IgA Nephropathy

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Immunoglobulin A nephropathy (IgAN) is defined by the predominant deposition of IgA in the glomerular mesangium. Light microscopic appearances and clinical features can vary considerably, reflecting the many patterns of histopathologic injury seen in this glomerulonephritis (GN) Closely associated with IgAN is Henoch-Schönlein purpura (HSP), a small-vessel systemic vasculitis characterized by small blood vessel deposition of IgA predominantly affecting the skin, joints, gut, and kidney. The nephritis of HSP is also characterized by mesangial IgA deposition and may be histologically indistinguishable from IgAN. Both clinical and laboratory evidence support a close relationship between IgAN and the nephritis of HSP (1). This article focuses on IgAN considering especially new information available since IgAN was last reviewed in the *Journal of the American Society of Nephrology* (2). In particular, we focus on our growing understanding of the pathogenesis of IgAN, and we discuss the impact of recently published randomized, controlled trials (RCT) on recommended treatment strategies.

Epidemiology and Clinical Features

The clinical course of IgAN is well established and has recently been reviewed elsewhere (3). There are a number of clinical features for which there is no certain explanation; these include the male preponderance, the apparent peak incidence in the second and third decades of life, the very wide range of presenting clinical features, and the variable tempo of disease after diagnosis. Data from Japan suggest that the prevalence of subclinical "lanthanic" IgAN may be even higher than already suspected, on the basis of renal biopsies in living kidney donors, in which 16% were found to have previously unknown mesangial IgA (4). The geographic differences in apparent prevalence of IgAN—higher in the Pacific Rim, where incidence in older patients is reported to be increasing, and Southern Europe, as opposed to northern Europe and North America—are still the subject of debate. Varying approaches to the use of renal biopsy in patients with mild urinary abnormalities are often cited as one explanation, but worldwide practice is becoming increasingly uniform, and fewer nephrologists now recommend renal biopsy for people with asymptomatic microscopic hematuria in the absence of sustained proteinuria. Most prevalence data are generated from centers in major industrialized cities in which the lifestyle is becoming increasingly uniform, suggesting that the varied incidence more likely represents true differences among racial groups, rather than environmental in origin. However, genetic studies have so far been unrewarding in defining the pathogenesis of IgAN.

The diagnosis of IgAN always requires renal biopsy. No clinical presentation is pathognomonic, not even the archetypal young male patient with episodic macroscopic hematuria after an upper respiratory tract infection, which is the presenting feature in 30 to 40% of cases. Most patients have only a few episodes of frank hematuria, and such episodes usually recur for a few years at most.

Asymptomatic urine testing identifies 30 to 40% of patients with IgAN in most series. Studies in which renal biopsy has been offered to patients with isolated microscopic hematuria suggest that up to half of such patients in all age groups will have IgAN, with the majority of the remaining patients having either thin-membrane nephropathy or normal biopsies (5,6). It is very rare for proteinuria to occur without microscopic hematuria in IgAN. Nephrotic syndrome is uncommon, occurring in only 5% of all patients with IgAN, but is more common in children and adolescents. Patients may develop nephrotic-range proteinuria at different stages of the disease, both when there is mild glomerular injury and when there is advanced glomerulosclerosis.

Acute renal failure is very uncommon (<5% of all cases) and develops by two distinct mechanisms. There may be acute, severe immune and inflammatory injury producing crescent formation: Crescentic IgAN—this may be the first presentation of the disease or can occur superimposed on known milder IgAN. Alternatively, acute renal failure can occasionally occur with mild glomerular injury when heavy glomerular hematuria leads to tubular occlusion and/or damage by red cells. This is a reversible phenomenon, and recovery of renal function occurs with supportive measures.

The remainder of patients with IgAN, typically older at presentation, already have proteinuria, renal impairment, and hypertension when they first receive the diagnosis. Rarely, IgAN may present with malignant hypertension. It is usually presumed that they have longstanding IgAN that was not detected earlier because the patient did not have frank hematuria or undergo routine urinalysis.

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Pathology

The range of pathologic features of IgAN is well described (7). Mesangial IgA deposits are the defining hallmark of the disease; they are diffuse and global, even if light microscopic change is focal or segmental. IgA deposits are also occasionally seen in glomerular capillary walls, where their presence has been associated with a worse prognosis. IgA is the sole Ig present in only 15% of biopsies; IgG and IgM accompany IgA in the majority of cases. C3 deposition is usual and has the same distribution as IgA.

