Overview of Treatment of IgA Nephropathy

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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 (<1g/24h) 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 and/or corticosteroids are used in patients with proteinuria between 1 and 3g/24h. Combinations of corticosteroids and cytotoxic drugs are given to patients with IgA nephropathy and deteriorating renal function or patients with a rapidly progressive course.

Keywords: ACE inhibitors, corticosteroids, cytotoxic drugs, IgA nephropathy, treatment, fish-oil.

Introduction

IgA nephropathy is the most common primary glomerulonephritis (GN) in many developed countries around the world accounting for 20-40% of cases in Singapore and Japan and for 10-20% of cases in Europe and North America [1]. It is more common in males (M/F: 2-3:1) and younger people (15-35 years old). The most common clinical patterns of the disease are episodes of macroscopic haematuria within 48-72 hours from the manifestation of a viral infection, usually of the upper respiratory tract and presence of asymptomatic microscopic haematuria with proteinuria (<2g/24h). However, nephrotic syndrome occurs in 5-10% and acute renal failure in less than 5% of cases [2,3]. The characteristic histological lesions of IgA nephropathy are proliferation of mesangial cells with expansion of extracellular matrix in light microscopy, mesangial deposition of IgA in immunofluorescence and paraneoplastic immune deposits in electron microscopy. According to Hass classification, the severity of histological involvement ranges from class I (minimal lesions) to class V (advanced glomerular sclerosis in more than 40% of the glomeruli of the biopsy sample and tubular atrophy in more than 40% of the cortex surface) [4,5]. Class III, characterized by focal hyperplastic disease with mesangial proliferation, endocapillary hyperplasia and sometimes crescents, represents the most common lesion observed in 40-50% of cases. The pathogenesis of the disease remains largely unknown. However, IgA immunoglobulin and its polymers are involved. IgA1 is exclusively found in the glomeruli of patients with primary IgAN and its deposition is related to defective galactosylation of the molecule due to reduced activity of β1,3-galactosyl-transferase, an enzyme promoting the addition of galactose in the IgA1 molecule. This ‘defective’ IgA1 molecule tends to accumulate, to create macromolecular components (polymers - plgA1) and to induce production of autoantibodies and immune-complexes that are deposited in the mesangium [2,3,6]. Then, complement activation and production of cytokines, chemokines (IL-6, IL-15, IL-1β, IL-8, TNF-α, MCP-1) and growth factors (PDGF, TGF-β1) lead to perpetuation of inflammatory process and development of glomerular sclerosis [7]. Although the clinical course is usually benign, about 25% of patients reach end-stage renal failure (ESRF) over 20 years. Various parameters, such as male gender, older age, high body mass index, hypertension, renal function impairment, proteinuria more than 2g/24h at diagnosis and after the first year of follow-up have been correlated with a poor clinical outcome [8,9]. Severe histopathological involvement with glomerulosclerosis, mesangial proliferation, interstitial inflammation and fibrosis has also been related to an adverse prognosis [8,9]. Several therapeutic regimens using immunosuppressive drugs (corticosteroids, cytotoxics, mycophenolate mofetil) or non-immunosuppressant agents (fish oil, angiotensin converting enzyme inhibitors [ACEi], angiotensin receptor blockers [ARBs]) have been used in different trials. However, there is no consensus for the necessity of treatment and for the suitable therapeutic regimen in
IgAN patients. In this review, a critical analysis of all large trials is attempted in order to identify the suitable groups of patients for immunosuppressive or non-immunosuppressive treatment.

