Immune Modulating Therapy for IgA Nephropathy: Rationale and Evidence

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Summary: Our current understanding of the initial pathogenetic steps in IgA nephropathy (IgAN) provides relatively limited rationale for immunosuppressive therapy. However, it is conceivable that immunosuppressive drugs might affect secondary inflammatory events triggered by glomerular immune deposits or even proteinuria per se. Some, but not all, randomized clinical trials on either corticosteroid monotherapy, mycophenolate mofetil monotherapy, or immunosuppressive combination therapy have provided evidence for a benefit on either surrogate parameters such as proteinuria or hard end points such as renal failure. The central problem of these studies is that most were designed in the 1980s or 1990s, when recommendations for supportive therapy were strikingly different from those of today. In the meantime an equal number of randomized clinical studies reporting a benefit of supportive therapy has been published only regarding patients with IgAN and, unfortunately, no head-to-head comparisons of these 2 approaches currently are available. Several ongoing clinical trials may help to resolve this dilemma. Until the data of such studies become available, a pragmatic approach is to first optimize supportive therapy and reserve immunosuppressive medication for those patients failing a supportive approach and remaining at risk for progressive loss of renal function.

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Despite the fact that IgA nephropathy (IgAN) is the most common type of glomerulonephritis in the Western world, there is a remarkable lack of large randomized controlled trials regarding this disease entity. In fact, a meta-analysis published in 2004 noted that no more than 13 randomized controlled trials involving a total of 623 patients had been published and that these trials were generally of poor quality.[1] However, the same meta-analysis concluded that immunosuppressive agents are a promising strategy and that this approach should be investigated further. In 2007 this situation has not changed and we still are left with some uncertainty about the role of immunosuppression in IgAN. As we discuss in this article, key reasons for this unsatisfactory situation include the continuing controversy about the role of immune-mediated pathogenic mechanisms in IgAN, and the lack of adequate trials comparing state-of-the-art nonimmune therapeutic approaches with immunosuppression. In addition, trials in IgAN, as in many other renal diseases, are hampered by the slowly progressive nature of the disease, with 10-year renal survival rates exceeding 85%; patient heterogeneity; lack of interest of the pharmaceutical industry in this patient group; and, at least in some countries, strong opinion-based therapeutic approaches to IgAN.

DO WE HAVE A RATIONALE FOR IMMUNE-MODULATING THERAPY IN IgAN?

Animal models, even if characterized by mesangial deposits of polymeric IgA (pIgA) as in human disease, are not particularly informative about the mechanisms that underlie human

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mesangial pIgA1 deposition, although they have provided many insights into events after IgA deposits have developed. One of the key problems is that significant species differences between rodents and human beings have been identified, especially in the IgA system.[2] For example, although in human beings 2 IgA isotypes, IgA1 and IgA2, can be distinguished, rodents have only 1 IgA isotype, which resembles IgA2 rather than IgA1, but only the latter is deposited in human IgAN. Also, almost all mammal IgA lacks the hinge region, namely the site of abnormal IgA glycosylation in human IgAN (reviewed by Novak, pp. 78-87). Thus, animal data are unlikely to provide a rationale for immune-modulating therapy in IgAN. It is noteworthy that a targeted mutation of β-1,4-galactosyltransferase-I, an enzyme involved in protein glycosylation in mice (ie, a nonimmune mechanism), results in an IgAN-like disease.[3]

WHAT EVIDENCE IN HUMAN BEINGS SUPPORTS A ROLE FOR IMMUNE-MODULATING THERAPY IN IgAN?

Serum IgA levels, including pIgA, are increased in one third of patients with IgAN. Studies in vitro indicate that IgA production by mononuclear cells is exaggerated in IgAN. Production of pIgA1 (ie, the pathogenetically relevant isoform), is down-regulated in the mucosa and up-regulated in the bone marrow. Impaired mucosal IgA responses allowing enhanced antigen challenge to the marrow could be the primary abnormality in IgAN. Alternatively, some mucosal IgA-producing plasma cells might translocate to the bone marrow in IgAN. Conceivably, immune-modulating therapy could affect these processes, however, this is unproven.