Light microscopic abnormalities may be minimal, but the most common appearance is mesangial hypercellularity. This most commonly is diffuse and global, but focal segmental hypercellularity is also seen. With progressive disease, there is relentless accumulation of mesangial matrix. Crescentic change may be superimposed on diffuse mesangial proliferative GN with or without associated segmental necrosis. Crescents are a common finding in biopsies that are performed during episodes of macroscopic hematuria with renal impairment. Tubulointerstitial changes do not differ from those seen in other forms of progressive GN, reflecting the final common pathway of renal parenchymal disease.

Mesangial and paramesangial electron dense deposits are the ultrastructural manifestation of mesangial IgA deposition. There is evidence that a proportion of patients with IgAN have diffuse uniform global thinning of the glomerular basement membrane indistinguishable from that seen in thin-membrane nephropathy. It is not yet clear whether this group of patients has any defining clinical or prognostic characteristics compared with typical cases of IgAN (8,9).

A number of classifications of IgAN based on light microscopic findings are in use, for example those of Lee and Haas (10–12), but there is little agreement about their relative utility. An international consensus on a pathologic classification for IgAN would be of great value in clinical practice and research in this field; the International IgA Nephropathy Network with the Renal Pathology Society, under the auspices of the International Society of Nephrology, are presently developing such a consensus, which it is expected will be announced in 2006.

Do these various clinical presentations and pathologic features of IgAN all arise from the same disease process? It is common to describe IgAN as a single disease, but our present limited understanding of the cause and pathogenesis of IgAN does not yet provide strong support for such a view. Mesangial IgA deposition and subsequent injury may eventually turn out to represent a final common path of glomerular response to a wide range of causative and pathogenic processes, and a very different classification may emerge in due course.

Pathogenesis

The initiating event in the pathogenesis of IgAN is the mesangial deposition of IgA, which is predominantly polymeric IgA of the IgA1 subclass (pIgA1). Co-deposits of IgG and complement are also commonly seen; however, these are not mandatory for disease activity or progression. The varied glomerular response to IgA deposition is reflected in the renal biopsy findings, clinical presentation, and outcome of patients with IgAN. Three key elements contribute to the development of IgAN, and the extent to which each is operational decides the severity, tempo, and eventual outcome of IgAN in any individual:

1. Synthesis, release, and persistence in the circulation of pIgA1 with characteristics that favor mesangial deposition;
2. The "reactivity" of the glomerular mesangium as judged by:
   - its susceptibility to mesangial deposition
   - its capacity to mount an inflammatory response to that deposition;
3. The tendency of the kidney to respond to injury by mounting a response that favors progressive renal injury rather than resolution of inflammation without ongoing glomerulosclerosis, tubular atrophy, and interstitial fibrosis.

The likely interactions of these elements of pathogenesis are shown in Figure 1. Each of these three elements may have a significant genetic component that influences the eventual phenotype of the disease in any individual.

Although mesangial IgA deposition and the initiation by IgA of glomerular inflammation are specific to IgAN, mechanisms of the subsequent renal injury followed either by resolution or progressive sclerosis are likely to be generic, not differing substantially from those seen in other forms of chronic GN. In this review, we focus on IgA-specific pathogenic mechanisms.

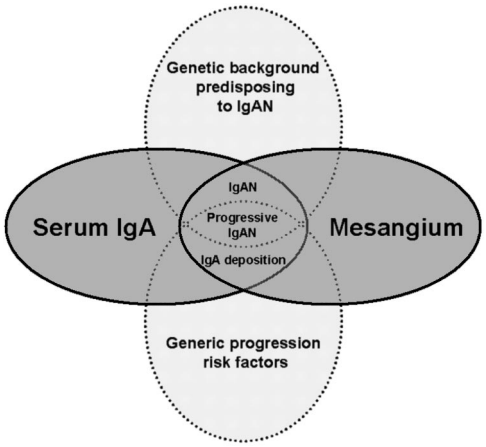

Figure 1. Interactions of major elements of pathogenesis of IgA nephropathy (IgAN). Total circulating serum IgA is the source of mesangial IgA deposits in IgAN. The fraction of total serum IgA that has a propensity for mesangial deposition, however, is small, and the fraction that is capable of initiating glomerulonephritis (GN) is smaller still. The response of the mesangium and, in particular, the mesangial cell (MC) to the deposited IgA is critical to the development of IgAN. Without an appropriate genetic predisposition to develop IgAN, IgA deposition can be a benign process with little or no risk for triggering GN. However, given an appropriate genetic background, serum IgA responses will favor mesangial IgA deposition, and the mesangial response will take on a proinflammatory phenotype, resulting in clinically significant IgAN of varying severity. Finally, if generic progression risk factors coincide, then this will increase the likelihood of progressive renal impairment and may ultimately determine the rate of decline in renal function.