Immunosuppressive regimens

Corticosteroids

In most studies corticosteroids have been used in IgAN patients with reasonable renal function (serum creatinine <1.5mg/dl or creatinine clearance >70ml/min) and proteinuria of moderate severity (1-3g/24h) or nephrotic syndrome. Lai et al. described remission of nephrotic syndrome in 80% of patients with mild glomerular histopathological changes treated by oral prednisolone (40-60mg daily) for 4 months compared to placebo treated patients in a randomized controlled trial [10]. However, complications related to corticosteroids such as cushingoid, gastritis and hypertension occurred in 40% of patients. A favorable long-term outcome (5- and 10-year renal survival rate of 100% and 80%, respectively) was reported by Kobayashi et al. using corticosteroids for a period of 18 months in patients with normal renal function and proteinuria 1 to 2g/24h [11]. The most important study of corticosteroids administration in patients with IgA nephropathy is the Italian multicentric prospective randomized trial [12]. In this study, 86 patients with proteinuria (1-3.5g/24h) and well preserved renal function (serum creatinine <1.5mg/dl) were randomly assigned to either a 6-month course of corticosteroids (1g methylprednisolone intravenously for three consecutive days every other month and oral prednisolone 0.5 mg/kgBW every other day) or supportive treatment alone [12]. A significantly better outcome with more frequent remissions of proteinuria was observed in steroid treated patients along with lack of important side effects with the alternate day administration of corticosteroids. These favorable results of corticosteroids were confirmed after a follow-up period of 10 years (preservation of renal function in 97% vs 57% of conservatively treated patients) [13]. In addition, the administration of corticosteroids was more frequently followed by reduction of proteinuria below 1g/24h after 1 year of follow-up (72% vs 30% of patients) [13]. Shoji et al. noticed that administration of corticosteroids for 1 year in patients with severe mesangial proliferation, serum creatinine <1.5mg/dl and proteinuria <1.5g/d were followed by reduction of proteinuria and significant improvement of mesangial proliferation and matrix accumulation as well as cellular crescent presenation in repeat renal biopsies [14]. A benefital effect in the reduction of proteinuria was observed by Katafuchi et al. with low prednisolone dose (20 mg/day) in patients with moderate histological changes in a controlled prospective trial [15] whereas administration of intravenous pulse steroid therapy for 3 days followed by oral steroid seemed to offer benefit in the kidney survival of patients with more severe IgA nephropathy [16]. In some Japanese studies tonsillectomy offered an additional benefit to pulse steroid therapy [17, 18].

The beneficial effect of corticosteroids in remission of proteinuria and reduction of the risk of development of end-stage renal disease in IgAN patients was confirmed in a recent meta-analysis of all randomized prospective trials [19]. However, the response to corticosteroids also depends on the presence of active or chronic histological lesions in the renal biopsy. Patients with high activity index (mesangial proliferation, crescents, interstitial inflammation) and low chronicity index (glomerular sclerosis, adhesions, interstitial fibrosis) respond more frequently to corticosteroids [20].

Cytotoxic drugs

Cytotoxic drugs have been used in combination with corticosteroids in patients with severe IgA nephropathy and deteriorating renal function.

The administration of methylprednisolone pulse intravenously for 3 days and cyclophosphamide 0.5g/m² intravenously per month for 6 months, in 12 patients with rapidly progressive IgA nephropathy with crescents resulted in improvement of renal function (serum creatinine decreased from 2.6 to 1.5mg/dl), reduction of proteinuria (from 4 to 1.3 g/24h) and reduction of cellular crescents in repeat renal biopsies [21].

Similar results were observed by Tumlin et al. in 12 patients with crescentic, proliferative IgA nephropathy and clinically progressive disease who had been treated with pulse steroids and intravenous cyclophosphamide for 6 months. Serum creatinine was reduced from 2.6 to 1.5mg/dl and proteinuria from 4.0 to 1.4g/d after 6 months whereas endocapillary proliferation, cellular crescents and karyorrhexis were eliminated in all patients [22]. The long-term efficacy of treatment was estimated by comparison of treated patients with 12 historical controls matched for the severity of the disease on initial biopsy. After 36 months, the rate of end-stage renal disease in the treated group was lower (1/12) than that in the historical control group (5/12) [22]. The beneficial effect of combination therapy with oral prednisolone and cyclophosphamide in patients with moderately advanced IgA nephropathy has also been shown in other retrospective studies [23,24].

However, the most important study is the prospective randomized trial by Ballardie et al. [25] in which 38 patients with progressive disease (serum creatinine between 1.4 and 2.8mg/dl, rising by at least 15% in the last year) and proteinuria were randomized to either treatment with prednisolone (initial dose 40mg/day) and cyclophosphamide (1.5mg/kgBW/day for 3 months), followed by azathioprine (at the same dose for 2 years) or no administration of immunosuppressive drugs [25]. The renal survival rate after 5 years of follow-up was significantly higher in treated patients (72% vs 0%, respectively) whereas proteinuria significantly reduced azathioprine-induced marrow suppression. Similar results were observed by Rasche et al. in an uncontrolled
from 4.4g/24h to 0.8g/24h. Treatment was discontinued in 2 patients, because of secondary diabetes mellitus and study including 21 patients with biopsy-proven IgAN without crescents and a serum creatinine of more than 2.0mg/dl and/or increase by more than 25% in the previous 3 months [26]. Stabilization of renal function and remission of proteinuria were observed in most patients. Although no clinically significant adverse reactions, apart from nausea in most patients and mycoplasma pneumonia in one, a favorable response to cyclophosphamide was associated with low white blood cell and platelet counts. This observation suggests that the intensity of immunosuppression seems to influence the outcome of these patients [26]. Recently, the results of the long-term follow-up (mean 7.8 years) of 18 IgAN patients treated for 10 weeks with an oral regimen of 40mg prednisolone and 100mg cyclophosphamide were reported [27]. Although persistent remission of proteinuria occurred in 13 and preservation of renal function in 16 of 18 patients, malignancies developed in 2 patients (renal cell carcinoma after 8 years and rectum carcinoma after 6 years).