The altered IgA1 glycosylation in IgAN may predispose to immune phenomena such as the formation of circulating IgA1-immune complexes, or it may modify IgA1 interactions with mesangial cell and/or monocyte Fc receptors.

Circulating antimesangial IgG, implying an element of autoimmunity, has been described in IgAN.[4] These data, however, remain unconfirmed.

Immunosuppression might affect the glomerular IgG deposits, which frequently co-exist with IgA deposits. Their role only recently has been elucidated in some detail.[5]

Finally, immune-modulating therapy may affect a number of secondary processes that follow deposition of IgA1 in the glomerulus. For example, IgA can engage inflammatory cells in the circulation or in the kidney and this will induce variable degrees of inflammation. Fc receptors for IgA (Fcα receptors) on myeloid and mesangial cells may play a key role in this process (reviewed by Moura, pp. 88-95). In addition, immunosuppressive agents such as mycophenolate mofetil (MMF) have been shown to exert beneficial effects on progressive renal disease in nonimmune rodent models, such as the 5/6 nephrectomy model.[6] Potential mechanisms underlying the latter observation may include a direct antiproliferative action of MMF on renal cells as well as a reduction of tubulointerstitial inflammation in proteinuric renal disease.

WHAT CLINICAL EVIDENCE ARGUES AGAINST IMMUNE-MODULATING THERAPY IN IgAN?

Altered IgA1 glycosylation in IgAN may impair IgA1 clearance by inhibiting IgA1 interactions with hepatic IgA receptors, and indeed hepatic clearance of IgA is reduced in IgAN. It appears unlikely that immunosuppression would affect this process.

High serum levels of IgA per se are not sufficient to cause IgAN; high circulating levels of monoclonal IgA (in myeloma) or pIgA (in acquired immune deficiency syndrome) only infrequently provoke mesangial IgA deposition.

IgAN regularly recurs after renal transplantation despite immunosuppression and so far not a single immunosuppressive agent has been described that will prevent recurrence.[7]

Taken together, the evidence available provides little rationale that immunosuppression affects any of the primary pathogenic processes in IgAN. However, secondary mechanisms, in particular glomerular inflammatory responses to the deposited IgA as well as nonspecific inflammatory reactions that characterize progressive tubulointerstitial damage in any progressive proteinuric renal disease, might well benefit from immunosuppression.

DOES CLINICAL EVIDENCE SUPPORT THE USE OF IMMUNE-MODULATING THERAPY IN IgAN?

In 1999 a review concluded that immunosuppressive therapy was of value only for a small group of patients (ie, those with [almost] normal renal function and nephrotic-range proteinuria).[8] In the present article we focus on randomized clinical trials of immunosuppression in patients with IgAN published since 1999 (Table 1). A number of different approaches has been investigated, including corticosteroids alone, MMF, or combinations of immunosuppressive agents. All studies have dealt with primary IgAN and usually patients with the nephrotic syndrome or a rapidly progressive course, suggesting a vasculitic manifestation of the disease, were excluded.

Corticosteroid Monotherapy

In 1999 Pozzi et al[9] published a randomized controlled trial in patients with a glomerular filtration rate (GFR) greater than 70 mL/min. Patients were assigned randomly to supportive therapy only or additional corticosteroids. In a 10-year follow-up study of that population,[10] serum creatinine levels had doubled in 1 of 43 patients in the steroid group versus 13 of 43 in the control group.

In 2000 Shoji et al[11] published a randomized trial in which 8 patients were randomized to receive antiplatelet therapy only, whereas 11 patients received additional oral prednisolone for 1 year. Proteinuria and histology were improved at 1 year in the steroid-treated group. The study mainly dealt with low-risk patients (normal blood pressure, mean GFR normal, and a mean proteinuria of 0.75 g/d).

In 2003 Katafuchi et al[12] published a randomized controlled trial in which 43 patients received oral prednisolone as compared with 47 patients in the control group. Although renal survival was not improved by the steroid therapy, proteinuria decreased in the steroid group only.

In 2006 Hogg et al[13] reported a randomized controlled trial in which 33 patients received prednisone and 31 patients received placebo. The number of patients reaching the primary end point (ie, a GFR decline exceeding 40%), was not different between the 2 groups.

