Kidney International, Vol. 65 (2004), pp. 341–355

NEPHROLOGY FORUM

Treatment of primary IgA nephropathy

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CASE PRESENTATION

A 36-year-old man was referred to the Department of Nephrology at the Hippokration General Hospital of Thessaloniki because of an episode of asymptomatic gross hematuria concomitant with febrile gastroenteritis 3 weeks before presentation. Subsequently, several urinalyses revealed persistent microscopic hematuria and proteinuria. Two years ago, he had noted an additional episode of "tea-colored" urine accompanied by a flu-like illness, but no further investigation was carried out. He had no family history of renal disease.

Physical examination on admission was unremarkable. Chest, abdomen, and extremities were normal. There was no rash or arthritis. His blood pressure was 140/95 mm Hg, the pulse rate was normal at 78 beats/min, and his temperature was 36.8°C. Neither dysuria nor oliguria was present. He did not complain of pain or discomfort in his lumbar region. No eye or ear abnormalities were detected.

Laboratory investigation revealed hemoglobin, 14 g/dL; glucose, 90 mg/dL; blood urea, 32 mg/dL; serum creatinine, 1.1 mg/dL; sodium, 140 mEq/L; potassium, 4.2 mEq/L; calcium, 9.5 mg/dL; phosphorus, 3.5 mg/dL; total protein, 6.8 g/dL; albumin, 4.1 g/dL; cholesterol, 274 mg/dL; triglycerides, 160 mg/dL; uric acid, 4.6 mg/dL; and alanine aminotransferase, 20 U/L. Glomerular filtration rate (GFR) estimated by plasma clearance of ^{51}Cr-EDTA was 115 mL/min. Serum markers for HBV, HCV, and HIV were negative. Serum immunoglobulins and complement were normal. Serum protein electrophoresis was normal and cryoglobulins were negative. No clotting abnormalities were detected. A search for ANA, anti-DNA, and ANCA antibodies was negative. The antistreptolysin titer was less than 100 U/mL. Ultrasonography disclosed two normal nonobstructed kidneys. Urinalysis revealed 50 to 60 red blood cells/high power field and few leukocytes. Approximately 80% of the urinary erythrocytes were dysmorphic. The 24-hour urinary protein excretion was 2.2 g. Urine cultures were sterile.

A percutaneous renal biopsy contained 20 glomeruli by light microscopy. One glomerulus was globally sclerotic. The remaining glomeruli manifested moderate to marked mesangial cell proliferation and matrix expansion with focal accentuation of the lobular pattern. Focal mesangial cell interposition and duplication of the basement membranes, usually with luminal narrowing, also were present. A few neutrophils infiltrated the glomeruli. No crescents or segmental necrotizing lesions were seen. Focal areas of tubular atrophy affecting less than 15% of the tubular cross-sections and mild interstitial fibrosis also were present. No significant vascular abnormalities were noted. Immunofluorescence study showed diffuse mesangial deposition of IgA and C3. Focal capillary wall staining by IgA also was present.

The patient was given perindopril (4 mg/day) and fish oil supplements (Maxepa, Seven Seas, Ltd. Hull, England, UK) in a dosage of 3 capsules twice daily, which provided 0.85 g of eicosapentaenoic acid and 0.57 g of docosahexaenoic acid. Over the following 6 months, his blood pressure became normal (110/70 mm Hg), his serum creatinine remained essentially unchanged (1.0 mg/dL), and the proteinuria decreased to 420 mg/24 hours. Then he deliberately discontinued the fish oil therapy. Five months later he visited our clinic again. His

The Nephrology Forum is funded in part by grants from Amgen, Incorporated; Merck & Co., Incorporated; Dialysis Clinic, Incorporated; and Bristol-Myers Squibb Company.

Key words: glomerulonephritis, end-stage renal disease, renal transplantation, ACE inhibitors, angiotensin II-receptor blockers, immunosuppressive therapy, fish oil therapy.

blood pressure had been well controlled with perindopril (120/80 mm Hg). The serum creatinine was normal (1.1 mg/dL) but proteinuria had increased to 1.2 g/24 hours. He was prescribed fish oil again in addition to antihypertensive treatment. During the subsequent several months his proteinuria gradually decreased to 310 mg/24 hours.

The patient was last examined 3 months ago, almost 9 years after diagnosis. His blood pressure was 125/80 mm Hg. Urinalysis revealed 10 to 15 red blood cells/high power field. The serum creatinine was 1.2 mg/dL; GFR by ^{51}Cr-EDTA, 109 mL/min; and the 24-hour urine protein excretion, 370 mg. Therapy with perindopril (4 mg/day) and fish oil was continued.

DISCUSSION

Dr. Efstathios Alexopoulos (*Associate Professor of Medicine and Nephrology, Department of Nephrology, Hippokration General Hospital, Thessaloniki, Greece)*: This case represents one of the most typical clinical presentations of primary IgA nephropathy (IgAN) and raises issues relating to prognosis and treatment of the most common form of primary glomerulonephritis worldwide. Two Nephrology Forums in the last decade or so have expertly addressed the pathogenesis of the disease and its immunogenetic associations [1, 2]. In today's presentation, I will provide an overview of the progress made in the prognosis and treatment of IgAN, focusing on the current status of various therapeutic approaches and the data upon which recommendations regarding their use are based.

Patients with IgAN usually present with hematuria [3–5]. Approximately 40% to 50% of patients have macroscopic hematuria frequently accompanied by an infection of the upper respiratory tract and, less often, pneumonia, gastroenteritis, or urinary tract infection. The episode is usually brief—about 24 hours—but can last as long as 1 week. This presentation usually occurs in children and in patients under 40 years of age, and loin pain often accompanies the hematuria. Microscopic hematuria, usually with proteinuria, constitutes the other common initial presentation in another 30% to 40% of patients. Macroscopic hematuria can complicate the course of about 20% to 25% of patients in this subgroup. This presentation is more common in older patients but is observed in patients of all ages. As many as 20% of patients with IgAN present with severe azotemia that represents long-standing disease. Acute renal failure occurs in less than 10% of patients, and the nephrotic syndrome is uncommon, occurring only in approximately 5% of all patients, usually children and adolescents [6].

The diagnosis of IgAN currently can be made only by kidney biopsy. The spectrum of light microscopic findings ranges from minor mesangial changes to focal and diffuse mesangial proliferation to crescentic glomerulonephritis.

Table 1. Clinical risk factors for progression in IgA nephropathy (IgAN)

Impaired renal function at discovery[a]
Magnitude and duration of proteinuria[a]
Hypertension at presentation[b]
Older age at onset
Absence of recurrent macrohematuria
Persistent microscopic hematuria
Male gender
Obesity
Hyperuricemia
Hypertriglyceridemia
Smoking
Familial disease

[a]Most significant independent predictors by multivariate analysis in almost all studies (reviewed in [8]).
[b]Significant by univariate analysis in almost all studies and by multivariate analysis in some (reviewed in [8]).

In addition to glomerular lesions, various tubulointerstitial and vascular lesions also can be seen, including tubular atrophy, interstitial fibrosis, interstitial cellular inflammation, and vascular sclerosis. However, the histopathologic criterion for IgAN is the dominance or co-dominance of IgA deposition in the mesangium [5, 7]. Although many other diseases also are associated with glomerular IgA deposits [5], I will not consider their prognosis and treatment in this review.

Clinical course and prognosis

The course of primary IgAN is highly variable, ranging from a totally benign condition to rapidly progressive renal failure. In a small fraction of patients, progression is rapid and associated with necrotizing glomerulitis and extensive crescent formation [8]. The majority of patients, however, have a slowly progressive decline in renal function over 10 to 20 years [8]. The wide variability in clinical course has been addressed in a number of reviews from around the world. The actuarial renal survival at 10 years reported by the majority of studies in Europe, Asia, and Australia is 81% to 87% [8–10]. However, poor renal survival rates, 67% and 57%, respectively, have been reported in two studies from the United States; these rates probably refer to more advanced renal disease at the time of diagnosis [11, 12].

Factors that predict the rate of progression of the disease have been identified over the last 10 years, and these include clinical, histologic, and genetic parameters (Tables 1 and 2). Multivariate analysis according to the Cox model confirmed that an elevated serum creatinine level at presentation and heavy proteinuria are powerful independent predictors of poor outcome [8] (Fig. 1). However, some caution should be exercised in liberally translating initial renal function as a prognostic tool. For poorly understood reasons, even patients with modest impairment of renal function (for example, serum creatinine 1.5 to 2.0 mg/dL) can exhibit long periods free

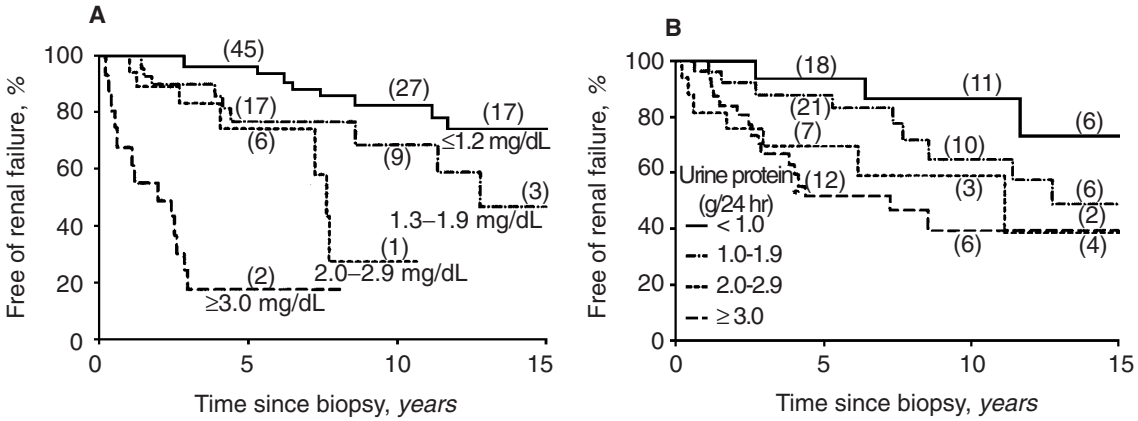

Fig. 1. Survival free of renal failure in patients with IgA nephropathy (IgAN) according to serum creatinine (*A*) and proteinuria (*B*) at renal biopsy. (Reprinted from [11] with permission.)