A beneficial effect of a 24-month course of prednisolone and azathioprine in the renal function preservation was observed in patients with heavy proteinuria (>3g/24h) and impaired renal function at presentation (serum creatinine between 1.4 and 2.5mg/dl), in our retrospective study over a long follow-up period of 10 years [28]. However, no effect of treatment was found in patients with severe chronic lesions and serum baseline creatinine above 2.5mg/dl. The beneficial effect of treatment might be related to the stability of histological changes (mesangial proliferation, glomerular sclerosis, interstitial fibrosis and inflammation) that was observed in 67% of patients who underwent a repeat renal biopsy 1 year after initiation of immunosuppressive treatment [29]. 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 patients after discontinuation of treatment. A superior effect of combination of corticosteroids, azathioprine, warfarin and dipyridamole to that of corticosteroids alone was reported [30]. The children had normal renal function (estimated creatinine clearance 147 and 157 ml/min per 1.73m², respectively) and proteinuria 1.3 and 1.2 g/m² per day, respectively. The primary and secondary end-points of the study were urinary protein excretion below 0.1g/m² per day and change in percentage of sclerosed glomeruli in repeat biopsies performed after 2 years of treatment. The primary endpoint was reached in 92% of children treated with combination and in 74% of steroid treated children (p=0.007) whereas the percentage of sclerosed glomeruli was unchanged in the former and increased in the latter (p=0.0003). The frequency of adverse effects was similar in the two groups (aseptic necrosis of femur in 1 patient from each group, glaucoma in 2 from each group, leucopenia in 4 from azathioprine group, hypertension in 5 from steroid group) [30]. However, in the recent Italian randomized prospective trial including 251 patients with proteinuria more than 1g/day, a combination of corticosteroids (1g methylprednisolone intravenously for three consecutive days every other month and oral prednisolone 0.5mg/kgBW every other day) and azathioprine 1.5mg/kg/day for 6 months was not proved to be superior to a 6-month course of corticosteroids alone [31]. The 5-year renal survival rate was 90% and 87%, respectively whereas the decrease of proteinuria was not different between the two groups (from 1.2g/24hr to 0.9g/24hr). However, serious side-effects (diabetes, infections, gastrointestinal symptoms, hypertension, anemia and leucopenia) were more frequent in patients who received azathioprine [31].

These studies clearly show that combination of corticosteroids and cytotoxic drugs should be used with caution and only in patients with aggressive disease such as those with deteriorating renal function and crescents in the renal biopsy because of the risk of serious side-effects.

**Mycophenolate Mofetil (MMF)**

Mycophenolate mofetil has been used in IgAN patients with proteinuria >1g/24h, mild or severe impairment of renal function (creatinine clearance between 20 and 70ml/min) and histological lesions of variable severity in four randomized controlled trials [32-35]. Chen X. et al. reported that MMF monotherapy (1.5 g/day) for at least 12 months was superior to prednisone in reducing proteinuria in patients with an unfavorable histological grading [32]. Mayes et al. showed no benefit on renal outcome or proteinuria reduction in 34 patients with decreased renal function (inulin clearance between 20 and 70ml/min), proteinuria >1g/day and histologically advanced disease, who were treated by ACE inhibitors and allocated to either MMF 2g/day for 3 years or placebo [33]. Similarly, lack of benefit was observed by Frisch et al. in patients with moderately advanced IgA nephropathy, proteinuria >1g/day despite treatment with ACE inhibitors or ARBs (angiotensin II receptor antagonists), and decreased renal function (Crcl between 20 and 80ml/min) [34]. However, a beneficial effect of MMF (1.5-2g/day) in lowering proteinuria was observed in patients with less advanced histological lesions and proteinuria >1g/day resistant to a 6-month course of ACE inhibitors or ARBs by Tang et al. [35]. The long-term results of the same study (after 6 years of follow-up) showed a better preservation of renal function in the MMF treated group of patients [36]. A recent meta-analysis including 162 patients from the above randomized controlled trials showed no difference in the reduction of proteinuria and preservation of renal function between MMF and placebo treatment [37]. However, one major deficiency steroids as one of the agents are used in the treatment of glomerular diseases. Hence, future trials with a large of these trials were administration of MMF as monotherapy. In most studies, combination
therapies including number of patients may be conducted to explore the effectiveness of combination therapy vs monotherapy [38].