IgA and IgA Production in IgAN

A number of abnormalities in circulating IgA and its production are reported in IgAN (13). However, patient cohorts are heterogeneous with respect to these abnormalities, supporting the notion that more than one pathogenic mechanism may result in the production of pathogenic circulating IgA. An increased plasma IgA level is not sufficient *per se* to produce mesangial IgA deposits; therefore, patients with IgAN must produce a pool of circulating IgA molecules with special characteristics that particularly promote mesangial deposition.

Molecular Characteristics of IgA in IgAN. There is no well-supported evidence that IgAN is driven by circulating IgA autoantibodies' binding to glomerular antigens. Increases in circulating IgA1 antibodies against a variety of antigens have certainly been described, but no single pathogenic antigen has been identified. Studies of serum IgA have by contrast demonstrated a number of unusual physical characteristics in IgAN (Table 1). Although some of these findings have been replicated for IgA eluted from renal biopsy specimens, it is not yet certain which of these features are responsible for the mesangial deposition and mesangial cell (MC) activation of IgAN.

Abnormal O-glycosylation of IgA1 in IgAN has been widely investigated, and there is now increasing evidence for its involvement in the pathogenesis of IgAN (14). The abnormality takes the form of reduced galactosylation of the IgA1 hinge region O-glycans, leading to increased frequency of truncated O-glycans. Altered sialylation of the IgA1 O-glycans in IgAN is more contentious, with increased and decreased O-sialylation being reported. Early reports were confined to studies of serum IgA, but two studies of IgA1 eluted from isolated glomeruli have now identified the same O-glycosylation abnormalities in mesangial IgA1, strongly implicating altered glycosylation in the mechanisms of IgA deposition (15,16). The functional effects of altered IgA1 hinge region O-glycosylation are under active investigation. Current *in vitro* evidence suggests that aberrantly glycosylated IgA1 molecules have an increased tendency both to self-aggregate and to form antigen-antibody complexes with IgG antibodies directed against IgA1 hinge epitopes, favoring the generation of macromolecular aggregates of pIgA1 and IgA immune complexes (IgA-IC), which would promote mesangial deposition (17,18). In addition, IgA1 molecules that lack terminal sialic acid and galactose units have increased *in vitro* affinity for the extracellular matrix components fibronectin and type IV collagen (18). Early studies in this field have relied on *in vitro* deglycosylation of IgA1, which produces a much more extensive alteration in glycosylation than the subtle abnormalities identified in serum and mesangial IgA1 in patients, so there is some uncertainty about the extrapolation of these findings to the human disease. *In vitro* studies using serum IgA1 isolated from patients with IgAN are now emerging and seem more likely to produce clinically relevant information (19).

A functional abnormality of the specific glycosyltransferases responsible for the O-glycosylation of IgA1 has been proposed as a mechanism for altered O-glycosylation in IgAN (20). β-1,3-Galactosyltransferase (β1,3-GT) is the key enzyme, catalyzing the addition of galactose to O-linked glycans, and although we reported some evidence for a functional defect in β1,3-GT in peripheral blood B cells (21), we have since found no overt defect in the activity of this enzyme in bone marrow B cells in IgAN (22). These studies have been hampered for some years by lack of information on the molecular genetics of glycosyltransferases; however, such work is now possible as the core β1,3-GT and its molecular chaperone, Cosmc, have now been characterized (23,24).

IgA Production in IgAN. The site of production of the pathogenic IgA in IgAN has been an area of extensive study. The association of episodic macroscopic hematuria with mucosal infections originally led to the suspicion that IgAN was intimately linked with abnormal mucosal antigen handling, particularly because both mesangial IgA and the increased IgA fraction in serum IgA are polymeric, which is normally produced at mucosal surfaces rather than in systemic immune sites. However, studies that were published several years ago indicate that the presence of pIgA in the circulation cannot be attributed simply to mucosal overproduction and "spillage" into the circulation. These studies indicated that mucosal pIgA plasma cell numbers are normal or even reduced in IgAN,

Table 1. Properties of IgA in normal subjects and in IgAN: The common features of serum and mesangial IgA in IgAN[a]

