Moving Points in Nephrology

Glomerular Diseases: Emerging Tests and Therapies for IgA Nephropathy

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Summary

The last decade has seen major progress in understanding the pathogenesis as well as the prognosis and treatment of patients with IgA nephropathy (IgAN). Although the diagnostic criterion of a kidney biopsy demonstrating dominant or codominant IgA deposition remains unchanged, much more is known about the genetic and environmental factors predisposing to disease development and progression. These advances have led to the identification of novel diagnostic and prognostic markers. Among the most promising clinically are genetic profiling, quantification of galactose-deficient IgA1 levels, and measurement of anti-IgA1 immunoglobulins. While targeted treatment for IgAN remains elusive, there is mounting evidence for therapeutic interventions that alter the disease course. The appropriate validation and integration of these discoveries into clinical care represent a major challenge, but one that holds tremendous promise for refining prognostication, guiding therapy, and improving the lives of patients with IgAN.

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Introduction

In 1968, Berger and Hinglais published the first modern report of IgA nephropathy (IgAN) (1). Using immunofluorescence microscopy, the authors identified a characteristic pattern of mesangial ("intercapillary") immune deposits that stained brightly with antisera to IgA. IgAN is now widely recognized as the most common primary GN worldwide (2–4). Overall incidence has been estimated to be 2.5 cases per 100,000 person-years, with a higher incidence in Eastern Asian populations and a very low incidence in African populations (4,5). IgAN is found in >40% of kidney biopsy specimens obtained for primary GN in China or Japan, >30% of those obtained in Europe, and >20% of those obtained in the United States (3). Although first described as "benign hematuria," IgAN was soon recognized as usually chronic and often progressive. The spectrum of pathology is broad, however, and includes a substantial proportion (4%–16%) with mesangial IgA deposits and mild or no urinary findings. Such cases may never come to clinical attention. One large Finnish series found IgA deposits with additional morphologic or clinical findings suggestive of kidney disease in 1.3% of all autopsies (6). Despite its often slow and benign-appearing course, the high prevalence of IgAN, coupled with its early age of onset, makes it a major contributor to the global burden of kidney disease. Among patients with biopsy-proven IgAN, 15%–20% reach ESRD within 10 years and 20%–40% by 20 years (7). Mortality in patients with IgAN correlates with GFR, although in contrast to other forms of CKD the risk of ESRD is substantially higher than the risk of death (8).

With its heterogeneous presentation and course, IgAN presents particular challenges to the clinician. Key among these are identifying patients at high risk of progression, accurately estimating the time course of renal decline, and selecting patients likely or unlikely to benefit from particular therapies. Recent advances in understanding the pathogenesis of IgAN have led to the development of promising new diagnostic and prognostic tests. Furthermore, mounting evidence supports specific treatments for improving the course of the disease.

Pathogenesis

The pathogenesis of IgAN has recently been reviewed in detail (9–11). The central mechanism is the generation of nephritogenic immune complexes, whose antigen is a poorly galactosylated form of IgA1. These complexes deposit in the glomerular mesangium, eliciting a subsequent inflammatory immune response that produces tissue injury and the clinical sequelae of GN (Figure 1). Whether immune complexes form primarily *in situ* or in the circulation (or both) remains an open question, although ample evidence suggests the importance of circulating factors. This includes (*a*) the isolation of circulating immune complexes with identical makeup to the glomerular immune deposits (12), (*b*) the recurrence of IgAN in many patients after kidney transplant, and (*c*) the observation that if donor kidneys containing IgA deposits are transplanted into patients with ESRD from other causes, the deposits disappear within weeks (13).

Human IgA1 normally contains 3–6 glycan chains *O*-linked to a unique proline-rich hinge region between the first and second constant heavy-chain regions (10,11). These glycan chains begin with *N*-acetylgalactosamine (GalNAc), with the subsequent addition of galactose