In 2007 Horita et al[14] published a randomized controlled trial in which 18 patients received 24 months of prednisolone alone and 22 patients received prednisolone plus 50 mg losartan. The combination but not prednisolone alone prevented a decline of the creatinine clearance, whereas proteinuria was reduced markedly in both arms.

Thus, at present, the best rationale for corticosteroids in patients with IgAN is derived from the study by Pozzi et al.[9,10] It needs to be stressed that these patients all had normal or near-normal GFR because older Japanese data suggest that corticosteroid monotherapy may be without effect in patients with a baseline GFR less than 70 mL/min.[15] Of note, other studies, using different corticosteroid regimens, were inconclusive as to a beneficial effect.[13,14]

MMF

In 2004 Maes et al[16] described a prospective study in 34 Belgian patients with impaired renal function who were randomized to 2 g of MMF (n = 21) or placebo (n = 13) after instituting angiotensin-converting enzyme (ACE) inhibitor therapy in all. After 3 years of follow-up evaluation, inulin clearances and proteinuria did not differ between the groups.

In 2005 Tang et al[17] described a prospective study in 40 Chinese patients with IgAN and impaired renal function who were randomized to 1.5 to 2.0 g MMF (n = 20) or continuation of contemporaneous medication only (n = 20) after instituting blockade of the renin-angiotensin system in all. MMF induced lasting remission of proteinuria. Creatinine clearances remained stable (ie, around 70 mL/min), and were not different at the end of the follow-up period (72 wk).

In 2005 Frisch et al[18] published a randomized controlled trial in which 32 patients with advanced IgAN (mean serum creatinine, 2.5 mg/dL) were randomized to MMF or placebo. The study was terminated prematurely after observing a trend toward worse outcome in the MMF group.

Data from another ongoing American study as well as from an Italian trial (http://www.igan-world.org) are not yet available.

Table 1. Summary of Randomized Controlled Trials Published in Patients With Primary IgAN Since 1999