Table 2. Histologic risk factors for progression in IgA nephropathy (IgAN)

Glomerular
Advanced glomerulosclerosis[a]
Mesangial hypercellularity
Segmental necrotizing lesions
Extensive crescents (>30%)
Capillary wall deposits of IgA
Tubulointerstitial
Marked tubulointerstitial fibrosis[a]
Intense interstitial infiltration
Arteriosclerosis/arteriolosclerosis

[a]Strong independent predictors by multivariate analysis of all reported series (reviewed in [8]).

from progression, particularly in the presence of trivial or modest proteinuria [13]. On the other hand, as many as 7% to 10% of patients with minimal proteinuria and normal renal function at presentation can progress to end-stage renal disease (ESRD) over the long term [abstract; Wong TU et al, *J Am Soc Nephrol* 11:77A–78A, 2001]. Nevertheless, patients with a slowly progressive course and a serum creatinine above 3.0 mg/dL seem to have passed the "point of no return" and will always progress to ESRD without remission, even with therapy [14].

The magnitude and character of proteinuria are powerful clinical indicators of an adverse outcome. At present, I believe that no sharp dividing point relates the magnitude of proteinuria to prognosis. Most investigators, however, believe that more than 1 g/day is a reasonable threshold for concern [11, 15]. Universal consensus exists that proteinuria >3 g/day is associated with a high likelihood of a subsequent progressive decline in renal function [11]. The presence of significant quantities of low-molecular-weight proteins (for example, α_1-microglobulin) in addition to albumin and gamma globulin, probably increase the likelihood for progressive disease or a poorer response to treatment [16], possibly because of the severity of the underlying tubulointerstitial damage, in addition to the primary glomerular disease.

Less concordant are the data for the prognostic value of arterial hypertension at presentation. High blood pressure (>140/90 mm Hg) can be an important factor associated with a more rapid progression in adults with IgAN [11, 17]. However, when this clinical factor was evaluated using multivariate analysis in several studies, it appeared to be significant in some but not all (reviewed in [8]).

Additional clinical and laboratory parameters that have been independently associated with progression have been recently identified (reviewed in [18]). These include persistent complement C3 activation, elevated levels of C-reactive protein, excessive weight or body mass index, hypertriglyceridemia and hyperuricemia, long-term occupational exposure to volatile hydrocarbons, dietary habits, and family history of nephritis. Male gender, older age at onset, absence of episodes of macroscopic hematuria, and persistent microscopic hematuria also have been associated with progression in some studies [11, 15, 17].

Renal histology can be a powerful tool that can aid in the estimation of progression. Different scoring systems have identified mesangial hypercellularity, global or segmental glomerulosclerosis, extracapillary proliferation, segmental necrotizing lesions, interstitial fibrosis, and vascular lesions as markers of a poor prognosis [11, 12]. In multivariate analysis, however, only the severity of glomerulosclerosis and interstitial fibrosis appear to be strong independent predictors of a progressive course [8]. The identification of different types of cells, mediator molecules, growth factors, or cell differentiation antigen in renal biopsies by specific immunohistochemical techniques also has added to the precision of histologic prognostication [19–22].

Immunogenetic factors such as human leukocyte antigen associations (for example, HLA-B35) do not seem to be helpful in predicting prognosis [2]. In addition, the

results of initial positive studies on the association between polymorphism of the angiotensin-converting enzyme (ACE) gene and progression of IgAN have not been confirmed in follow-up studies [23]. Data on other candidate genes are fragmentary.

These outcome studies illustrate that different clinical and pathologic prognostic markers or the composite of clinicopathologic determinants at the time of diagnosis can be used to predict patients with IgAN who are at risk for progression. However, candidate factors and their prognostic values vary from one study to another, and none has been widely accepted. More important, for the majority of the patients, prognostic indicators are weak on an individual basis. Even with clinical or histologic scoring systems, the predictive value reaches statistical significance only with larger cohorts. Nonetheless, attempts at relating these factors in a way that will provide better prognostication in individual patients have met with some success. For example, Bartosik et al [24] constructed a formula to predict subsequent change in GFR using data on urinary protein excretion and mean arterial blood pressure over 2 to 3 years of observation in 298 patients with IgAN. This formula only accounted for about one-third of the total variability in progression. Interestingly, pathology was not an independent predictor of outcome in this study. Many factors other than proteinuria and blood pressure undoubtedly participate in determining the long-term outcome of IgAN. In the future, the development of methods assessing the activity of the disease likely will help provide more accurate prognosis of IgAN. At present, clinical and pathologic features should be considered complementary with respect to assessment of prognosis and selection of candidates for therapeutic intervention.

Treatment

In the 1980s, the role of IgAN as a major cause of ESRD was firmly established. In the 1990s, the focus of clinical studies has shifted from defining the natural history of the disease to the development of therapeutic strategies. The therapeutic nihilism prevalent in the early years following the initial description of IgAN seems to be giving way in the 21st century to a modicum of optimism. But this view is based on small trials with a short follow-up, differences in study design and statistical evaluation, and inclusion of heterogeneous populations of patients. Carefully conducted, randomized, prospective trials are still few, and side-by-side comparisons of therapies thought to be effective are lacking. One also must keep in mind an important caveat: namely, that the underlying pathogenesis of IgAN remains poorly understood and, as a consequence, most therapeutic efforts are empiric in nature or are based on unproved assumptions regarding disease mechanism.

Should all patients with IgAN be treated? Given the usually benign course of patients with normal renal function, minimal (<1.0 g/day) or no proteinuria, normal blood pressure, and minimal or mild lesions on renal biopsy, there is widespread consensus not to offer specific treatment to such patients but rather to keep them under periodic review [25]. On the other hand, patients with one or more adverse prognostic features such as hypertension, proteinuria >1 g/day, slowly progressive renal failure, and moderate to severe changes in renal biopsy histology could be candidates for one or even several therapeutic modalities [4, 5, 25]. We will now look at the current approaches to treating adults with primary IgAN and arrive at my recommendations for treatment.

ACE inhibitors. Control of blood pressure remains the cornerstone of treatment as for patients with other types of kidney disease [26, 27]. The therapeutic benefit of antihypertensive drugs is thought to be a putative reduction of glomerular hypertension that provides protection against glomerular injury. Because of their ability to specifically reduce intraglomerular pressure, ACE inhibitors have attracted the most attention as the ideal antihypertensive drugs for the treatment of hypertension in renal disease, including IgAN. The effectiveness of ACE inhibitors in reducing progression of renal dysfunction is posited to be a consequence of their antiproteinuric effect rather than attributable to their blood- pressure-lowering effect alone. Moreover, ACE inhibitors also might attenuate the effect of angiotensin II on renal cell growth and proliferation and might inhibit extracellular matrix component release that culminates in sclerosis [29].

The relative therapeutic efficacy of ACE inhibitors over other antihypertensive drugs in IgAN is supported by some, but not all, studies. In a trial by Rekola, Bergstrand, and Bucht [30] in 56 patients with IgAN and hypertension, 22 patients were treated with enalapril, and 34 patients treated with beta blockers served as controls. After 1.7 years of follow-up, renal function was stable in the enalapril-treated group but deteriorated in the beta blocker–treated group despite equivalent blood pressure control levels. A similar beneficial effect on renal function of ACE inhibitors also has been demonstrated in two small studies in patients with IgAN and either normal renal function [26] or progressive disease [31]. However, no change in proteinuria was observed in these studies.

In contrast, two randomized clinical trials found that a variety of ACE inhibitors moderately lowered urinary protein excretion without improving renal function [32, 33]. Interestingly, Maschio et al [32] showed that ACE inhibitors reduced proteinuria even in normotensive patients with IgAN. An additional large, retrospective cohort study by Cattran, Greenwood, and Ritchie [34] suggested a slower rate of decline in renal function and a higher percentage of remission of proteinuria

when hypertension accompanying IgAN was treated with ACE inhibitors as compared with other antihypertensive agents. They observed maximal benefit in retarding progression in patients with proteinuria >3 g/day, and the beneficial effects stongly correlated with the extent to which proteinuria decreased with treatment. However, we here in Thessaloniki have not been able to confirm the superiority of ACE inhibitors over other antihypertensive treatments either in reducing proteinuria or preserving renal function in patients with IgAN of mild to moderate severity [35].

Despite the apparent discrepancies among the results of different studies, ACE inhibitors are used widely in the treatment of patients with IgAN who have significant proteinuria or hypertension, both of which are considered modifiable risk factors for progressive disease [36]. Whether these agents also are beneficial in nonhypertensive or nonproteinuric patients remains uncertain. Some investigators have suggested that the ACE/DD genotype is a marker for an up-regulated renin-angiotensin system that causes a more rapid progression of IgAN and that ACE inhibitors might improve renal function in patients who possess the ACE/DD polymorphism [37]. These findings have not yet been consistently confirmed, however.

The role of angiotensin II receptor blockers (ARBs) is not yet firmly established. Perico et al [38] demonstrated that enalapril and irbesartan are equally effective in reducing proteinuria in patients with IgAN. The combination of losartan and ACE inhibitors appeared to have an additive effect on the reduction of proteinuria, whereas doubling the dose of monotherapy had no effect [39]. These short-term studies, however, did not demonstrate a blood pressure–independent reduction in proteinuria, and the combination therapy has not been proven to be more antiproteinuric than a combination of ACE inhibitors or ARBs with any other antihypertensive agent. In addition, the renoprotective effect in these trials has been difficult to separate from the blood pressure–lowering effect, and it is not clear whether this combination preserves renal function more effectively than do ACE inhibitors alone [40].