Properties of IgA	Controls		IgAN	
	Serum IgA	Mucosal IgA	Serum IgA	Mesangial IgA
Size	Mostly mIgA	Mostly pIgA	Increased pIgA	pIgA
Subclass	Mostly IgA1	IgA1 and IgA2	Increased IgA1	IgA1
Proportion of λ light chain compared with normal serum IgA	—	Not known	Increased	Increased
Charge compared with normal serum IgA	—	Not known	Anionic	Anionic
O-glycosylation	Heavily galactosylated and sialylated	Unknown galactosylation, decreased sialylation	Reduced galactosylation, increased or decreased sialylation	Reduced galactosylation and sialylation

[a]IgAN, IgA nephropathy.

whereas pIgA antibody levels in mucosal secretions are not elevated and are sometimes lower than controls. However, increased pIgA1 plasma cell numbers are found in the bone marrow in IgAN, and systemic antigen challenge results in increased titers of circulating pIgA1 antibodies, with normal levels in mucosal secretions. Therefore, the overproduction of pIgA1 is likely to be based within systemic immune sites such as the bone marrow, with both systemic and mucosal antigen challenges resulting in aberrant systemic immune responses (13). The origin of the plasma cells that secrete this pIgA1 remains a matter for debate. One possibility is that they are displaced mucosally derived plasma cells that have taken up residence in systemic sites rather than back home to their mucosal site of origin; this requires further investigation. γδ T cells are a minority T cell population that play a role in mucosal immunity and promote IgA production. Abnormal patterns of V (variable) region usage by γδ T cells have been reported in both the mucosa and the marrow in patients with IgAN (25,26), although the functional implications of these findings have not yet been elucidated.

Little yet is known of specific mechanisms that may control IgA synthesis in the different immune sites. There is emerging evidence that in health, the degree of IgA O-glycosylation can vary between immune sites possibly through local differences in β1,3-GT activity. Rather than a generalized β1,3-GT defect being the explanation for altered O-glycosylation of serum IgA1, it may be that undergalactosylated pIgA1 is a normal glycoform of IgA in some immune sites, such as the mucosa, the excess of this IgA glycoform in the serum in IgAN being a consequence of misplaced mucosally derived plasma cells' secreting mucosal-type IgA into the circulation. Whatever the reason for the altered serum IgA1 glycosylation, the effect is that the mesangium is exposed to undergalactosylated IgA glycoforms that would not normally require handling by mesangial clearance pathways. Ineffective processing of such IgA as a result of its unusual glycosylation may drive the IgA accumulation and mesangial activation characteristic of IgAN.

Systemic IgA Clearance in IgAN. Failure of normal IgA and IgA immune complex clearance mechanisms will facilitate their persistence in the serum. *In vivo* studies that have tracked the clearance of radiolabeled IgA from the circulation indicate a key role for the liver, with reduced liver clearance in IgAN (27). An alternative route for IgA catabolism is through the Fc receptor for IgA, CD89 (FcαRI), which mediates IgA endocytosis and catabolism (28). In IgAN, CD89 expression is downregulated on myeloid cells, which may lead to reduced clearance of IgA from the circulation and contribute to increased serum IgA levels (29). It has also been shown that IgA binds less well to CD89 in IgAN, and this may act to disrupt further the efficiency of systemic IgA clearance in IgAN (29,30).

IgA and the Mesangium

Not all mesangial IgA deposition is associated with the development of glomerular inflammation; neither is IgA deposition necessarily irreversible: Mesangial IgA deposits disappear when kidneys with subclinical IgAN are inadvertently transplanted into recipients who originally did not have IgAN, whereas sequential biopsy studies suggest that clinical remission is accompanied by disappearance of IgA deposits (31,32). In IgAN, mesangial IgA accumulation occurs because the rate of IgA deposition exceeds this clearance capacity and/or the deposited IgA is in some way resistant to mesangial clearance.

Mesangial IgA Deposition. In animal models, macromolecular immunoglobulins are particularly prone to mesangial deposition. It seems probable that the increased levels of serum IgA macromolecules in IgAN promote mesangial deposition through nonspecific size-dependent mesangial trapping, perhaps enhanced by the O-glycosylation defect. There is also evidence from transgenic mice that soluble CD89-IgA complexes that are generated after binding of IgA to membrane-bound CD89 are associated with massive mesangial IgA deposition (33). This has led to the suggestion that CD89-IgA complexes may form part of the circulating pool of macromolecular IgA in human IgAN, although other data suggest that CD89-IgA complexes may not be specific to IgAN (34).