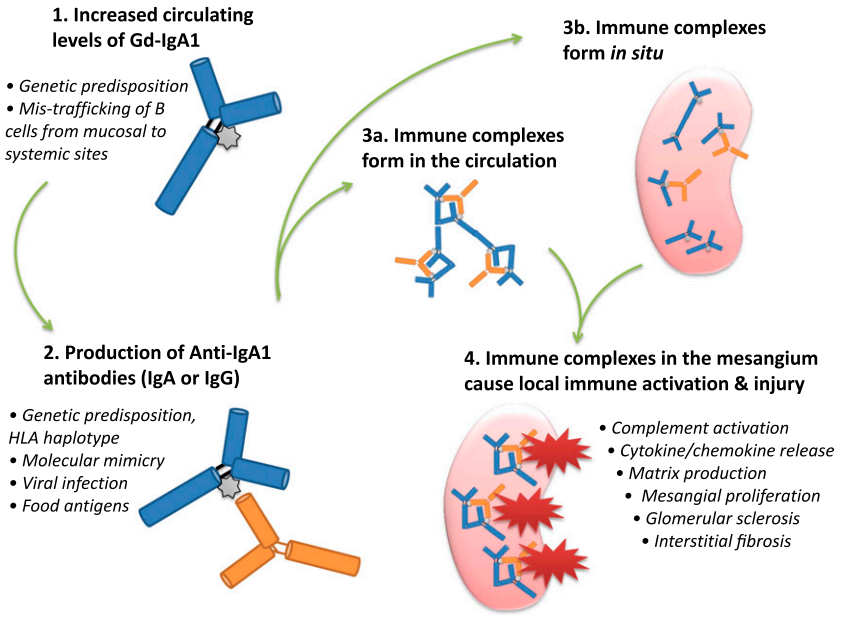

Figure 1. | **Pathogenesis of IgA nephropathy: a proposed multistep model of IgA nephropathy, demonstrating the interaction of genetics, environmental factors, and both innate and acquired immunity**. *Step 1*: Elevated circulating levels of galactose-deficient IgA1 (Gd-IgA1) are produced, probably due to genetic factors. Mis-trafficking of B cells from mucosal to systemic compartments may also be responsible, although this may also be influenced by genotype. *Step 2*: IgA or IgG antibodies directed against the underglycosylated hinge region of Gd-IgA1 (represented by the gray star) are produced, possibly driven by molecular mimicry. It is likely that these pathogenic antibodies are more likely to be produced in the setting of specific *HLA* haplotypes. *Step 3*: Immune complexes of Gd-IgA1 and antiglycan antibodies are formed. This may happen in the circulation (3a), or it may happen *in situ* against previously deposited IgA1 (3b). *Step 4*: The presence of immune complexes activates the complement cascade, induces mesangial cell proliferation and activation, and ultimately leads to the irreversible damage in the form of segmental or global glomerular sclerosis and interstitial fibrosis.

or sialic acid residues. Most patients with IgAN have elevated levels of circulating IgA1 molecules whose *O*-linked glycans are deficient in galactose, leaving a terminal or sialylated GalNAc (14). Although galactose-deficient IgA1 (Gd-IgA1) makes up only a small portion of circulating IgA1, it makes up the majority of the IgA deposited in the mesangium in IgAN (15).

Elevated levels of Gd-IgA1 alone, however, are insufficient to cause IgAN. Many healthy relatives of patients with IgAN also have high circulating Gd-IgA1 levels compared with unrelated controls. This implies both that other events are necessary to convert the presence of Gd-IgA1 into clinical nephritis and that a prominent genetic component underlies the overproduction of Gd-IgA1 (16). Gd-IgA1 levels have high heritability (ranging from 50% to 70%) and follow a segregation pattern consistent with a major dominant gene effect among relatives (16,17). This suggests that identification of specific genetic variants responsible for glycosylation defects may be feasible with use of quantitative genetic mapping approaches. Once such variants are discovered, targeted genetic tests could become useful in identifying relatives at risk of IgAN and suitable related donors for kidney transplantation.

The next step required to induce nephritis is the generation of antibodies directed against the galactose-deficient *O*-linked glycans of the Gd-IgA1 hinge region (12). Why these antiglycan autoantibodies form is a subject of ongoing investigation and debate. Molecular mimicry is one hypothesis; the evidence is circumstantial but includes the fact that certain viruses and bacteria express potentially antigenic GalNAc-containing epitopes on their surfaces and observations that exacerbations of hematuria and proteinuria often follow mucosal infections (9). Food-derived antigens have also been implicated (11). Another hypothesis follows from the observation that mesangially deposited IgA1 in IgAN shares several features with normal mucosal IgA1, including relative galactose deficiency. It has been proposed that after encountering antigens in the mucosa, IgA-expressing plasmablasts may mis-traffic to systemic sites (9). They thereby inappropriately produce Gd-IgA1 in the systemic circulation rather than the intended mucosal target, presenting an antigenic stimulus for antiglycan antibody production.

Ultimately, tissue damage results from immune activation in response to the mesangial immune complexes. The mechanisms involved are complex and involve mesangial cell activation, matrix deposition, and release of inflammatory signaling molecules. Complement activation plays an important role as evidenced by genetic, histopathologic, and functional studies (18).

Diagnostic and Prognostic Testing

IgAN is defined by mesangial deposits of IgA, which are dominant or codominant with IgG or IgM and variably accompanied by C3 (19). Lupus nephritis and other forms of immune-complex GN may present similarly and must be excluded. Secondary causes of glomerular IgA deposition should be considered, especially hepatic disease (where impaired hepatic clearance of IgA is probably the

cause). Many other conditions have been variably associated with IgA deposition, especially autoimmune diseases, diseases affecting the intestinal mucosa (such as celiac disease and inflammatory bowel disease), malignancies, and chronic infections (20). In most of these conditions it is unclear whether the associations are spurious or due to a true shared or overlapping pathogenesis with IgAN (21). One important exception is Henoch-Schönlein purpura, in which circulating IgA immune complexes cause small vessel vasculitis in many organ systems and a renal pathology indistinguishable from IgAN.

Because kidney biopsy remains the only definitive method of diagnosing IgAN, many cases may never be confirmed in routine practice (6). Differences in local kidney biopsy practices may also explain some of the geographic differences in prevalence (4).