Hopefully, the specific role of ACE inhibition in the treatment of IgAN will be clarified by large-scale trials, which are currently underway in the United States and Europe [41, 42]. Other agents, such as beta blockers and nondihydropyridine calcium antagonists, appear to have some antiproteinuric potential, which correlates with the magnitude of decline in blood pressure, whereas dihydropyridines might not have a similar beneficial profile [25]. What should be the goal of treatment with ACE inhibitors and/or ARBs in IgAN? The consensus is that blood pressure should be reduced to the lowest value obtainable without inducing side effects, certainly ≤130/80 mm Hg [18, 25]. If this target is not achievable with an ACE inhibitor or ARB, a nondihydropyridine calcium channel antagonist should be added. Although it is not clear what threshold of proteinuria corresponds to an increased risk of progressive renal failure, lowering the protein excretion from baseline to <1.0 g/day might be preferable. Adding an ARB to an ACE inhibitor might be more effective in this regard. In clinical practice, however, this goal might not be achievable in the majority of the patients. Thus I believe that adult patients with persistent proteinuria (for example, >1 g/day), despite adequate treatment with an ACE inhibitor and/or an ARB, can be considered for more aggressive therapy [25].

Steroids. Steroids were among the first agents used for the treatment of IgAN. In an early, randomized, prospective, controlled trial in adult patients with IgAN and the nephrotic syndrome, 4 months of therapy with moderate doses of oral steroids did not produce any benefit except in patients with very mild histologic lesions [43]. Also, Kobayashi et al [44, 45] reported beneficial effects of steroids given in moderate doses for periods of 1 to 3 years in patients with moderate or heavy proteinuria. In both studies, renal function was preserved in patients with an initial creatinine clearance of >70 mL/min but not in those with more severe impairment of renal function. The same authors also have demonstrated that daily steroids for 18 months in IgAN patients with normal renal function and moderate proteinuria produced a better preservation of renal function and a greater reduction in proteinuria 10 years after therapy when compared with an untreated group [46].

In a recent Italian multicenter prospective study [47], 86 adult patients with IgAN, proteinuria of 1.0 to 3.5 g/day, and a serum creatinine below 1.5 mg/dL were randomly assigned to supportive or steroid therapy (intravenous methylprednisolone, 1 g/day for 3 days at the beginning of months 1, 3, and 5 accompanied by oral prednisone 0.5 mg/kg every other day for months 1 to 6). Pretreatment renal histology, serum creatinine, and proteinuria did not differ between the groups. After 5 years of follow-up, 21% of the steroid-treated patients had a doubling of serum creatinine from baseline values, whereas 33% of the patients in the untreated group experienced a similar rise in serum creatinine ($P < 0.05$). Proteinuria significantly decreased in the steroid-treated group to 40% of baseline values; it remained unchanged in the untreated group. An interesting finding in this study was the loss of the significant benefit of steroid therapy on renal function after reduction in proteinuria at 6 months was added to the multivariate analysis as a covariate. These studies strongly suggest that in patients with IgAN accompanied by moderate to heavy proteinuria but reasonably well-preserved renal function, long-term steroid treatment (6 months to 2 years) protects against subsequent progression by reducing the magnitude of proteinuria. More prolonged treatment with steroids appeared no more

effective in the long-term protection of renal function [abstract; Kobayashi Y et al, *J Am Soc Nephrol* 13:680A, 2002]. The effect of steroids might be related to their ability to reverse proliferative lesions in the early phase of the disease and prevent fibrosis [48]. However, patients with impaired renal function and more severe pathologic changes on renal biopsy appear to respond less favorably to steroids alone, despite claims to the opposite [49]. These patients could be considered for more aggressive therapy. Certainly, steroids are indicated for patients with the nephrotic syndrome and minimal change lesions on biopsy. I'll return to this topic in a moment.

Immunosuppressive drugs. There is limited experience with the use of azathioprine in the treatment of IgAN in adults. Goumenos et al [50] published a retrospective study that used long-term azathioprine combined with low-dose prednisone in patients with progressive renal disease accompanied by proteinuria and moderate to severe histologic changes. Eighty percent of patients receiving azathioprine exhibited stable renal function, but only 36% of the group treated conservatively. There was no effect on proteinuria. Interestingly, however, approximately one-third of patients who had features suggestive of a high likelihood of progression remained stable, even with persistently impaired renal function. Extending their observations at 10 years, the same authors found no differences in the overall clinical course between treated and untreated patients [51]. However, treatment with prednisolone and azathioprine appeared to be beneficial in a subgroup of patients with heavy proteinuria (>3 g/day), baseline serum creatinine between 1.4 and 2.5 mg/dL, and histologic lesions of moderate severity. No effect was observed in patients with more advanced renal failure (serum creatinine >2.5 mg/dL) and severe histologic lesions. Serious side effects were frequently seen, however. Controlled trials are needed to confirm these data before this treatment is recommended. Such a multicenter trial comparing steroids plus azathioprine with steroids alone is in progress in Italy [52].

Cyclophosphamide has been used in a limited number of trials. Some of these studies used a combination of cyclophosphamide, dipyridamole, and warfarin [53, 54] and chiefly showed a reduction in proteinuria. A consistent protective effect on renal function could not be demonstrated, however. Because of the multiplicity of the combinations used, it is difficult to ascertain whether the results were due to cyclophosphamide or the other components. Furthermore, the 6-month treatment with cyclophosphamide was associated with significant gonadal dysfunction, making this therapy unacceptable in young patients. Interestingly, in a recent retrospective study in patients with moderately advanced IgAN, the combination of low-dose cyclophosphamide with steroids and antiplatelet agents significantly reduced proteinuria and better preserved renal function as compared with patients treated with antiplatelet drugs alone [55]. Adverse effects related to the immunosuppressive drugs were identified in 14% of the patients, but no case of gonadal toxicity was noted. Until results of additional trials are available, cyclophosphamide should not be used in patients with IgAN of mild or moderate severity [27]. However, cyclophosphamide might have a therapeutic role in patients with severe glomerular inflammation and extensive crescent formation.

Cyclosporine was tested in a randomized single-blind trial conducted by Lai, Lai, and Vallance-Owen [56]. The drug was given for 12 weeks to 24 patients with proteinuria of at least 1.5 g/day and reduced renal function. They showed a modest reduction in proteinuria, unfortunately often accompanied by a rise in serum creatinine. These changes were reversed after cessation of the treatment. Thus, while cyclosporine is likely to display an antiproteinuric effect in IgAN, the risk of nephrotoxicity limits its usefulness. Limited trials of mycophenolate mofetil (MMF) have been reported. In a few case reports and a small uncontrolled trial, MMF, 1 to 2 g/day alone or combined with steroids for several months, decreased proteinuria and stabilized serum creatinine in patients with severe IgAN [57]. Also, in a recent small study in patients with severe IgAN, treatment with MMF for 1 year produced a more effective reduction in proteinuria, higher rate of complete remission, and better preservation of renal function as compared with a 1-year course of steroid therapy [abstract; Chen X *et al*, *J Am Soc Nephrol* 13:14A, 2002]. These findings are too limited to draw any definitive conclusion. Several regional and multicenter clinical trials are underway to further evaluate this therapy.

Little information is available about the role of other immunosuppressive strategies in IgAN. Rostoker et al [58] studied the effects of high-dose intravenous immunoglobulins in an uncontrolled study with 11 patients with IgAN or Henoch-Schönlein purpura who had moderate to severe histologic lesions, heavy proteinuria (>2 g/day), and rapid deterioration of renal function. After treatment, proteinuria decreased modestly and the rate of decline in GFR decreased from 3.78 mL/min/month to 0 mL/min/month. Repeat renal biopsy revealed a reduction in the activity index and a decrease in the staining intensity of glomerular IgA and C3 deposits. This might be a promising approach, especially in patients with a relatively rapid course of declining renal function. Whether similar beneficial effects would be obtained in patients with milder or more slowly progressive disease is as yet unknown.

Fish oil. Interest in fish oil as a treatment of IgAN has recently intensified. Fish oil is rich in ω-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). These compete with arachidonic acid and produce biologically less-effective prostaglandins and

leukotrienes that might retard renal damage by decreasing glomerular and interstitial inflammation, platelet aggregation, and vasoconstriction [5]. Twenty years ago, Hamazaki, Tateno, and Shishido [59] reported in a preliminary trial involving 20 patients with IgAN that the treatment group who received fish oil for 1 year maintained a stable renal function as opposed to untreated controls. Since then, two randomized controlled trials [60, 61] have failed to demonstrate any beneficial effect of 1.8–3.3 g/day of EPA combined with 1.2–1.8 g/day of DHA. Most of these studies were relatively short term and involved small numbers of patients. However, a study of 106 patients in a double-blind, placebo-controlled trial from the Mayo Clinic provided strong evidence of a protective effect of fish oil therapy [62]. This trial selected patients with heavy proteinuria (average, 2 g/day) and mildly impaired renal function (average serum creatinine, 1.5 mg/dL; creatinine clearance, 82 mL/min). Patients were treated with 1.8 g of EPA and 1.2 of DHA daily for 2 years. By the end of treatment, 6% of the fish oil–treated patients and 33% of the placebo group had reached the study end point, a doubling of serum creatinine. The annualized median decrease in creatinine clearance was only 0.3 mL/min/1.73 m^2 of body surface area in patients treated with fish oil, as compared with a decrease of 7.1 mL/min/1.73 m^2 in patients given the placebo. Interestingly, the authors noted no beneficial effect in urinary protein excretion. After observation for an additional 2 years, the cumulative percentage of patients who developed ESRD or died was 40% in the placebo group versus 10% in the fish oil group [63]. The study was criticized because of the rapid loss of renal function in the placebo group but was as expected for patients with baseline characteristics of a high likelihood of progressive disease. These results have been confirmed by our recent prospective study in 44 patients with normal or mildly impaired renal function [35]. Treatment with fish oil for 4 years better preserved renal function. The mean annual change in GFR was $+1.7 \pm 8.4$ mL/min in the treated group as compared with -4.8 ± 9.4 mL/min in the untreated group ($P < 0.05$). Interestingly, proteinuria decreased significantly only in the subgroup of patients treated with fish oil in combination with an ACE inhibitor. A meta-analysis of all reported trials of fish oil therapy in IgAN conducted by Dillon [64] concluded that treatment with fish oil has a small, statistically insignificant benefit on renal function, with an estimated preservation of creatinine clearance of 1 to 2 mL/min/year.