As well as passive trapping, there is evidence that IgA deposition may be influenced by interactions between IgA and specific mesangial matrix components. IgA1 glycosylation seems to influence matrix interactions, whereas the anionic pI of mesangial IgA may also promote interactions with mesangial matrix proteins.

Mesangial IgA Clearance and IgA Receptors. The principal candidate pathway for IgA clearance is through MC receptor–mediated endocytosis and catabolism of IgA deposits. The precise nature of the MC IgA receptor(s) remains controversial. The transferrin receptor (CD71) is expressed by human MC in culture, it binds IgA, and aberrantly glycosylated pIgA1 may preferentially bind to it (35,36). There is one report of increased mesangial CD71 expression in IgAN, although this is not supported by another study (37,38). There is also preliminary evidence that human MC may in addition express a novel FcαR, an asialoglycoprotein receptor, and an Fc α/μ receptor (39–41). Regardless of which receptor is involved, there is *in vitro* evidence that human MC are capable of receptor-mediated endocytosis and catabolism of IgA (42). It is possible that impaired binding could lead to defective mesangial IgA clearance and thereby contribute to IgA accumulation and the development of GN, although as yet there is no direct evidence for this in humans.

Development of Glomerular Injury. IgAN is not generally associated with a marked cellular infiltrate into glomeruli, suggesting that most of the glomerular injury is mediated by an expansion in resident glomerular cells. Although IgG and complement components are often co-deposited, IgA alone seems to be sufficient to provoke glomerular injury in the susceptible individual. This occurs predominantly through IgA-induced activation of MC and local complement activation.

MC Activation. There is strong *in vitro* evidence that cross-linking of MC IgA receptors with macromolecular IgA elicits a proinflammatory and profibrotic phenotypic transformation in MC (13). Consistent with the mesangial hypercellularity seen in renal biopsy specimens, MC proliferate in response to IgA. Furthermore, exposure to IgA has been shown to upregulate secretion of both extracellular matrix components, the profi-

brotic growth factor TGF-β, and components of the renin-angiotensin system (RAS). IgA is also capable of altering MC–matrix interactions by modulating integrin expression, and this may have an important role in remodeling of the mesangium after glomerular injury. Exposure of MC to IgA is also capable of initiating a proinflammatory cascade involving MC secretion of platelet activating factor (PAF), IL-1β, IL-6, TNF-α, and macrophage migration inhibitory factor (MIF); the release of the chemokines monocyte chemotactic protein-1, IL-8, IP-10; and development of an amplifying proinflammatory loop involving IL-6– and TNF-α–induced upregulation of MC IgA receptors. There is also evidence that MC activation by co-deposited IgG may synergistically contribute to the development of a proinflammatory MC phenotype and thereby influence the degree of glomerular injury.

It is not yet clear which specific physicochemical properties of mesangial IgA affect MC activation; however, there is some *in vitro* evidence that undergalactosylated IgA glycoforms from patients with IgAN can both increase and reduce MC proliferation rates, increase nitric oxide synthesis and the rate of apoptosis, and enhance integrin synthesis in cultured MC (14). This together with the overrepresentation of aberrantly glycosylated IgA in mesangial IgA suggest that IgA1 O-glycosylation plays a role in both the deposition of IgA and the subsequent injury.

Complement Activation. Although involvement of the complement cascade is not essential for the development of IgAN, there is evidence that local complement activation can influence the extent of glomerular injury. Mesangial IgA activation of C3 probably occurs through the mannan-binding lectin (MBL) pathway, and this ultimately leads to the generation of C5b-9, sublytic concentrations of which can activate MC to produce inflammatory mediators as well as matrix proteins (43). C3 and MBL not only are deposited in the kidney in IgAN but also can be synthesized locally by the MC and, in the case of C3, by podocytes as well. It is likely, therefore, that having bound IgA, MC are capable of local complement activation using endogenously generated C3 and MBL, independent of any systemic complement activity. The contribution of this *in situ* complement synthesis and activation to progressive glomerular injury is not known. MC also synthesize complement regulatory proteins, which may explain why C5b-9 generation in IgAN does not usually result in mesangiolysis.

