is followed by better long-term outcome of high-risk patients.[13]

These studies show that although fish oil has no effect on proteinuria it may have a favorable effect in the delay of progressive renal failure. In addition, it is well tolerated and is not followed by serious side effects. Even if it is not generally accepted, fish oil can be used in patients with renal insufficiency and chronic histological lesions in the renal biopsy.

ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS AND ANGIOTENSIN II RECEPTOR ANTAGONISTS

The use of ACE inhibitors in patients with IgAN is mainly based on their antihypertensive action and on their antiproteinuric effect via reduction of intraglomerular pressure. Furthermore, an additional benefit of these drugs might be related to a potential amelioration of angiotensin II induced mesangial cell proliferation.

In a large retrospective study, Cattran et al. compared the effect of ACE inhibitors to other antihypertensive drugs in the renal function and remission rate of proteinuria in 115 patients with IgAN and urinary protein >1 g/24 h over a follow-up period of 29 months.[14] These patients were grouped and examined into three categories: hypertensive on ACE inhibitors, hypertensive on other antihypertensive drugs and non-hypertensive patients. Despite comparable renal function abnormalities, patients treated by ACE inhibitors experienced a significantly slower rate of renal function decline as measured by slope of creatinine clearance (−0.4 mL/min/month vs. −1.0 mL/min/month) and a higher percentage of remission in proteinuria (18.5% vs. 1.8%), compared

to patients receiving other medication. Furthermore, despite a much lower initial serum creatinine, less severe pathology and longer observation period, patients without hypertension who received no medication had a comparable rate of renal function decline to that of hypertensive patients treated by ACE inhibitors that also had remission of proteinuria.

A favorable effect of ACE inhibitors in the clinical course of chronic proteinuric nephropathies was also found in the REIN trial with the use of ramipril.[15] GFR fell by 4.4 mL/min/1.73 m^2/year among ramipril-treated patients versus 6.1 mL/min/1.73 m^2/year among patients who were treated with other antihypertensive medications. The main determinants of renal function decline were elevated blood pressure and degree of proteinuria. Thus among patients with primary glomerular disease, including IgA nephropathy, the hypertensive ones and those with proteinuria >2 g/24 h gained the most from ACE inhibitor treatment.

Given that the recommended target levels of blood pressure in patients with renal disease and proteinuria are low (125/75 mmHg in patients with proteinuria >1g/24 h) strict control of hypertension is necessary. ACE inhibitors represent the drugs of choice since apart from their effect in the control of hypertension they also reduce proteinuria.

Although no large studies for angiotensin II receptor antagonists are available, they are probably equally effective to ACE inhibitors in reducing urinary protein excretion and they may have additive antiproteinuric effect to ACE inhibitors when given in combination.

OTHER THERAPIES

Plasma exchange and high-dose intravenous immune globulin have been tried in a few patients with severe IgAN, heavy proteinuria and rapid decline of renal function with good results in stabilization of renal function and remission of proteinuria. Phenytoin administration is followed by depression of IgA levels in serum but has no effect on renal function. Gluten-free and low antigen-content diet as well as danazol, antiplatelet drugs, urokinase and sodium chromoglycate also do not influence the natural course of the disease.

Tonsillectomy is also followed by decrease of hematuria, proteinuria and serum IgA levels but has no effect on renal function. It might be recommended in patients with recurrent macroscopic hematuria episodes in conjunction with tonsillitis.[2]

CONCLUSIONS

Treatment of IgA nephropathy continues to be a matter of debate. Although several therapies have been suggested to alter the natural course of the disease, a controversy exists as to which patients should be treated and with what therapeutic regimen.