In a more recent, randomized, open-label, parallel-group clinical trial, the same group of Mayo Clinic investigators demonstrated that doubling the dose of ω-3 fatty acids (3.76 g/day of EPA and 2.9 g/day of DHA) for 2 years was equally effective in slowing the rate of renal function loss in high-risk patients with IgAN when compared with the low-dose regimen employed in previous trials

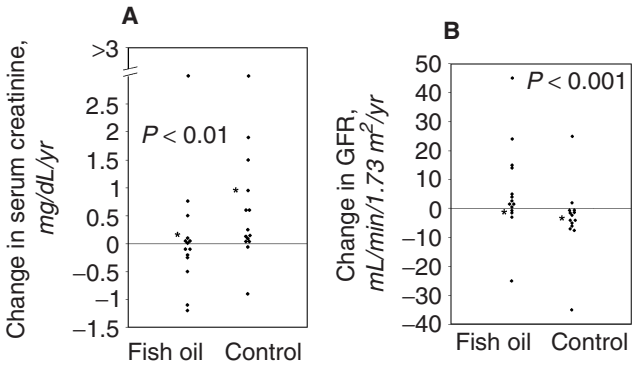

Fig. 2. Annual rate of change in serum creatinine (*A*) and glomerular filtration rate (*B*) in patients with severe IgA nephropathy (IgAN) treated with fish oil. Mean values are indicated by the asterisk. (Reprinted from [35] with permission.)

[65]. We also have tested the hypothesis whether an even lower dose of ω-3 fatty acids might be effective in progressive IgAN in a randomized, prospective controlled trial [abstract; Alexopoulos E et al, *Nephrol Dial Transplant* 17(Suppl 11):28, 2002]. Fourteen patients were assigned to receive a "very low" dose of fish oil (0.85 g/day of EPA and 0.57 g/day of DHA) for 4 years; 14 patients were treated symptomatically and used as controls. During treatment, one patient (7%) in the fish oil–treated group and six in the control group (43%) had an increase of 50% or more in serum creatinine ($P < 0.01$). The mean annual change in GFR was significantly higher in the control group (−3 mL/min) than in the fish oil–treated group (−1.4 mL/min)(Fig. 2). Interestingly, proteinuria was significantly lower in the treated patients at the end of follow-up. Further investigations are needed to clarify the discrepancy of results in clinical trials testing fish oil and to determine the optimal dose. Nevertheless, it remains a promising and safe approach for patients with IgAN at risk for progression. Combinations of fish oil with other regimens such as prednisolone or azathioprine, although attractive, have not yet been tested for efficacy. In the United States, a randomized controlled trial is underway comparing fish oil, alternate-day prednisolone, and ACE inhibitors in children and young adults with IgAN [41]. The results of this trial should considerably clarify whether steroids or fish oil is better for patients at risk for progressive renal disease.

Anticoagulant and antiplatelet drugs. Anticoagulant and antiplatelet therapy have long been used in the treatment of IgAN. Most of the early trials were uncontrolled and small in size [53, 54]. In addition, many of the regimens included steroids and/or cytotoxic agents, so interpretation of the results was difficult. Lee et al [66] used a combination of dipyridamole and low-dose warfarin for 3 years in 11 patients and 10 controls with serum creatinine between 1.6 and 3.0 mg/dL. At the end of the

trial, creatinine clearance was stable in the treated group but had deteriorated in the control group. No changes in proteinuria were noted. Administration of urokinase demonstrated beneficial effects on renal function and proteinuria early, but these effects were not sustained over long-term follow-up [25]. Also, preliminary results have shown a reduction in proteinuria in patients with advanced IgAN after long-term treatment with intravenous heparin [abstract; Ho Y et al, *J Am Soc Nephrol* 13:458A, 2002]. At present the potential benefits of antiplatelet and anticoagulant therapy remain unclear. However, these approaches could be considered second-line therapy, especially in patients with contraindications or intolerance to other forms of treatment [25].

Other treatment considerations. Numerous other approaches to the therapy of IgAN have been described. These include the use of mizoribine, phenytoin, danazol, sodium chromoglycate, 5-amino-salicylic acid, gluten-free and low-antigen-content diets, hepatic 3-methyl-glutaryl-coenzyme A reductase inhibitors, and doxycycline. Most of these treatments have been recently reviewed in detail and appear to offer minimal, if any, long-term benefit [25].

Tonsillectomy also has been recommended for patients with IgAN, but its role remains controversial. Removal of the tonsils in patients with chronic or recurrent tonsillitis reduces serum IgA levels, circulating immune complexes, proteinuria, and episodic hematuria. Patients most likely to benefit from tonsillectomy had preserved renal function (serum creatinine <1.4 mg/dL) and mild changes on histology. These benefits were not observed in patients with more advanced renal disease [67].

Tonsillectomy in combination with pulse steroid therapy might produce higher rates of clinical remission [68]. However, no study to date has shown long-term preservation of renal function in patients who have undergone tonsillectomy. Tonsillectomy has not yet been tested in a controlled randomized trial, so this approach should be reserved for recurrent episodes of macroscopic hematuria or relief of chronic recurrent tonsillitis [27].

Treatment of specific groups

IgAN associated with the nephrotic syndrome. The nephrotic syndrome (NS) is an uncommon presentation of IgAN [4]. Nephrotic patients with IgAN and minimal change lesions on renal biopsy seem to respond to steroids or have spontaneous remissions of the NS. In a controlled trial in adults with IgAN presenting with the NS and varying severity of histology on renal biopsy, the use of 40 to 60 mg of prednisolone/day yielded a high rate of remission of NS (80%) among patients with mild glomerular histologic changes, but many patients experienced side effects [43]. The NS runs a course similar to idiopathic minimal change disease, with relapses that usually remain steroid-responsive. For patients intolerant to steroids, long-term fish oil therapy in combination with ACE inhibitors has been recommended [25, 35]. Cyclophosphamide has been suggested for patients with frequent relapses [25]. However, nephrotic patients with more severe histologic features do not appear to benefit from a short course of prednisolone. The best treatment for this subset of IgA patients has not yet been determined. More prolonged treatment with steroids [69] or the combination of prednisolone with azathioprine [51] has been recommended for IgA patients with heavy proteinuria and less favorable renal histology. A meta-analysis by Schena, Montenegro and Scivittaro in 1990 [70] also concluded that steroids and/or cytotoxic drugs are beneficial when administered to patients with heavy proteinuria whether or not it is associated with NS.

IgAN with a rapidly progressive course. This uncommon presentation usually occurs in association with diffuse crescentic glomerulonephritis or following an episode of macroscopic hematuria, when renal biopsy reveals minor glomerular changes but marked acute tubular necrosis and red cell casts in the tubules [69]. Because of the rarity of patients with rapidly progressive crescentic glomerulonephritis, no controlled therapeutic studies have been undertaken. In sporadic reports and small series, pulse steroids, cytotoxic agents, anticoagulants, intravenous immunoglobulins, and MMF have been claimed to stabilize the course of the disease, at least temporarily [25, 27]. Habib, Niaudet, and Levy [71] found pulse methylprednisolone beneficial in crescentic IgAN. The combination of prednisolone and cytotoxic agents also might benefit patients with extensive crescents [72]. In a recent controlled trial in 38 patients with moderately rapidly progressive disease, combined treatment with prednisolone and oral cyclophosphamide for 3 months, followed by azathioprine for 2 years or more, resulted in better preservation of renal function and a lower degree of proteinuria than did placebo [73].

The role of plasmapheresis in these patients is controversial. Plasmapheresis added to steroids and cytotoxic agents stabilizes renal function during treatment [74]. However, no consistent data exist on the course of the disease following cessation of therapy; some studies report a deterioration of renal function, and others note a sustained effect. Moreover, the usual combination of plasmapheresis with other drugs makes interpretation of the results difficult. Until more data are available, patients with crescentic IgAN and a rapidly progressive course should be treated like those with other forms of crescentic glomerulonephritis: they should be given pulses of methylprednisolone followed by oral prednisolone and oral cyclophosphamide [27]. Plasmapheresis also can be added in resistant cases or in dialysis-dependent patients and can be tailored according to the clinical progress of the patient. Patients with rapid

progression with or without extensive crescents also can be considered candidates for intensive intravenous immunoglobulin therapy [58].

Treatment of patients who present with macrohematuria and rapidly deteriorating renal function accompanied by acute tubular lesions on renal biopsy is only supportive, and no specific measures are recommended [27]. Dialysis is indicated during the period of acute renal failure, which is usually reversible. In rare cases in which acute interstitial nephritis predominates, a short course of oral steroids may be indicated.

Recurrence of IgAN after renal transplantation. Renal transplantation is often required in the treatment of patients with IgAN who progress to ESRD. After transplantation, the disease recurs in 20% to 60% of grafts, with the higher percentages reported from centers that perform serial biopsies. Recurrence occurs equally both in living related and cadaveric donor organ recipients [4, 5]. However, the recurrence rate is somewhat higher in recipients of living related kidneys, particularly HLA-identical sibling grafts, than in recipients of cadaver kidneys [75]. Initial reports considered recurrent IgAN a relatively benign condition. In fact, the 5-year graft and patient survival did not differ from patients with other forms of glomerulonephritis who received renal grafts [75]. It is now apparent, however, that recurrent IgAN is not a benign condition. Starting at approximately 5 years after transplantation, recurrent disease becomes a relevant clinical problem and can cause a decline in renal function and graft loss in as many as 15% of the grafts. This graft loss is distinct from graft failure due, for example, to allograft rejection [76]. Poorer 10-year survival has been reported in patients with IgAN in the presence of clinically apparent recurrent disease [77]. The interval between transplantation and development of recurrence of IgAN or significant loss of graft function is approximately 2 and 3 years, respectively.