Study	Inclusion Criteria	Treatment Groups	Outcome Parameters + Follow-Up Period, y	Major Findings in Immunosuppressed Group Versus Control Group	Evidence Level
Corticosteroid monotherapy					
Pozzi et al,[9,10] 1999	Uprot 1-3.5 g/d, Scr < 1.5 mg/dL	n = 43: supportive therapy; n = 43: methylprednisolone intravenously 1 g/d for 3 days in months 1, 3, and 5, + oral prednisone 0.5 mg/kg on alternate days for 6 mo	50% or 100% increase in Scr concentration from baseline; FU, 1-10	Significant reductions of patients with 50% or 100% increase in Scr	A
Shoji et al,[11] 2000	Diffuse proliferative IgAN, Scr <1.5 mg/dL, Uprot <1.5 g/d	n = 8: antiplatelet therapy; n = 11: oral prednisolone 0.8 mg/kg/d tapered to 10 mg on alternate days at 1 year	Uprot, histology; FU, mean 1.1	Reduction of Uprot, improved histology at 1 y*	B
Katafuchi et al,[12] 2003	Scr < 1.5 mg/dL and glomerular score 4-7 (max, 12)	n = 47: dipyridamole only; n = 43: oral prednisolone 20 mg/d tapered to 5 mg/d at 18 mo	Uprot and ESRD; FU, mean 5.4	Significant reduction in Uprot† but not ESRD frequency	A
Hogg et al,[13] 2006	Age <40 y, eGFR >50 mL/min, Uprot > 1 g/g creatinine‡	n = 33: oral prednisone 60 mg/m²/48 h tapered to 30 mg/m²/48 h at 12 mo; n = 31: placebo	GFR decline >40%; FU, 2	No significant difference between groups	B
Horita et al,[14] 2007	Ccr > 50 mL/min, Uprot >1 g/d	n = 18: oral prednisolone 30 mg/d tapered to 10 mg/d at 24 mo; n = 22: oral prednisolone + 50 mg/d losartan	Uprot and Ccr; FU, 2	Significant reduction in Uprot in both groups; Ccr stable in combination group only	B
MMF					
Maes et al,[16] 2004	GFR 20-70 mL/min and/or Uprot >1 g/d	n = 13: placebo; n = 21: MMF 2 g/d for 3 y	Inulin clearance, Uprot; FU, 3	No effect of MMF on either outcome parameter	B
Tang et al,[17] 2005	Uprot > 1 g/d despite ACEI or ARB, Scr <3.4 mg/dL	n = 20: no treatment; n = 20: MMF 1.5-2.0 g/d depending on body weight for 6 mo	Uprot, Scr; FU, 1.4	Significant reduction in Uprot* but no effect on GFR	B
Frisch et al,[18] 2005	Uprot > 1 g/d + 1 further risk factor for progression	n = 15: placebo; n = 17: MMF 2 g/d for 1 y	50% increase in Scr or 50% decrease in Uprot; FU, mean 1.2	No effect of MMF on either outcome parameter	B
Immunosuppressive combination therapy					
Yoshikawa et al,[20] 1999	Severe IgAN (ie, a mean of 20%-25% of glomeruli with crescents)	n = 38: supportive therapy (anticoagulants: heparin followed by warfarin and dipyridamole); n = 40: oral prednisolone (maximum, 80 mg/d for 4 wk tapered to alternate steroid at 1 mg/kg until end of year 2) + azathioprine (2 mg/kg) for 2 y + anticoagulants	Uprot, histology; FU, 2	Significant reduction in Uprot and sclerosed glomeruli at follow-up evaluation	B
Yoshikawa et al,[21] 2006	Diffuse mesangial proliferation, age <15 y	n = 40: oral prednisolone (2 mg/kg/d tapered to alternate-day steroid at 1 mg/kg until end of year 2); n = 40: oral prednisolone + azathioprine (2 mg/kg/d for 2 y) + warfarin + dipyridamole	Uprot <0.1 g/m²/d; FU, 2	92% versus 74% primary end points in combination versus monotherapy	A
Ballardie et al,[22] 2002	Progressive renal failure with Scr ranging from 1.48 to 2.84 mg/dL	n = 19: supportive therapy; n = 19: oral prednisolone (40 mg/d tapered to 10 by 2 y) and cyclophosphamide 1.5 mg/kg/d for 3 mo, followed by azathioprine 1.5 mg/kg/d for at least 2 y	Renal survival, slope of 1/creatinine, Uprot; FU, 2-6	Significant reduction of rate of renal function loss from 3 y on	A

Evidence level was graded based on the following[43]: A: RCT that showed a statistically significant difference in at least one important outcome or, if the difference was not statistically significant, an RCT that can exclude a 25% difference in relative risk with 80% power, given the observed results; B: best level of evidence is an RCT that does not fulfill grade A criteria.

Abbreviations: Uprot, proteinuria; Scr, serum creatinine; Ccr, creatinine clearance; FU, follow-up period; ESRD, end stage renal disease; ACEI, ACE inhibitor; eGFR, estimated glomerular filtration rate.

*Higher blood pressure during study period in antiplatelet therapy group (see Table 2).

†Higher reduction in Uprot may relate to significantly higher baseline Uprot in steroid group.

‡Alternatively Uprot >0.5 g/g creatinine plus renal biopsy changes indicating risk for progression.

At present we are therefore left with uncertainty as to the value of MMF in patients with IgAN. In 1 study it improved proteinuria,[17] whereas in 2 other studies it had no detectable effect.[16,18] In the study by Frisch et al,[18] it is possible that the patients were too advanced in the course of their disease for a beneficial effect of MMF to be expected. However, in the 2 other studies by Tang et al[17] and Maes et al,[16] the baseline GFR was virtually identical in the MMF-treated and control patients and the baseline proteinuria was also very similar. This raises the important possibility that IgAN in Asians and Caucasians may be partially different entities. Indeed, only 30% of patients in the Chinese study were male,[17] as opposed to 76% of the Belgian patients,[16] which reflects that IgAN is distributed equally across the sexes in Asian populations, whereas it has a male predominance and worse prognosis in males in Caucasian populations.[19]

Immunosuppressive Combination Therapy

In 1999 Yoshikawa et al[20] published a randomized controlled trial in Japanese children with normal GFR treated with supportive therapy or immunosuppression (corticosteroids plus azathioprine). During 2 years of follow-up evaluation the proteinuria decreased from 1.0 to 0.9 in controls and from 1.4 to 0.2 g/d in the immunosuppressed group. The GFR remained normal in all but 1 child.