There is general agreement that patients with normal renal function, mild proteinuria (<1 g/24 h) and mild histopathological involvement need only observation, whereas patients with heavy proteinuria, impaired renal function and moderate to severe histopathological involvement, are candidates for specific treatment.[2]

Treatment can start with ACE inhibitors and/or angiotensin II receptor antagonists that can be used in patients with arterial hypertension and/or proteinuria 1–2 g/24 h. Corticosteroids are indicated in patients with heavy proteinuria (>3 g/24 h), in progressive disease despite treatment with ACE inhibitors and in cases with severe proliferation and active disease on the renal biopsy. Fish oil can be used in patients with renal insufficiency and chronic histological lesions in which the use of corticosteroids is not appropriate. Combinations of corticosteroids and cytotoxic drugs should be given in patients with aggressive IgA nephropathy and a rapidly progressive course.

However, treatment of IgAN is still under investigation and more information will probably arise from the results of ongoing trials that compare the combination of corticosteroids with azathioprine to corticosteroids alone or estimate the efficacy of mycophenolate mofetil in the therapeutic approach of patients with IgA nephropathy.

REFERENCES

1. D'Amico, G. Influence of clinical and histological features on actuarial renal survival in adult patients with idiopathic IgA nephropathy, membranous nephropathy and membranoproliferative glomerulonephritis: survey of the recent literature. Am. J. Kidney Dis. **1992**, *20* (4), 315–323.
2. Nolin, L.; Courteau, M. Management of IgA nephropathy: evidence-based recommendations. Kidney Int. **1999**, *55* (Suppl. 70), S56–S62.
3. Lai, K.N.; Lai, I.M.; Ho, C.P.; Chan, K.W. Corticosteroid therapy in IgA nephropathy with nephrotic syndrome: a long-term controlled trial. Clin. Nephrol. **1986**, *26* (4), 174–180.
4. 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* (2), 237–242.
5. Pozzi, C.; Bolasco, P.G.; Fogazzi, G.B.; Andrulli, S.; Altieri, P.; Ponticelli, C.; Locatelli, F. Corticosteroids in IgA nephropathy: a randomized controlled trial. Lancet **1999**, *353*, 883–887.
6. Locatelli, F.; Del Vecchio, L.; Pozzi, C. The patient with IgA glomerulonephritis—what is the role of steroid treatment? Nephrol. Dial. Transplant. **1999**, *14* (5), 1057–1060.
7. Locatelli, F.; Pozzi, C.; Del Vecchio, L.; Andrulli, S.; Pani, A.; Fogazzi, G.; Altieri, P.; Ponticelli, C. Combined treatment with steroids and azathioprine in IgA nephropathy: design of a prospective randomized multicenter trial. J. Nephrol. **1999**, *12* (5), 308–311.
8. Ballardie, F.W.; Roberts, I.S. Controlled prospective trial of prednisolone and cytotoxics in progressive IgA nephropathy. J. Am. Soc. Nephrol. **2002**, *13* (1), 142–148.
9. Goumenos, D.; Davlouros, P.; El Nahas, A.M.; Ahuja, M.; Shortland, J.R.; Vlachojannis, J.G.; Brown, C.B. Prednisolone and azathioprine in IgA nephropathy? Nephron Clin. Pract. **2003**, *93* (2), C58–C68.
10. Pettersson, E.E.; Rekola, S.; Berglund, L.; Sundqvist, K.G.; Angelin, B.; Diczfalusy, U.; Bjorkhem, I.; Bergstom, J. Treatment of IgA nephropathy with omega-3-polyunsaturated fatty acids: a prospective double-blind randomized study. Clin. Nephrol. **1994**, *41* (4), 183–190.
11. Donadio, J.V. Jr.; Bergstralh, E.J.; Offord, K.P.; Spencer, D.C.; Holley, K.E. A controlled trial of fish oil in IgA nephropathy. Mayo Nephrology Collaborative Group. N. Engl. J. Med. **1994**, *331* (18), 1194–1199.
12. Dillon, J.J. Fish oil therapy for IgA nephropathy: efficacy and interstudy variability. J. Am. Soc. Nephrol. **1997**, *8* (11), 1739–1744.
13. Donadio, J.V.; Grande, J.R.; Bergstralh, E.J.; Dart, R.A.; Larson, T.S.; Spencer, D.C. 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*, 1772–1777.
14. Cattran, D.C.; 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* (2), 247–254.
15. 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* (6), 116–1155.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016