Younger patients seem to be at higher risk of recurrence; HLA-2 antigen might play a protective role [77]. In addition, no relationship was found between the aggressiveness of the primary disease and the rate of recurrence of the disease [76]. Patients who lost a previous graft from recurrent IgAN might be at higher risk for repeated graft loss because of recurrence upon retransplantation [4].

The optimal approach for treating recurrent disease has not been defined. Immunosuppression with corticosteroids, azathioprine, and/or cyclosporine A does not prevent recurrence of the disease, either histologically or clinically [4]. Whether MMF can prevent recurrence or be effective in attenuating recurrent disease, as suggested by a recent study [75], remains to be established. Also Oka et al recently suggested that treatment of recurrence with ACE inhibitors is beneficial [78].

Physicians and patients should be aware that recurrent disease can induce graft loss even after 5 years and beyond. As recent data showed equal rates of recurrence in cadaveric kidneys and kidneys from living related donors, transplantation from living related donors should not be discouraged [4, 5]. However, I do not believe that retransplantation with living related kidneys should be encouraged for patients who have already lost a graft due to recurrent IgAN.

Conclusions

For the moment, no consensus exists on the best treatment of IgAN. Before making any therapeutic decisions, clinicians should keep in mind the chronic nature of the disease and the possibility of a good outcome without therapy. Treatment, therefore, should be relatively nontoxic and probably limited to patients who have reasonable evidence of a poor long-term prognosis.

Hypertension should be treated aggressively, mainly with ACE inhibitors or ARBs. General agreement exists that patients with normal renal function, no or trivial proteinuria (<0.5 g/day), normotension, and minimal or mild lesions on renal biopsy should be managed conservatively with regular follow-up. It is not known whether patients with proteinuria > 0.5 g/day but <1 g/day should be treated. In my opinion, even if they are normotensive, one should attempt to lower proteinuria to <0.5 g/day by giving these patients fish oil and an ACE inhibitor or an ARB.

Patients with greater proteinuria (>1 g/day), normal or mildly impaired renal function (serum creatinine <1.4 mg/dL), and mild-to-moderate renal lesions should initially receive fish oil in combination with an ACE inhibitor or ARB in an attempt to lower proteinuria to <1 g/day. If this reduction cannot be achieved, then a course of low-dose steroids on a daily or alternate-day basis for 3 to 6 months is indicated. Whether the combination of these two therapies is more effective is not clear as yet.

Patients with persistent proteinuria >1 g/day, impaired renal function (serum creatinine >1.4 mg/dL), and moderate to severe histologic changes are less likely to respond to steroids. Again, these patients could be successfully treated with fish oil in combination with ACE inhibitors or ARBs, as indicated by the international experience and our own. Alternatively, azathioprine or MMF and low-dose alternate day prednisolone could be considered. When contraindications to prednisolone or immunosuppressive drugs exist, low-dose warfarin combined with dipyridamole could be used.

Patients with NS and minimal glomerular changes appear to respond to steroids. For nephrotic patients with more severe histologic changes, a combination of steroids with immunosuppressive drugs is indicated, as they appear to respond less favorably to steroids alone. Fish oil also might be effective in some of these patients.

Patients with rapidly progressive crescentic glomerulonephritis can benefit from steroids, either pulse therapy or oral prednisolone in combination with cyclophosphamide, and sometimes supplemented by plasma exchange. High-dose intravenous immunoglobulin therapy also might be of benefit in this group. Patients with acute renal failure after a bout of macrohematuria demonstrating a paucity of crescents (<30% segmental crescents) on renal biopsy but predominantly tubulointerstitial changes seem to spontaneously heal and recover even if dialysis is required. Patients with chronic renal failure (serum creatinine > 3 mg/dL) should be treated symptomatically. Fish oil combined with an ACE inhibitor or an ARB might stabilize progression in some of these patients. For the moment, there is no specific therapy for recurrent IgAN in renal allografts. The use of ACE inhibitors might be beneficial and MMF might prevent recurrent disease.

QUESTIONS AND ANSWERS

Dr. Nicolaos E. Madias (*Dean ad Interim, Tufts University School of Medicine, Boston, Massachusetts, USA*): Currently, IgAN is being diagnosed only by renal biopsy. What other diagnostic approaches might be used in the future to better characterize the nature of the nephropathy?

Dr. Alexopoulos: If one could design a sensitive method for measuring the degree or character of abnormal IgA1 galactosylation, the cytokine profile of patients' peripheral blood lymphocytes, and/or the level of circulating aggregates in the serum, theoretically it ought to be a reasonable, noninvasive diagnostic test. However, two key issues emerge as potential limitations. First, such tests might be related to IgA deposition, or to susceptibility to IgA deposition, rather than to IgAN per se. For example, first-degree relatives of patients with IgAN have abnormally high Th2 responses in vitro without evidence of glomerular disease, even after close scrutiny [2]. On the other hand, normal people can have some galactose-deficient IgA1 in their circulation, and this can give rise to false positives, which would destroy the test's value as a diagnostic tool for IgAN. Second, prognostic information available at present from the biopsy might not derive from the in vitro tests. Indeed, the correlation between the levels of circulating immune complexes and severity or course of glomerulonephritis in general has been particularly disappointing [7, 79]. In addition, it is worthwhile to remember that aggregates in the circulation might represent a fraction that is less prone to glomerular deposition. Such tests, however, might be helpful in the future in defining the prognosis or therapeutic response in patients with biopsy proven IgAN. Today, the only way to diagnose IgAN is to do a renal biopsy.

Dr. Dimitrios Tsakiris (*Director, Department of Nephrology, General Hospital of Veria, Veria, Greece*): For many years, IgAN has been associated with respiratory or gastrointestinal infections. Are there specific antigens that trigger the pathogenetic mechanisms of the disease?

Dr. Alexopoulos: Two types of antigens seem to be involved in the pathogenesis of IgAN: environmental respiratory or gastrointestinal infectious agents and food antigens. Antibodies to several viruses or bacteria (such as cytomegalovirus, herpes simplex, hepatitis B, adenovirus, *Haemophilus parainfluenzae*, Epstein-Barr virus, and *Escherichia coli*) and dietary components (including gluten, soy, cow milk, ovalbumin, and rice proteins) have been detected in the mesangium of some patients with IgAN usually, but not always, coincident with IgA1 deposits [80]. Nevertheless, the plethora of infectious and inert antigens implicated in the pathogenesis of IgAN have little in common, mitigating the likelihood of an in situ mechanism of deposit formation [7]. Because similar circulating antibodies specific to environmental antigens are present in normal subjects as well as in patients with IgAN, the array of deposited antibodies likely has little or nothing to do with the nature of the particular antigens [7]. Until now, no one has been able to unequivocally identify specific antigens that are responsible for the formation of IgA deposits in patients with IgAN.

Dr. George Sakellariou (*Director, Department of Nephrology, "Papageorgiou" Hospital, Thessaloniki, Greece*): I have been impressed by the effectiveness of intravenous immunoglobulins in the treatment of patients with severe IgAN and rapidly declining renal function. What is the potential mechanism by which these immunoglobulins act? Also, is there evidence of a similar effect of intravenous immunoglobulins on the course of chronic disease?

Dr. Alexopoulos: With regard to your first question, intravenous immunoglobulins are effective in several immune-mediated diseases. Numerous mechanisms have been proposed to explain their beneficial action, but none satisfactorily explains all clinical situations [81]. In IgAN, abnormalities in the IgA immune system and a deficiency in the IgG1 subclass might favor viral and bacterial infections [58]. Immunoglobulin therapy inhibits B-cell differentiation and immunoglobulin production by acting on the B-cell IgG Fc receptor and might regulate excessive B-cell IgA production. Immunoglobulins also improve T-suppressor function, which is deficient in this disease, and modulate monocyte function, thus reducing cytokine production. The immunoglobulins prevent active C3 fragments from binding to target surfaces and the formation of C5b-9, and they accelerate the decay of C3b to an inactive form [58, 81]. Immunoglobulins also contain anti-idiotypic antibodies that can either bind to and modulate the activity of autoreactive B and T cells or bind to

circulating pathogenic antibodies. Finally, they restore the serum IgG1 deficiency that can favor the expansion of the medullary IgA B-cell compartment, which is increased in IgAN [58, 81].

In regard to your second question, no data exist so far on the use of this therapy in patients with chronic IgAN. Although intravenous immunoglobulin therapy might be a promising approach, one has to consider the high rate of relapses after treatment is discontinued [58] and, of course, the potential risks of such therapy [81].

Dr. Nicolaos Zoubaridis (*Director, Renal Unit, General Hospital of Edessa, Edessa, Greece*): Could you tell us a bit more about familial IgAN? How frequent is this form of the disease? Are there differences in the clinical course of the disease between familial and nonfamilial (sporadic) cases?

Dr. Alexopoulos: The true frequency of familial IgAN remains uncertain, but perhaps it accounts for about 10% of all patients with the disease [18]. Schena, Scivittaro and Ranieri [82] found urinary abnormalities in approximately 23% of 269 relatives from 48 families of IgAN patients, but this percentage might be even higher (>50%). In addition, a variety of abnormalities of IgA immunobiology also were noted in these relatives. In a recent multicenter study in which 30 kindreds of multiplex families with IgAN were studied, the investigators defined a very strong linkage with the trait 6q22-23 in 60% of kindreds, with a maximal likelihood of odds score of 5.6 [83]. More recently, Schena's group also described two novel loci on chromosomes 4 and 7 affecting the development of the disease (personal communication). Such findings support the suggestion that familial IgAN is a complex disease initiated by one or more genes, probably in combination with environmental conditions. Whether similar genes are responsible for the progression of the disease needs to be determined. Clinical findings at presentation cannot distinguish sporadic cases from those with familial disease [2]. It is interesting, however, that a recent report demonstrated worse renal outcome in cases of familial versus sporadic IgAN [84].