In 2006 the same investigators[21] published another randomized controlled trial in Japanese children who were randomized to prednisolone monotherapy versus prednisolone plus azathioprine plus warfarin and dipyridamole. In the combination group about 20% more children reached the end point of remission (ie, proteinuria <0.1 g/d).

In 2002 Ballardie and Roberts[22] published a randomized, controlled, single-center study on patients with progressive loss of renal function. Patients were randomized to prednisolone and cytotoxic agents or supportive therapy only. Renal survival in treated patients showed considerably better preservation of function at 5 years (72% compared with 6% in controls).

Results of a study comparing corticosteroid therapy with corticosteroids plus azathioprine (http://www.igan-world.org) have not yet been published, however, preliminary data (reported at the ERA-EDTA Congress, Barcelona, Spain, 2007) showed no significant difference in outcome between the 2 groups.

Probably the most important study is the study by Ballardie and Roberts,[22] which reports a dramatic benefit in IgAN patients at very high risk of renal failure, namely those with a progressive decline in GFR before randomization. Their study therefore provides nicely complementary evidence to the study by Pozzi et al,[9] which focused on patients with more or less preserved renal function at baseline.

Other immunosuppressive approaches that have been assessed in recent studies in patients with IgAN include leflunomide,[23] mizoribine,[24] intravenous immunoglobulins,[25] and sequential cyclophosphamide-MMF therapy.[26] The study design, nonrandomized nature, lack of controls, and/or the small group sizes preclude any firm conclusions to be drawn from these trials.

WHAT ARE THE PROBLEMS OF STUDIES ON IMMUNE-MODULATING THERAPY IN IgAN?

Adverse effects in the studies in which immunosuppressive monotherapy was administered generally were reported to be mild. Considerable side effects, however, were noted in those studies using immunosuppressive combinations (Table 2).

Apart from adverse effects the central problem of the studies available to date is that most were designed in the 1980s or 1990s, when recommendations for supportive therapy were strikingly different from those of today. In particular, no published study initiated a comprehensive supportive approach at baseline.[27,28]

With respect to one of the most important progression factors in glomerular disease, namely hypertension,[19] several of the studies shown in Table 1 either contain no or incomplete data on blood pressures achieved during the study period and/or data on the antihypertensive medication used (Table 2). In 2 of the major studies (ie, those of Pozzi et al[10] and Ballardie and Roberts[22]) detailed information on

Table 2. Summary of Supportive Therapy and Adverse Effects Noted in the Trials Shown in Table 1

Study	Achieved Blood Pressure During Study, mm Hg	Blockade of Renin-Angiotensin System	Major Adverse Effects of Immunosuppression
Corticosteroid monotherapy			
Pozzi et al,[9,10] 1999	134/84 mm Hg mean	ACEI in 54% of patients during parts of the study or follow-up period	1 patient with new type 2 diabetes mellitus
Shoji et al,[11] 2000	109 mm Hg systolic (corticosteroid group) versus 116 systolic mean (control group)	ACEI not allowed in study protocol	None
Katafuchi et al,[12] 2003	120-130 mm Hg systolic and 70-80 mm Hg diastolic in both groups	7/90 patients	None
Hogg et al,[13] 2007	N/A	ACEI in hypertensive patients only	None
Horita et al,[14] 2007	101/65 mm Hg (ARB group) versus 125/75 mm Hg mean	ARB in 1 group only	N/A
MMF			
Maes et al,[16] 2004	125/74 (MMF) versus 124/71 mm Hg at end of study	ACEI in all patients*	1 patient with reactivation of pulmonary tuberculosis, 2 patients with gastrointestinal complaints
Tang et al,[17] 2005	122/71 (MMF group) versus 127/72 mm Hg mean	ACEI and/or ARB in all patients at baseline	3 patients with transient anemia, 1 patient with diarrhea, 2 patients with urinary tract infections, 1 patient with cervical lymphadenitis
Frisch et al,[18] 2005	129/82 mm Hg mean	ACEI and/or ARB in all patients at baseline	None
Immunosuppressive combination therapy			
Yoshikawa et al,[20] 1999	N/A	N/A	1 child each with glaucoma, cataract, depression, peptic ulcer, alopecia, and anemia; significant growth retardation and weight gain in immunosuppressed children
Yoshikawa et al,[21] 2006	N/A	ACEI or ARB not allowed in study protocol	2 children with aseptic necrosis of femoral head, 4 with glaucoma, 4 with leukopenia (total study population, 80); significant increase in body mass index in both groups
Ballardie et al,[22] 2002	Mean arterial pressure around 110 mm Hg	N/A	1 patient with azathioprine-induced bone marrow suppression, 1 with new diabetes mellitus, 1 with activation of pulmonary tuberculosis (total study population, 38)