Genetics of IgAN

There is little doubt that there are genetic components to the pathogenesis and clinical expression of IgAN. This has been inferred from the existence of familial forms of IgAN, the presence of elevated serum IgA levels and overproduction of IgA by cultured B cells in otherwise unaffected family members, and the failure of exposure to mesangial IgA deposits to lead to IgAN in all individuals. Most population studies in IgAN to date have been relatively small case-control genetic association studies that have examined single-nucleotide polymorphisms in single candidate genes. The lack of concordance across many of these studies reflects both small sample sizes and the methodologic limitations of using such a strategy in studying a complex polygenic disease. This is compounded by uncertainty as to whether IgAN is truly a single entity and the realization that IgAN may exist as a subclinical condition in apparently normal control populations. Furthermore, many of the published studies have reported on genetic factors that influence progression of renal failure in IgAN (likely generic to many chronic kidney diseases) rather than on disease pathogenesis (44).

Genome-wide linkage analysis in 30 multiplex kindreds has demonstrated linkage of IgAN to 6q22–23 (45). There are no obvious candidate genes within the linked interval, and no linkage was found in the same kindreds for a number of other candidate genes that all have been implicated in the pathogenesis of IgAN. Further definition of the genes involved within the IGAN1 locus is still awaited. It is not certain that genetic findings from these unusual multiplex families will have direct bearing on more typical sporadic cases of IgAN.

Natural History and Prognosis

Fewer than 10% of all patients with IgAN have complete resolution of urinary abnormalities. IgAN has the potential for slowly progressive chronic renal impairment, leading eventually to ESRD. Approximately 25 to 30% of any published cohort will require renal replacement therapy within 20 to 25 years of presentation. From first symptoms, 1.5% of patients with IgAN have been calculated to reach ESRD per year. The perceived overall cohort risk of course will be influenced by the diagnostic approach, because centers with a low threshold for renal biopsy for patients with mild urine abnormality will likely diagnose IgAN in a larger number of patients with mild disease and good prognosis, thus favorably influencing the overall outcome of the cohort.

Many studies have identified features at presentation that mark a poor prognosis (Table 2). Although these prognostic features may be informative for populations of patients, they as yet do not have the specificity to identify an individual prognosis with complete confidence. An approach that incorporates sequential information on BP and proteinuria can refine further the prediction of progression risk (46–48), although this still will only account for 30% of overall risk (44). In milder disease, one study suggested that proteinuria may in fact be a less powerful predictive factor than expected (49). Although prognostic formulas that use simple clinical and laboratory data have been proposed (44,49), there is not yet sufficient consensus to recommend that they be used in clinical practice for the prediction of individual progression risk. It remains uncertain whether pathologic classification adds predictive power in the individual patient; progress in defining the answer has been limited by the lack of international consensus on pathologic classification of IgAN.

Recurrence after Renal Transplantation

Recurrence of IgAN after renal transplantation has been recognized for 30 years. It is assuming increasing importance as a cause of graft failure as control of rejection improves. It typically is slowly progressive, although occasional patients will have a rapidly progressive course. Available evidence indicates

Table 2. Prognostic markers at presentation in IgAN

Clinical	Histopathologic
Poor prognosis	**Poor prognosis**
increasing age	*light microscopy*
duration of preceding symptoms	capsular adhesions and crescents
severity of proteinuria	glomerular sclerosis
hypertension	tubule atrophy
renal impairment	interstitial fibrosis
increased body mass index	vascular wall thickening
Good prognosis	*immunofluorescence*
recurrent macroscopic hematuria	capillary-loop IgA deposits
No impact on prognosis	*ultrastructure*
gender	mesangiolysis
ethnicity	GBM abnormalities
serum IgA level	**Good prognosis**
	minimal light microscopic abnormalities
	No impact on prognosis
	intensity of IgA deposits
	co-deposition of mesangial IgG, IgM or C3

at 5 yr a 5% risk for graft failure as a result of recurrence, a 13% risk for significant graft dysfunction, and at least 50% risk for IgA deposition. The risk for graft loss increases markedly to 25% when a first graft was lost to recurrence. There is no consistent evidence that these risks differ between living and cadaveric donors (50). There is no evidence that any particular immunosuppressive regimen alters the incidence of IgAN recurrence after transplantation or of the prognosis of recurrence in the short term. Because most recurrent IgAN is only very slowly progressive, it is not possible yet to ascertain whether newer immunosuppressive regimens may have a favorable long-term effect.

Treatment of IgAN

Several aspects of the treatment of IgAN remain controversial. Despite the prevalence of IgAN, published RCT are few in number, and even recent RCT are not always sufficiently powered to provide definitive information on tested interventions. Still no treatment is known to modify mesangial deposition of IgA, and available treatment options are directed mostly at downstream immune and inflammatory events that may lead on to renal scarring.