Non-immunosuppressive regimens

Fish oil

Fish oil, rich in omega-3-polyunsaturated fatty acids that are involved in the synthesis of arachidonic acid and lead to reduction of glomerular and interstitial inflammation, has been tried in various studies with conflicting results. Apart from its anti-inflammatory effect, fish oil also reduces mesangial cell proliferation and activation of transcription factors [39].

A preliminary report by Hamazaki et al. showing a beneficial effect of fish oil to stabilize the reciprocal of serum creatinine [40] was not confirmed in a prospective trial by Bennett et al. [41] and in a case study [42].

No influence of fish oil on renal function and proteinuria was found in a prospective randomized trial by Pettersson et al. in which 32 patients with well preserved renal function were allocated to either 6g of fish oil daily or placebo for 6 months [43]. On the other hand, it was found to be effective in preservation of renal function in a large randomized prospective trial in which 106 patients with proteinuria >1g/24h and serum creatinine between 1.5 and 3.5mg/dl were randomized to either fish oil (12g/day) or placebo for at least two years [44]. A significantly slower rate of serum creatinine increase (0.03mg/dl vs. 0.14mg/dl annually) and lower incidence of ESRF development (10% vs. 40% in 4 years) was observed with application of fish oil. There was only a minimal effect on proteinuria whereas no serious adverse reactions were observed [44]. However, a meta-analysis of all clinical trials of fish oil in IgA nephropathy published in 1997 failed to show a conclusive benefit [45]. More recently, Donadio et al. showed that early and prolonged treatment with fish oil is followed by better long-term outcome (follow-up of 8 years) in high-risk patients [46].

Similar encouraging results in slowing renal function deterioration were observed in high-risk patients with advanced IgAN (serum creatinine 2.2 mg/dl) with a low dose fish oil regimen for 4 years [47]. However, others do not report any benefit in patients with renal insufficiency and proteinuria [48].

More recently fish oil, corticosteroids and placebo treatment were compared in a randomized controlled double blind trial including 96 patients with IgAN [49]. All patients were less than 40 years old, had estimated GFR higher than 50ml/min per 1.73m² and proteinuria. Patients were randomly assigned to prednisone for 12 months, omega-3-fatty acids 4g/day for 2 years and placebo treatment for 2 years. Patients treated with steroids and fish oil had a higher degree of proteinuria than the placebo treated. According to the results, treated group showed no benefit over the placebo group with respect to time to failure (reduction of GFR <60%). However, a dose-dependent beneficial effect of omega-3 fatty acids in the proteinuria reduction was found in a post hoc analysis [50]. Furthermore, a higher degree of proteinuria reduction was observed after 6 months of combined therapy with renin-angiotensin blockers (ramipril and irbesartan) (RASB) and polyunsaturated fatty acids (3g/day) in comparison to RASB alone in patients with proteinuria >1g/day despite treatment with ACE inhibitors and/or ARBs [51]. This is probably due to an anti-inflammatory effect, as suggested by the significant reduction of hematuria, a known marker of inflammation in IgAN patients [51].

These studies show that fish oil 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 blockers (ARBs)

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. Angiotensin II causes glomerular hypertension and hyperfiltration, acts as a profibrogenic cytokine and potentiates the renal scarring process by promoting actions of TGF-beta [52].

In a large retrospective study, Catran et al. compared the effect of ACE inhibitors to other antihypertensive drugs in the renal function and remission rate of proteinuria [53]. Despite comparable renal function abnormalities, patients treated by ACE inhibitors experienced a significantly slower rate of renal function decline (measured by slope of creatinine clearance) and a higher remission rate of 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. A favorable effect of ramipril in the clinical course of chronic proteinuric nephropathies was also found in the REIN trial [54].

The effect of enalapril in comparison to other antihypertensive drugs was estimated in a prospective study including 44 IgAN patients with normal renal function (serum creatinine <1.5mg/dl) and proteinuria >0.5g/24h [55]. For the same blood pressure levels (target <140/80 mmHg), enalapril was found to be more effective in proteinuria reduction and renal function preservation (increase of baseline serum creatinine by 50% in 13% vs 57% of patients) over a follow-up period of 7 years [55].

The beneficial effect of ACE inhibitors in slowing the progression of renal failure seems to The beneficial effect of ACE inhibitors was confirmed in a recent randomized prospective trial by Coppo et al. occur regardless of the degree of tubulointerstitial fibrosis at presentation [56].