Abbreviations: N/A, information not available; ACEI, ACE inhibitor.
*Dosage almost twice as high in MMF group.

blood pressures throughout the study duration was published. In the study by Pozzi et al[9] the mean systolic and diastolic blood pressures were around 135 and 85 mm Hg, respectively, during the study period. In the study by Ballardie and Roberts[22] only mean arterial pressures were given, which fluctuated around 105 mm Hg (corresponding, for example, to 135/90 mm Hg) during most of the study period. This is clearly different from today's recommended target blood pressure of 125/75 mm Hg in patients with renal disease and proteinuria exceeding 1 g/d.

Other studies are difficult to interpret because proteinuria, another major risk factor for progression,[19] was significantly higher at baseline in patients receiving immunosuppression versus those receiving supportive care only.[12] This concern is particularly relevant for the many noncontrolled retrospective analyses on immunosuppression in IgAN, which are not discussed in this review but that we have reviewed recently.[29] Finally, hardly any study administered antagonists of the renin-angiotensin system to all proteinuric patients (ie, independent of blood pressure), despite the fact that virtually all studies required significant proteinuria as an entry criterion (Table 2). No study mentioned that an attempt was made to titrate ACE inhibitor or angiotensin receptor blocker (ARB) dosage to the maximum tolerated level or to combine them to optimize their antiproteinuric effect (see later).

Finally, in almost all of the studies shown in Table 1, information on additional progression factors, such as smoking, dietary salt and protein intake, or regular consumption of analgesics is lacking.

ARE THERE ESTABLISHED NON–IMMUNE-MODULATING APPROACHES TO TREAT IgAN?

Patients with progressive IgAN, similar to those with other progressive glomerular diseases, benefit from low blood pressure. This has been shown convincingly in large studies, in which about 20%[30] to 50%[31] of the patients had IgAN, as well as in studies specifically investigating patients with IgAN.[32] In the latter study, lowering blood pressure to 129/70 versus 136/76 mm Hg in a control group determined whether patients with IgAN, (almost) normal renal function, and a mean proteinuria of 1 g/d either lost no renal function or had a 15% reduction in renal function, respectively, over 3 years. Even so-called *normotensive* patients, usually defined as patients with blood pressures less than 140/90 mm Hg and not treated, may not have a normal blood pressure. In patients with IgAN and office blood pressures less than 140/90 mm Hg and no antihypertensive therapy, increased 24-hour pressure as compared with healthy age- and body mass index– matched controls as well as cardiac changes suggestive of hypertensive damage were shown.[33]

Antiproteinuric therapy achieved via blockade of the renin-angiotensin system also is established firmly in IgAN patients (reviewed by Dillon[34]). Thus, Praga et al[35] noted significantly better renal survival in patients receiving enalapril as compared with those receiving other classes of antihypertensive drugs, despite identical blood pressure levels over the observation period. The same conclusion was reached in a recent study by Coppo et al.[36] In a Hong Kong study[37] a similar benefit was shown for valsartan. Co-administration of an ACE inhibitor and an ARB resulted in an additive antiproteinuric effect in IgAN patients[38] and in the long term markedly retarded the loss of renal function.[31] There is also evidence that ACE inhibitors or ARBs may retard the course of recurrent IgAN after renal transplantation, a condition so far believed to be untreatable. Thus, Courtney et al[39] studied 75 patients with end-stage renal disease caused by IgAN, of whom 39 had been prescribed an ACE inhibitor or ARB. In the group in which an ACE inhibitor/ARB was not prescribed, 4 of 4 with recurrent IgAN progressed to end-stage renal disease, compared with 3 of 9 in the group treated with an ACE inhibitor/ARB.