Recurrent Macroscopic Hematuria

Episodes of recurrent macroscopic hematuria are self-limiting and provoked by a range of mucosal, most commonly respiratory, infections. In a minority of patients, recurrent episodes are provoked by bacterial tonsillitis, and tonsillectomy may be advised. Although this will help to prevent episodic hematuria in the short term, the proponents of tonsillectomy argue that it also gives long-term renoprotection. Two large, retrospective studies from Japan support its efficacy, although follow-up of >10 yr is required before benefit becomes apparent, and the concomitant use of other treatment modalities makes these data difficult to interpret (51,52). An RCT of tonsillectomy in IgAN would be valuable, and such a study is now being planned in Japan.

Isolated Microscopic Hematuria and Little or No Proteinuria

The consensus remains that there is no specific treatment required for patients with isolated microscopic hematuria and little or no proteinuria, although prolonged surveillance is indicated. A threshold for proteinuria of 1 g/24 h is usually recommended to identify those who are at higher risk, although this is an arbitrary value, and the risk attributable to proteinuria is almost certainly a continuum.

Slowly Progressive IgAN

The main area of treatment controversy is for patients with IgAN who are at risk for slowly progressive renal dysfunction—typically those with hypertension, proteinuria >1 g/24 h, or reduced GFR at the time of diagnosis. Because progression is usually slow, large studies with prolonged follow-up are necessary to determine the efficacy of any therapeutic intervention with confidence, and many recently published studies are insufficiently powered to answer these questions. All such trials in IgAN use clinical entry criteria—typically the presence of hypertension, proteinuria 1 to 3 g/24 h, with variable reduction in GFR. This is in contrast, for example, to studies in lupus nephritis, in which histologic criteria usually dominate recruitment and reflect the lack of consensus on a histopathologic classification of IgAN.

In the past few years, new data have been reported on a number of interventions that are intended to slow immune and inflammatory events that are implicated in progressive IgAN, including corticosteroids, cyclophosphamide, and mycophenolate. Because of the long duration required to identify with confidence the benefit of interventions, it is inevitable that recruitment into a number of these studies goes back 10 yr or more, at a time when the generic approach to progressive glomerular disease was less well defined. The modern approach to such proteinuric patients emphasizes rigorous BP control to a target of 125/75 mmHg and comprehensive RAS

blockade to minimize proteinuria (53). Increasingly vigorous BP control has been recommended in recent years for IgAN, predominantly by extrapolation from other studies of progressive proteinuric renal disease, although one small RCT in IgAN supported the additional benefit of an angiotensin-converting enzyme (ACE) inhibitor on progressive renal disease to achieve additional reduction in proteinuria despite equivalent BP control (54). Furthermore, the COOPERATE study provided evidence for additive renoprotection when an angiotensin receptor blocker (ARB) is given in combination with an ACE inhibitor in nondiabetic proteinuric renal disease, additional reduction in proteinuria being achieved with no further lowering of BP; 131 patients in this large study had IgAN (55).

Corticosteroids. A meta-analysis of six available trials of sufficient quality suggested that corticosteroid therapy may be effective in reducing proteinuria and reducing risk for ESRD, although the impact on protecting renal function is less clear (56). The large Italian study of corticosteroids now has 10 yr of follow-up with impressive benefit from treatment in reducing proteinuria and preventing ESRD (57). However, this high-dose corticosteroid regimen is regarded by many physicians as likely to carry considerable toxicity, even though none is reported by the investigators. RAS blockade was used in only a minority of patients in this study, although equally distributed among the participants, and achieved BP was not in line with current recommendations (Table 3). Another recent RCT of corticosteroids showed only a modest reduction in proteinuria with no protection of GFR (58), a difference attributed by the investigators to the lower dose of corticosteroids, but BP control was tight even though RAS blockade was not used (Table 3). This remains a controversial area, and in our view, corticosteroids should be considered only when proteinuria persists >1 g/24 h despite optimal BP control and maximum RAS blockade.

Most trials of corticosteroids in progressive IgAN exclude patients with nephrotic-range proteinuria, because many physicians regard this as an indication for corticosteroid therapy. However, the only RCT that addressed this question showed a response to corticosteroids only in patients with minimal or minor histologic abnormality on light microscopy (59). The use of corticosteroids when nephrotic syndrome complicates IgAN with histologic features other than minimal change is controversial, and we do not routinely take this approach.