Dr. Dimitrios Vlahakos (*Assistant Professor, Department of Nephrology, Aretaieion Hospital, Athens, Greece*): What is the rationale for combining ACE inhibitors with ARBs?

Dr. Alexopoulos: The rationale for this combination therapy is the assumption that ARBs would counteract the AT1-mediated effect of residual angiotensin II formation by non-ACE enzymes like chymase, whereas ACE inhibitors would additionally increase the level of kinins. Furthermore, ACE inhibitors as well as ARBs would synergistically elevate the levels of angiotensin (1–7), which also might promote vasodilation. Finally, combining both drug classes might simply provide a higher degree of blockade of the classic renin-angiotensin system pathways [85]. In a small study in selected patients with IgAN, combination therapy demonstrated a greater antihypertensive and antiproteinuric effect than did either drug class alone [39]. Also, the recent "Cooperate" study that included 131 patients with IgAN indicated that this combination offers superior renoprotection over either ACE inhibitor or ARB alone in non-nephrotic proteinuric renal disease [86].

Dr. Vasilios Vargemezis (*Professor of Nephrology, University of Thrace, Alexandroupolis, Greece*): You mentioned that a combination of fish oil supplements with an ACE inhibitor has a more potent antiproteinuric effect than either drug alone. Could you speculate on the potential mechanism?

Dr. Alexopoulos: I am afraid I do not have a precise answer to your question. I can offer a hypothesis, however. Experimental studies in rats subjected to subtotal renal ablation demonstrated that fish oil therapy reduced mean arterial pressure and efferent arteriolar resistance and decreased glomerular capillary pressure [87]. Both proteinuria and glomerulosclerosis were lessened by this therapy. Fish oil might exert these hemodynamic effects by reducing angiotensin II–dependent signaling events, such as phospholipid hydrolysis, or by limiting synthesis of the potent renal vasoconstrictor thromboxane A_2. The latter findings are reminiscent of those observed following the administration of ACE inhibitors and thus support the notion that these compounds act through a parallel pathway [87]. Large-scale trials, some of which are underway, are needed to test this hypothesis. Regardless, our results combined with the experimental data provide a physiologic rationale that could potentially be applied to the treatment of progressive IgAN.

Dr. Constantinos Sombolos (*Director, Renal Unit, "Papanicolaou" General Hospital, Thessaloniki*): What are the indications for treatment with steroids and/or immunosuppressive agents? For how long should this therapy be continued?

Dr. Alexopoulos: There are only two circumstances in which steroid therapy is definitely indicated in IgAN: (*1*) NS with mild glomerular changes on histology, and (*2*) rapidly progressive crescentic glomerulonephritis where steroids are used in combination with a cytotoxic agent and/or plasmapheresis [69]. In other forms of the disease, steroids are recommended for patients with moderate to heavy proteinuria (>2 g/day), well-preserved renal function (creatinine clearance > 70 mL/min), and mild histopathologic changes [45, 47]. For these patients, relatively long-term steroid treatment (6 months to 2 years) can have a beneficial effect, as shorter treatments seem not to offer any particular benefit [25]. For patients with more severe histologic lesions and impaired renal function (creatinine clearance < 70 mL/min) steroids alone will not likely be of much benefit [25]. In this circumstance, combined treatment of steroids for 18 months and azathioprine for 24 months might be more effective

[51, 70]. For patients with rapidly progressive crescentic glomerulonephritis, high-dose steroids combined with cyclophosphamide for 6 months is recommended [73]. We do not know with a measure of certainty how long these therapies should be continued. Perhaps long-term, adequately sized trials combined with repeat biopsies will determine the optimal duration of treatment with these drugs.

Dr. Athanasios Agrafiotis (*Director, Department of Nephrology, "Asclepieion" General Hospital, Athens*): Do you stop fish oil treatment in patients who respond to it?

Dr. Alexopoulos: No. Treatment with fish oil is continued in all patients unless they reach ESRD.

Dr. Athanasios Dimitriadis (*Director, Department of Medicine, "Aghios Dimitrios" Hospital, Thessaloniki*): Do we have treatments aiming at reducing the frequency of episodic macrohematuria or the severity of microscopic hematuria? Would you treat a patient with macroscopic hematuria but no significant proteinuria?

Dr. Alexopoulos: Although we have no specific therapy for hematuria, several approaches are associated with reductions in hematuria. Tonsillectomy has been associated with a reduction in the episodes of macroscopic hematuria, as well as in microscopic hematuria [88]. Phenytoin also reduced the number of episodes of macrohematuria [89]. Treatment with doxycycline (100 mg daily) for 12 months decreased microscopic hematuria to normal counts [90]. Finally, the use of steroids in several studies reduced episodes of macroscopic hematuria and led to the disappearance of microscopic hematuria in a significant proportion of patients [91, 92]. Regarding your second question, I would treat this particular patient if his biopsy revealed extensive crescent formation or significant acute interstitial nephritis.

Dr. Charalambos Stathakis (*Director, Department of Nephrology, Laikon Hospital, Athens*): Does tonsillectomy affect long-term renal prognosis of IgA patients? Which are the current recommendations for tonsillectomy?

Dr. Alexopoulos: The role of tonsillectomy in the long-term prognosis of IgAN remains unclear. In some studies, no effect of tonsillectomy on disease progression could be appreciated [67]. In a more recent retrospective study, however, tonsillectomy was associated with better long-term preservation of renal function and lower risk for development of ESRD [93]. Clearly, a prospective controlled study of the effect of tonsillectomy on the long-term renal prognosis in patients with IgAN is needed. Until more data are available, tonsillectomy might be recommended for treatment of recurrent episodes of macroscopic hematuria in conjunction with chronic tonsillitis in patients with well-preserved renal function (serum creatinine < 1.4 mg/dL) [25, 27]. However, since we have no proof of efficacy in progressive disease, this approach cannot currently be recommended on a routine basis.

Dr. Dimitrios Goumenos (*Assistant Professor, Renal Unit, University Hospital, Patras, Greece*): You demonstrated that widely accepted clinical and pathologic prognostic factors, although useful in cohort studies, cannot be easily applied for predicting outcome in individual cases. Do you think that other approaches based on modern molecular biology that assess disease activity might be a more useful guide for identifying patients at risk for progression? Would you recommend a repeat renal biopsy to estimate disease activity after treatment?

Dr. Alexopoulos: Various mediator systems such as cytokines, complement, chemokines, and growth factors very likely influence the propensity for disease progression in a given individual. Several investigators have demonstrated that, for example, the deposition of α-smooth muscle actin in renal tissue [19], as well as the presence of $\gamma\,\delta$ T cells and perhaps PCNA(+) infiltrates within the interstitium have a prognostic importance [94]. Our group also has demonstrated the prognostic value of increased expression of LFA-1 integrin and C5b-9 in early biopsies of patients with IgAN [22, 95]. Large numbers of interstitial macrophages also were related to poorer outcome [21]. Interestingly, the numbers of interstitial macrophages were closely related to the amount of MCP-1 excreted in the urine [abstract; Papagianni A et al, *XXXVII Cong ERA/EDTA,* p 126, 2000]. Parameters such as the ratio of interleukin-6 (IL-6):epidermal growth factor (EGF) in the urine or increased transforming growth factor-β (TGF-β) excretion might be other approaches to refining prognosis [35, 96]. The identification and characterization of these and other "progression-associated" molecules in renal tissue or in the urine might offer new ways for us to determine individual prognosis at early stages of disease and to better assess disease activity. Until these modern techniques are refined, I would recommend a repeat biopsy only in the context of research projects or in patients with unexplained deterioration of renal function.

Dr. Aikaterini Papagianni (*Lecturer, Department of Nephrology, Hippokration General Hospital, Thessaloniki*): You did not mention how to manage patients with proteinuria of more than 0.5 g/day but less than 1.0 g/day. What would you suggest?

Dr. Alexopoulos: It is not known whether patients with these values of protein excretion should be treated. We must remember, however, that as many as 7% to 10% of these patients will wind up with ESRD after several years. Appel and Glassock [18] suggested the use of ACE inhibitors and/or ARBs in this group of patients, even if they are normotensive, in an attempt to lower proteinuria to <0.5 g/day. In a recent prospective trial, Praga et al [97] demonstrated better preservation of renal

function in IgA patients whose proteinuria exceeded 0.5 g/day and who were treated with ACE inhibitors. The authors suggest early initiation of treatment, when renal function is still normal. My own policy is to treat these patients with a combination of fish oil and an ACE inhibitor; in our experience, ACE inhibitors alone were not effective in patients with low-grade proteinuria.

Dr. Madias: Considering the ongoing advances in the pathogenesis of IgAN and the mechanisms mediating disease progression, could you speculate on the future treatment directions of this disease?

Dr. Alexopoulos: Future directions for treatment of IgAN would probably include the modulation of the immune response as well as enzymatic approaches. The inhibition of gene expression by antisense oligonucleotides might be a potential therapeutic strategy. This treatment might arrest the synthesis of abnormal IgA or block specific gene effects of cytokines involved in IgA synthesis (that is, IL-5 and TGF-β) or inhibit or suppress the synthesis of IgG (or IgA and IgM) antibodies specific for truncated glycans. The aberration in IgA galactosylation might be diminished or abrogated by blockade of one of the Th2 cytokines that underlies the abnormal galactosylation or administration of an inhibitor [such as interferon-gamma (IFN-γ)] of the effects of the Th2 cytokines.