In which 66 young patients with proteinuria (between 1 and 3.5g/day per 1.73m²) and good renal function (cre-
Combination of conservative and immunosuppressive treatment

Combination of ACE inhibitors and immunosuppressive drugs

Recent studies show that both steroids and angiotensin converting enzyme inhibitors improve kidney survival and decrease proteinuria in IgAN patients. In a randomized controlled trial, 63 patients with proteinuria of 1 to 5g/day were assigned to cilazapril alone or steroids plus cilazapril. Patients treated by combination showed a significantly better kidney survival, defined as a 50% increase in baseline serum creatinine (97% vs 66% at 36 months) and a significant reduction of urinary protein excretion [63]. Similar results were observed in 97 patients with IgAN and histological lesions of moderate severity with proteinuria >1g/day and estimated GFR >50 ml/min who were randomly allocated to a 6-month course of oral prednisolone plus ramipril or ramipril alone. After a follow-up period of 96 months, 4.2% of patients from the combination treatment group and 26.5% of monotherapy group reached the combined outcome of doubling serum baseline creatinine or end-stage kidney disease. Furthermore, 2% of patients from combination group and 14% of patients from monotherapy group reached the end-point of ESKD. In addition, a decrease of proteinuria to less than 1g/day was observed in 75% of patients treated by combination and in 67% of patients from monotherapy group [64]. We also noted a remission of proteinuria and preservation of renal function in all 17 patients with proteinuria >1.3 g/24hr and serum creatinine <1.5mg/dl treated with combination of ACE inhibitor and oral corticosteroids for 12 months [65]. These results suggest that combination of steroids and ACE inhibitors provides additional benefit to ACE inhibitor alone. Corticosteroids may reduce proliferative and exudative lesions in the acute phase of IgAN, but long-term control of proteinuria is necessary. ACE inhibitors stabilize systemic and renal blood pressure, reduce the traffic of proteins and slow the decline of glomerular filtration rate. Furthermore, significant attenuation of histological lesions was found in repeat biopsies of a small number of children with severe IgA nephropathy and proteinuria >2g/day treated by corticosteroids, cytotoxic drugs and a combination of enalapril and losartan in comparison to patients treated by immunosuppressives alone [66].

Many studies using a combination of ACE inhibitors and immunosuppressive drugs are ongoing. The effect of ramipril and MMF vs ramipril alone is estimated in an Italian multicenter randomized controlled trial [67]. The effect of addition of corticosteroids or corticosteroids and cyclophosphamide to ACE inhibitors and ARBs is estimated in relation to treatment with ACE inhibitors and ARBs in patients with persistent proteinuria above 0.75g/day after 6 months on ACE inhibitors and ARBs in a large randomised controlled trial in Germany [68].

Therapeutic targets in IgA nephropathy - recommendations

Therapeutic targets in patients with IgA nephropathy are regulation of blood pressure to levels below 130/80 mmHg and for patients with proteinuria >1g/24h to less than 125/75 mmHg, long-term preservation of renal function, proteinuria reduction to levels below 1g/24h and correction of lipid abnormalities with diet and/or antilipidemic agents and fish oil.

Although guidelines are difficult to be given, the following recommendations based in both evidence and clinical practice are suggested. There is general agreement that patients with normal renal function, mild proteinuria (<1g/24h) and mild histopathological involvement need only observation, whereas patients with heavy proteinuria, impaired renal function and moderate be used for blood pressure control. Persistent proteinuria represents a risk factor for an unfavorable outcome. In cases with proteinuria >1g/24h and well preserved renal function at presentation, treatment can start with ACE to severe histopathological involvement, are candidates for specific treatment. ACE inhibitors and ARBs should inhibitors and/or ARBs. If proteinuria persists after 6 months of treatment, corticosteroids should be added. It is important to try steroids without delay in order to ac
hieve decrease of proteinuria since every year of persistent proteinuria means a decrease in GFR by 6-7 ml/min. Recent studies show that the combination of corticosteroids with ACE inhibitors from the beginning is more effective than administration of ACE inhibitors alone. Although further studies are necessary, combined treatment may represent the treatment of choice of proteinuric patients with IgA nephropathy. In patients with more aggressive disease (deteriorating renal function, presence of cellular/fibrocellular crescents and severe interstitial inflammation) a combination of corticosteroids with cyclophosphamide or azathioprine represents the most suitable immunosuppressive regimen. In patients with serum creatinine above 2.5-3 mg/dl with extensive fibrosis in the kidney tissue, immunosuppressive treatment is not indicated. These patients receive conservative management and possibly fish oil. However, the clinical course of such patients is poor and end-stage renal disease ensues after a short period of time.

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References