Cyclophosphamide. There is evidence in one study for the efficacy of cyclophosphamide followed by azathioprine in conjunction with high-dose prednisolone that is given to patients who are at very high risk for progression (ESRD predicted in all cases within 5 yr) (60). However, these are only a small minority of patients encountered in clinical practice. Again, BP control and use of RAS blockade fell outside current recommendations (Table 3), and in our view, there is insufficient evidence to justify the use of cyclophosphamide in IgAN except in crescentic IgAN with rapidly progressive renal failure (see below).

Mycophenolate. Two published studies gave no consistent indication of the benefit of mycophenolate (61,62), and it is noteworthy that the study that showed no benefit achieved rigorous blood control with use of an ACE inhibitor (Table 3). One preliminary report suggested a transient benefit of mycophenolate on proteinuria (63), whereas another showed no benefit of mycophenolate in more advanced disease (mean serum creatinine at entry 2.6 mg/dl) (64). The relatively small size of the studies so far available justifies further evaluation, and other studies are in progress (65). At this time, we do not recommend the use of mycophenolate.

Fish Oil. Although the original study of fish oil that showed outstanding benefit remains impressive (66), there are still no further studies to support its role, and a meta-analysis that included other published studies did not suggest efficacy (60). The preliminary report of a more recent RCT showed no benefit of 2 yr of treatment with fish oil compared with corticosteroids and placebo (67). We do not recommend the use of fish oil.

BP and RAS Blockade. The achieved BP in the COOPERATE study was significantly better than is reported in most of these recent RCT (Table 3). The efficacy and low adverse reaction rate suggest that combined RAS blockade with ACE inhibitor and ARB should be the "standard regimen" against which any additional therapeutic intervention be judged. As well as achieving a BP target of 125/75 mmHg in all proteinuric patients with IgAN, we recommend dual ACE inhibitor/ARB

Table 3. Treatment of IgAN: Achieved BP and use of RAS blockade in recent randomized, controlled trials[a]

Treatment	Reference	Benefit	Mean Achieved BP	ACE Inhibitor or ARB
ACE inhibitor ± ARB	55	Reduction in proteinuria and preserved GFR; best with ACE inhibitor plus ARB	125/70	ACE inhibitor or ARB or combination
Corticosteroids	57,69	Reduction in proteinuria and reduced ESRD at 10 yr	134/84	43%; used equally in both study groups
Corticosteroids	58	Small reduction in proteinuria; no effect on GFR	125/80	8%; most used in responders
Corticosteroids and cyclophosphamide	60	Renoprotection in very-high-risk patients	145/85	Unclear
Mycophenolate	62	None	125/73	100%
Mycophenolate	61	Reduction in proteinuria; no effect on GFR	Uncertain	None

[a]Optimum BP control with RAS blockade is achieved in few trials, and in those trials, there is less benefit for the tested intervention. RAS, renin-angiotensin system; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

therapy when proteinuria reduction is insufficient with a single agent.

In our opinion, additional therapy with corticosteroids or other agents should be considered only when there is still sustained proteinuria >1 g/24 h despite achieving a target BP of 125/75 mmHg with full RAS blockade. In our experience, few patients fulfill these criteria, and it should be understood that corticosteroids, cyclophosphamide, and mycophenolate have not been evaluated adequately in the context of such a "standard regimen." Data on achieved BP or RAS blockade were not available in the published meta-analysis that suggested benefit for corticosteroids and immunosuppressive agents, so the possibility that these were confounding factors was not evaluated (56).

It unfortunately is becoming increasingly difficult to judge the efficacy of any proposed new therapeutic interventions. The renoprotective efficacy of the "standard regimen" means that evaluation of any additional intervention will require increasingly large and prolonged RCT to prove benefit unless robust surrogate measures of outcome are developed to enable studies to be scaled down without loss of power.

Crescentic IgAN

Crescentic IgAN is an uncommon clinical presentation. There are no RCT of immunosuppressive therapy in crescentic IgAN associated with rapidly progressive renal failure, although recent observational studies are increasingly optimistic about the value of treatment with corticosteroids usually in combination with cyclophosphamide (68). Nevertheless, overall renal survival in crescentic IgAN is significantly inferior to that in other forms of crescentic GN, including systemic vasculitis and Goodpasture's disease. Background chronicity in IgAN is a powerful negative influence, and immunosuppressive therapy in crescentic IgAN is recommended only when there is active crescentic injury without major background chronic damage. In such circumstances, we use corticosteroids and cyclophosphamide in a regimen similar to that applied in renal vasculitis, although in our view, there is insufficient evidence to justify the addition of plasma exchange.

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