Truncated glycans might be selectively "repaired" by the appropriate exogenous galactosyltransferase(s). In addition, IgA aggregates in the circulation and/or in the glomerular deposits might be irreversibly dissociated by proteolytic enzymes, such as IgA1 proteases. These and other future therapeutic attempts have been recently reviewed [98], but their efficacy awaits clinical confirmation.

Dr. Parashos Koukoudis (*Associate Director, Renal Unit, General Hospital of Kilkis, Kilkis, Greece*): You emphasized that recurrent IgAN in a kidney graft can result in declining renal function and graft loss in about 15% of the grafts despite immunosuppressive therapy. Do you think fish oils have a place in the management of these patients?

Dr. Alexopoulos: I have no personal experience, nor am I aware of any published trials on the efficacy of fish oil in the outcome of recurrent IgAN. In a recent case report, however, the use of fish oil resulted in a remarkable and prompt resolution of proteinuria and microscopic hematuria in a child with biopsy-proven post-transplantation IgAN [99]. But no immunofluorescence data from the patient's native kidney biopsy were available, so it is not clear whether the IgA deposits found in the renal transplant were recurrent or de novo in nature. Larger controlled trials are definitely needed to fully assess the overall impact of fish oil therapy in recurrent IgAN.

ACKNOWLEDGMENT

The Principal Discussant thanks Mrs. Kyriaki Lahakliotou for excellent secretarial assistance. This Nephrology Forum was held at the Bourazani Environmental Park and Conference Center, Bourazani, Greece.

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REFERENCES

1. Van Es LA: Nephrology Forum: Pathogenesis of IgA nephropathy. *Kidney Int* 41:1720–1729, 1992
2. Schena FP: Nephrology Forum: Immunogenetic aspects of primary IgA nephropathy. *Kidney Int* 48:1998–2013, 1995
3. Ibels LS, Gyory AZ: IgA nephropathy: Analysis of the natural history, important factors in the progression of renal disease, and a review of the literature. *Medicine* (Baltimore) 73:79–102, 1994
4. Floege J, Feehally J: IgA nephropathy: Recent developments. *J Am Soc Nephrol* 11:2395–2403, 2000
5. Donadio JV, Grande JP: IgA nephropathy. *N Engl J Med* 347:738–748, 2002
6. Hogg RJ: Usual and unusual presentations of IgA nephropathy in children. *Contrib Nephrol* 104:14–23, 1993
7. Emancipator SN: IgA nephropathy: Morphologic expression and pathogenesis. *Am J Kidney Dis* 23:451–462, 1994
8. D'Amico G: Natural history of idiopathic IgA nephropathy: Role of clinical and histological prognostic factors. *Am J Kidney Dis* 36:227–237, 2000
9. Nicholls KM, Fairley KF, Dowling JP, Kincaid-Smith P: The clinical course of mesangial IgA associated nephropathy in adults. *Q J Med* 53:227–250, 1984
10. Woo KT, Edmondson RPS, Wu AYT, *et al*: The natural history of IgA nephritis in Singapore. *Clin Nephrol* 25:15–21, 1986
11. Radford MG Jr, Donadio JV Jr, Bergstralh EJ, Grande JP: Predicting renal outcome in IgA nephropathy. *J Am Soc Nephrol* 8:199–207, 1997
12. Haas M: Histologic subclassification of IgA nephropathy. A clinicopathologic study of 244 cases. *Am J Kidney Dis* 29:829–842, 1997
13. D'Amico G, Ragni A, Gandini E, Fellin G: Typical and atypical natural history of IgA nephropathy in adult patients. *Contrib Nephrol* 104:6–13, 1993
14. Scholl U, Wastl U, Risler T, *et al*: The "point of no return" and the rate of progression in the natural history of IgA nephropathy. *Clin Nephrol* 52:285–292, 1999
15. Frimat L, Briancon S, Hestin D, *et al*: IgA nephropathy: Prognostic classification of end-stage renal failure. *Nephrol Dial Transplant* 12:2569–2575, 1997
16. Woo JT, Lau YK, Lee GSL, *et al*: Pattern of proteinuria in IgA nephropathy. *Nephrology* 3:31–34, 1997
17. Alamartine E, Sabatier JC, Guerin C, *et al*: Prognostic factors in mesangial IgA glomerulonephritis: An extensive study with univariate and multivariate analyses. *Am J Kidney Dis* 18:12–19, 1991
18. Appel GB, Glassock RJ: Glomerular, vascular, tubulointerstitial and genetic diseases. Nephrology self-assessment program. *J Am Soc Nephrol* (Suppl 1) 1:11–19, 2002
19. Ranieri E, Gesualdo L, Grandaliano G, *et al*: The role of α-smooth muscle actin and platelet-derived growth factor-β receptor in the progression of renal damage in human IgA nephropathy. *J Nephrol* 14:253–262, 2001
20. Lim CS, Zheng S, Kim YS, *et al*: Th1/Th2 predominance and proinflammatory cytokines determine the clinicopathological severity of IgA nephropathy. *Nephrol Dial Transplant* 16:269–275, 2001
21. Alexopoulos E, Seron D, Hartley RB, *et al*: The role of interstitial infiltrates in IgA nephropathy. A study with monoclonal antibodies. *Nephrol Dial Transplant* 4:187–195, 1989
22. Alexopoulos E, Kelesidis A, Papadimitriou M: Increased glomerular and interstitial LFA-1 expression in proteinuric IgA nephropathy. *Am J Kidney Dis* 27:327–333, 1996

23. Schena FP, D'Alti C, Cerullo G, *et al*: ACE gene polymorphism and IgA nephropathy: an ethnically homogeneous study and a meta-analysis. *Kidney Int* 60:732–740, 2001
24. Bartosik LP, Lajoie G, Sugar L, *et al*: Predicting progression in IgA nephropathy. *Am J Kidney Dis* 38:728–735, 2001
25. Glassock RJ: The treatment of IgA nephropathy at the end of the millenium. *J Nephrol* 12:288–296, 1999
26. Kanno Y, Okada H, Saruta T, *et al*: Blood pressure reduction associated with preservation of renal function in hypertensive patients with IgA nephropathy: A 3 year follow-up. *Clin Nephrol* 54:360–365, 2000
27. Nolin L, Courteau M: Management of IgA nephropathy: Evidence-based recommendations. *Kidney Int* 55 (Suppl 70):S56–S62, 1999
28. Remuzzi A, Perticucci E, Ruggenenti P, *et al*: Angiotensin converting enzyme inhibition improves glomerular size-selectivity in IgA nephropathy. *Kidney Int* 39:1267–1273, 1991
29. Fogo A, Yoshida Y, Yared A, Ichikawa I: Importance of angiogenic action of angiotensin II in the glomerular growth of maturing kidneys. *Kidney Int* 38:1068–1074, 1990
30. Rekola S, Bergstrand A, Bucht H: Deterioration rate in hypertensive IgA nephropathy: Comparison of a converting enzyme inhibitor and a β-blocking agent. *Nephron* 59:57–60, 1991
31. Feriozzi S, Pierucci A, Roscia E: Angiotensin-converting enzyme inhibitor delays the progression of chronic renal failure in hypertensive patients with immunoglobulin A nephropathy. *J Hypertens* 7(Suppl):563–564, 1989
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* 9:265–269, 1994
33. Bannister KM, Weaver A, Clarkson AR, Woodroffe AJ: Effect of angiotensin-converting enzyme and calcium channel inhibition on progression of IgA nephropathy. *Contrib Nephrol* 111:184–192, 1995
34. Cattran DC, Greenwood C, Ritchie S: Long-term benefit 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* 23:247–254, 1994
35. Stangou M: *Pathogenetic Mechanisms in IgA Nephropathy: The Therapeutic Role of ω-3 Fatty Acids*. MD Thesis, Medical School, University of Thessaloniki, 2002, pp 1–190
36. Jafar TH, Stark PC, Schmid CH, *et al*: Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. *Kidney Int* 60:1131–1140, 2001
37. Yoshida Y, Mitari T, Kawamura T, *et al*: Role of deletion polymorphisms of the angiotensin converting enzyme gene in the progression and therapeutic responsiveness of IgA nephropathy. *J Clin Invest* 86:2162–2169, 1995
38. Perico N, Remuzzi A, Sangalli F, *et al*: The anti-proteinuric effect of angiotensin antagonism in human IgA nephropathy is potentiated by indomethacin. *J Am Soc Nephrol* 9:2308–2317, 1998
39. Russo D, Pisani A, Balletta MM, *et al*: Additive antiproteinuric effect of converting enzyme inhibitor and losartan in normotensive patients with IgA nephropathy. *Am J Kidney Dis* 33:851–856, 1999
40. Reddan D, Owen W: IgA nephropathy and inhibitors of the renin-angiotensin system: Is reduction in proteinuria adequate proof of efficacy? *Am J Kidney Dis* 38:182–185, 2001
41. Hogg RJ: A randomized, placebo-controlled, multicenter trial evaluating alternate-day prednisone and fish oil supplements in young patients with immunoglobulin A nephropathy. *Am J Kidney Dis* 26:792–796, 1995
42. Coppo R, Chiesa M, Peruzzi L, Amore A: Treatment of IgA nephropathy with angiotensin converting enzyme inhibitors: design of a prospective randomized multicenter trial. *J Nephrol* 14:447–452, 2001
43. Lai KN, Lai FM, Ho CP, Chan KW: Corticosteroid therapy in IgA nephropathy with nephrotic syndrome: A long-term controlled trial. *Clin Nephrol* 26:1740–1780, 1986
44. Kobayashi Y, Fujii K, Hiki Y, *et al*: Steroid therapy in IgA nephropathy: A prospective trial in moderately proteinuric cases. *Q J Med* 234:935–943, 1986
45. Kobayashi Y, Hiki Y, Fujii K, *et al*: Moderately proteinuric IgA nephropathy: Prognostic prediction of individual clinical courses and steroid therapy in progressive cases. *Nephron* 53:250–260, 1989
46. Kobayashi Y, Hiki Y, Kokubo T, *et al*: Steroid therapy during the early stage of progressive IgA nephropathy: A 10-year follow-up study. *Nephron* 72:237–242, 1996
47. Pozzi C, Bolasco C, Fogazzi GB, *et al*: Corticosteroids in IgA nephropathy: A randomized trial. *Lancet* 353:883–887, 1999
48. 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* 35:194–201, 2000
49. Tamura S, Ueki K, Ideura H, *et al*: Corticosteroid therapy in patients with IgA nephropathy and impaired renal function. *Clin Nephrol* 55:192–195, 2001
50. Goumenos D, Ahuja M, Shortland J, Brown C: Can immunosuppressive drugs slow the progression of IgA nephropathy? *Nephrol Dial Transplant* 10:1173–1181, 1995
51. Goumenos DS, Davlouros P, El Nahas M, *et al*: Prednisolone and azathioprine in IgA nephropathy: A ten-year follow-up study. *Nephron Clin Pract* 93:c58–c68, 2003
52. Locatelli F, Pozzi C, Del Vecchio L, *et al*: Combined treatment with steroids and azathioprine in IgA nephropathy: Design of a prospective randomized multicentre trial. *J Nephrol* 12:308–311, 1999
53. Woo KT, Edmondson RPS, Yap HK, *et al*: Effects of triple therapy on the progression of mesangial proliferative glomerulonephritis. *Clin Nephrol* 27:56–64, 1987
54. Walker RG, Yu SH, Owen JE, *et al*: The treatment of mesangial IgA nephropathy with cyclophosphamide, dipyridamole and warfarin; a two year prospective trial. *Clin Nephrol* 34:103–107, 1990
55. Tsuruya K, Harada K, Hirakata H, *et al*: Combination therapy using prednisone and cyclophosphamide slows the progression of moderately advanced IgA nephropathy. *Clin Nephrol* 53:1–9, 2000
56. Lai KN, Lai FM, Vallance-Owen T: A short-term controlled trial of cyclosporin A in IgA nephropathy. *Transplant Proc* 20(Suppl 4):297–303, 1988
57. Nowack R, Birck R, van der Woude F: Mycophenolate mofetil for systemic vasculitis and IgA nephropathy. *Lancet* 349:774, 1997
58. Rostoker G, Desvaux-Belghiti D, Pilatte Y, *et al*: High dose immunoglobulin therapy for severe IgA nephropathy and Henoch-Schönlein purpura. *Ann Intern Med* 120:476–484, 1994
59. Hamazaki T, Tateno S, Shishido H: Eicosapentaenoic acid and IgA nephropathy. *Lancet* 1:1017–1018, 1984
60. Bennett WM, Walker RG, Kincaid-Smith P: Treatment of IgA nephropathy with eiocosapentaenoic acid (EPA): A two year prospective trial. *Clin Nephrol* 31:128–131, 1989
61. Petterson EE, Rekola S, Berglund L, *et al*: Treatment of IgA nephropathy with omega-3-polyunsaturated fatty acids: A prospective, double-blind, randomized study. *Clin Nephrol* 41:183–190, 1994
62. Donadio JV Jr, Bergstralh EJ, Offord KP, *et al*: A controlled trial of fish oil in IgA nephropathy. *N Engl J Med* 331:1194–1199, 1994
63. Donadio JV Jr, Grande JP, Bergstralh EJ, *et al*: The long-term outcome of patients with IgA nephropathy treated with fish oil in a controlled trial. *J Am Soc Nephrol* 10:1772–177, 1999
64. Dillon JJ: Fish-oil therapy for IgA nephropathy: Efficacy and interstudy variability. *J Am Soc Nephrol* 8:1739–1744, 1997
65. Donadio JV Jr, Larson TS, Bergstalh 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* 12:791–799, 2001
66. Lee GSL, Choong HL, Chiang GSC, Woo KT: Three-year randomized controlled trial of dipyridamole and low-dose warfarin in patients with IgA nephropathy and renal impairment. *Nephrology* 3:117–121, 1997
67. Rasche FM, Schwarz A, Keller F: Tonsillectomy does not prevent a progressive course in IgA nephropathy. *Clin Nephrol* 51:147–152, 1999
68. Hotta O, Miyazaki M, Furuta T, *et al*: Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy. *Am J Kidney Dis* 38:736–743, 2001