Less well established nonimmunosuppressive approaches to patients with IgAN include fish oil, antiplatelet drugs, and anticoagulants. In a meta-analysis of fish oil therapy in patients with IgAN no statistically significant benefit was noted, although the probability of at least a minor effect was 75%.[40] Antiplatelet drugs and anticoagulant drugs are used mostly in the Asian region for the treatment of IgAN. A

Table 3. Proposal of a Pragmatic Approach to the Therapy of Patients With IgAN Until More Study Data Are Available

Clinical Scenario	Proposed Therapy
Asymptomatic isolated microhematuria	No therapy; annual medical check-ups
Proteinuria <0.5 g/d with or without microhematuria; GFR normal	No therapy; annual medical check-ups
Proteinuria 0.5-1.0 g/d with or without microhematuria; GFR normal	Consider initiating ACE inhibitor or ARB and up-titration even if formally normotensive; medical check-ups every 6 mo; aim for proteinuria <0.5 g/d and low normal blood pressure[27,28]
Proteinuria >1.0 g/d with or without microhematuria; GFR normal or slowly decreasing but still >30 mL/min	Optimize supportive therapy[27,28]; if persistent proteinuria >1.0 g/d after 6 mo consider immunosuppression (ie, corticosteroid monotherapy following the protocol of Pozzi et al[9] in patients with a GFR >70 mL/min or following the protocol of Ballardie and Roberts[22] in patients with a declining GFR between 30 and 70 mL/min)
Nephrotic syndrome	Follow earlier-described proposal but verify with pathologist that no IgAN–minimal change disease overlap exists (in the latter case follow therapy recommendations for minimal change disease)
GFR <30 mL/min	Optimize supportive therapy; do not consider immunosuppression any longer* except for patients with rapidly progressive course and active glomerular necrosis/crescent formation (see later)
Rapidly progressive renal failure with >50% crescents and/or glomerular necrosis in the biopsy	Consider treatment approach similar to that in patients with ANCA-associated rapidly progressive glomerulonephritis[44,45]

Abbreviation: ANCA, anti-neutrophil cytoplasmatic antibodies.
*Virtually all randomized studies on immunosuppression have excluded patients with a GFR less than 30 mL/min.

small study suggested a benefit from dipyridamole (75 mg 3 times a day) and warfarin (international normalized ratio, 1.3-1.5) as compared with no treatment, but ACE inhibitors were avoided in these patients.[41]

WHICH THERAPY TO CHOOSE FOR WHICH IgAN PATIENT?

The treatment of patients with slowly progressive IgAN or those at risk for progression currently represents a dilemma. Although on the one hand there are a few studies that convincingly describe a benefit of immunosuppression, on the other hand there are an equal number of studies reporting a benefit of supportive therapy. Unfortunately, no head-to-head comparison of these 2 approaches is available, except for a small Korean study. In this study, testing cyclophosphamide plus prednisolone + ACE inhibitor versus ACE inhibitor alone, a better outcome was observed with supportive care only as compared with immunosuppression.[42] It also is noteworthy that at least in 1 study the addition of an ARB to corticosteroid monotherapy resulted in a considerable benefit, whereas corticosteroids without renin-angiotensin system blockade failed to protect from progressive renal failure.[14]

Two ongoing trials may help to resolve this nonsatisfactory situation.

The first trial is the Supportive versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN). This trial, initiated by ourselves, will test whether the addition of immunosuppression to an optimized supportive therapy confers added benefit in patients with IgAN and persistent proteinuria greater than 0.75 g/d despite supportive therapy (http://www.igan-world.org).

The second study is comparing 6 months of oral prednisone plus ramipril versus ramipril alone in IgAN patients with a proteinuria greater than 1 g/d and a GFR greater than 50 mL/min (http://www.igan-world.org).

An update of ongoing trials is available through the website of the International IgA Nephropathy Network (http://www.igan-world.org). Until these data are available, we recommend a pragmatic approach to the various patients with IgAN (Table 3).

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