69. Lee G, Glassock R: Immunoglobulin A nephropathy, in *Treatment of Primary Glomerulonephritis*, edited by Ponticelli C, Glassock RJ, Oxford, Oxford Medical Publications, 1997, p 186
70. Schena FR, Montenegro M, Scivittaro V: Meta-analysis of randomized controlled trials in patients with IgA nephropathy (Berger's disease). *Nephrol Dial Transplant* 5(Suppl 1):47–52, 1990
71. Habib R, Niaudet P, Levy M: Schönlein-Henoch purpura nephritis and IgA nephropathy, in *Renal Pathology*, edited by Tisher C, Brenner BM, Philadelphia, JB Lippincott, 1994, p 472
72. McIntyre CW, Fluck RJ, Lambie SH: Steroid and cyclophosphamide therapy for IgA nephropathy associated with crescentic change: An effective treatment. *Clin Nephrol* 56:193–198, 2001
73. Ballardie FW, Roberts IS: Controlled prospective trial of prednisolone and cytotoxics in progressive IgA nephropathy. *J Am Soc Nephrol* 13:142–148, 2002
74. Roccatello D, Ferro M, Coppo R, *et al*: Treatment of rapidly progressive IgA nephropathy. *Contrib Nephrol* 111:177–183, 1995
75. Ponticelli C, Traversi L, Felicianni A, *et al*: Kidney transplantation in patients with IgA mesangial glomerulonephritis. *Kidney Int* 60:1948–1954, 2001
76. Frohnert PP, Donadio JV, Velosa JA, *et al*: The fate of renal transplants in patients with IgA nephropathy. *Clin Transplant* 11:127–133, 1997
77. Wang AYM, Lai FM, Yu AW, *et al*: Recurrent IgA nephropathy in renal transplant allografts. *Am J Kidney Dis* 38:588–599, 2001
78. Oka K, Imai E, Moriyama T, *et al*: A clinico-pathological study of IgA nephropathy in renal transplant recipients: Beneficial effect of angiotensin converting enzyme inhibition. *Nephrol Dial Transplant* 15:689–695, 2000
79. Allen AC, Feehally J: IgA1 glycosylation and the pathogenesis of IgA nephropathy. *Am J Kidney Dis* 35:551–556, 2000
80. Kim MJ, Hong SP: Immunological aspects of IgA nephropathy. *Nephrology* 3:55–61, 1997
81. Kazatchkine MD, Kaveri SV: Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med* 345:747–755, 2001
82. Schena FP, Scivittaro V, Ranieri E: IgA nephropathy: Pros and cons for a familial disease in IgA nephropathy. The 25th year. *Contrib Nephrol* 104:36–45, 1993
83. Gharavi AG, Yan Y, Scolari F, *et al*: IgA nephropathy, the most common cause of glomerulonephritis, is linked to 6q22–23. *Nat Genet* 26:345–357, 2000
84. Schena FP, Cerullo G, Rossini M, *et al*: Increased risk of end-stage renal disease in familial IgA nephropathy. *J Am Soc Nephrol* 13:453–460, 2002
85. Hilgers KF, Mann JFE: ACE inhibitors versus AT1 receptor antagonists in patients with chronic renal disease. *J Am Soc Nephrol* 13:1100–1108, 2002
86. Nakao N, Yoshimura A, Morita Y, *et al*: Combination treatment of angiotensin-II receptor blocker and angiotensin-converting enzyme inhibitor in non-diabetic renal disease (CO-OPERATE): A randomized controlled trial. *Lancet* 361:117–124, 2003
87. Schmitz PG, Lane PL, Dalal R, *et al*: ω-3 fatty acids attenuate glomerular capillary hydraulic pressure in rats with renal ablation. *Kidney Int* 48:1792–1800, 1995
88. Bene MC, Hurault de Ligny B, Kessler M, *et al*: Tonsils in IgA nephropathy. *Contrib Nephrol* 104:153–161, 1993
89. Egido J, Rivera F, Sancho J, *et al*: Phenytoin in IgA nephropathy: A long-term controlled trial. *Nephron* 38:30–39, 1984
90. Kincaid-Smith P, Nicholls K: Mesangial IgA nephropathy. *Am J Kidney Dis* 3:90–102, 1983
91. Waldo B, Wyatt RJ, Kelly DR, *et al*: Treatment of IgA nephropathy in children: Efficacy of alternate-day prednisolone. *Pediatr Nephrol* 7:529–532, 1993
92. Kincaid-Smith P: Treatment of mesangial immunoglobulin A glomerulonephritis. *Semin Nephrol* 19:166–172, 1999
93. Xie Y, Nishi S, Ueno M, *et al*: The efficacy of tonsillectomy on long-term renal survival in patients with IgA nephropathy. *Kidney Int* 63:1861–1867, 2003
94. Woodroffe AJ: Chronic tubulointerstitial disease in IgA nephropathy. *Nephrology* 3:19–21, 1997
95. Alexopoulos E, Papagianni A, Papadimitriou M: The pathogenetic significance of C5b-9 in IgA nephropathy. *Nephrol Dial Transplant* 10:1166–1172, 1995
96. Schena FP: Role of cytokines in the progression of renal damage in IgA nephropathy. *Nephrology* 3:67–72, 1997
97. Praga M, Gutierez E, Gonzalez E, *et al*: Treatment of IgA nephropathy with ACE inhibitors: A randomized and controlled trial. *J Am Soc Nephrol* 14:1578–1583, 2003
98. Lai KN: Future directions in the treatment of IgA nephropathy. *Nephron* 92:263–270, 2002
99. Butani L, Palmer J: Effect of fish oil in a patient with post-transplantation IgA nephropathy. *Nephrology Dial Transplant* 15:1264–1265, 2000