A noninvasive diagnostic test for IgAN would provide many benefits. In the proper clinical setting, a specific test could preclude the need for an exhaustive diagnostic workup to rule out other causes of nephritis. A noninvasive test would also help to evaluate potential living-related kidney donors with mild urinary abnormalities who might share genetic risk. Additionally, a test related to pathogenic mechanism might prove useful as a guide to selecting therapy. Finally, the research value of a noninvasive test would be substantial, especially for clarifying disease epidemiology and exploring the causes behind phenotypic heterogeneity.

A separate issue, but one related to diagnosis, is that of establishing prognosis. An ideal prognostic marker would (*1*) quantify the risk and rate of progression accurately and early in the disease; (*2*) guide treatment decisions by differentiating immunologically "active" disease from hemodynamic damage due to hypertension, hyperfiltration, and other factors; and (*3*) provide a longitudinal marker of disease activity and response to therapy.

Considerable effort has been spent in developing and evaluating diagnostic and prognostic assessments of IgAN. Current and emerging tests are summarized in Table 1.

Histopathology

Although kidney biopsy remains the definitive way to establish the diagnosis of IgAN, its ability to independently predict prognosis is less certain. Major progress was made in 2009 with the publication of the Oxford classification, which includes four pathologic variables: mesangial cellularity, endocapillary hypercellularity, segmental sclerosis, and tubular atrophy/interstitial fibrosis (19). These variables were shown to predict outcomes independently of clinical features at presentation or during follow-up. Since publication of the classification, several studies have attempted to validate it. Each of the four variables was predictive in some, but not all, of these studies (22,23). The tubular atrophy/interstitial fibrosis score has been the most consistently validated across different cohorts and ethnicities, and represents a reliable histologic predictor of poor renal outcome.

Although the Oxford classification represents a significant advance for standardizing kidney biopsy reports and suggesting prognosis, nontraditional histologic features may prove to be additionally informative. For example, the number of fibroblasts in IgAN biopsy specimens (identified by immunohistochemistry for the marker FSP1) was a more powerful predictor of GFR loss than was either baseline proteinuria or hypertension (24). This fibroblast marker also accurately discriminated which patients with IgAN would respond to corticosteroids (25). A recently published paper showed that immunostaining for URG11, a protein involved in hypoxia-induced renal tubular epithelial-mesenchymal transition and fibrosis, was inversely correlated with GFR and independently predicted prognosis in IgAN (26). In another study, the measurement of glomerular density (the number of nonsclerotic glomeruli per cortical area) in biopsy specimens from Japanese patients with IgAN and normal kidney function robustly predicted halving of GFR or ESRD at 10 years (27). Similarly, inclusion of a "C" component (for crescentic disease) into a classification scheme has been advocated (26), although

Table 1. Traditional and emerging prognostic tests for IgA nephropathy

Traditional Markers	Novel Tests That Use Commonly Available Samples or Techniques	Emerging Tests, Requiring Specialized Laboratory Expertise
Robust prognostic value Proteinuria Hypertension GFR on presentation Atrophy/fibrosis on biopsy Inconsistent prognostic value Age at diagnosis Male/female sex Race Persistent microhematuria Isolated macroscopic hematuria Biopsy features besides atrophy/fibrosis	Clinical risk score of Xie *et al.* (incorporating GFR, hemoglobin, albumin, and systolic BP at presentation) (30) Genetic risk score (requires genotyping of 7 GWAS SNPs) Glomerular density measurement on biopsy	Galactose-deficient IgA1 levels Antiglycan autoantibodies Markers of oxidative stress (*e.g.*, AOPPs) Immunohistochemistry for FSP1 or other fibroblast markers Urine and serum proteomics MicroRNA profiling and other analyses of gene expression

GWAS, genome-wide association studies; SNP, single-nucleotide polymorphism; AOPP, advanced oxidation protein product.

the cases used to establish the Oxford classification did not contain sufficient cases with crescents to demonstrate its predictive value.

Traditional Risk Factors

A variety of clinical and demographic risk factors predict renal outcomes, either independently or in multivariable analyses. The most robust are hypertension, proteinuria, and GFR at diagnosis (7). Less consistent associations have been found with sex and persistent microscopic hematuria, whereas gross hematuria may be associated with lower risk (perhaps because of lead-time bias) (7). Longitudinal trends of BP and proteinuria are both associated with disease progression (28,29). In particular, a decrease in proteinuria to <1 g/d has been associated with improved prognosis regardless of peak proteinuria (28,29).

Clinical Risk Scores

Several different risk scores quantify the risk of progression in IgAN (29,30). One recent score used retrospective data from 619 Chinese patients with IgAN followed over 41 months and identified four baseline variables with significant independent effects on the risk of ESRD: GFR, serum albumin, hemoglobin, and systolic BP (30). It can be used to predict a patient's risk of ESRD at 5 and 10 years with a convenient online calculator (http://www.columbiamedicine.org/divisions/gharavi/calc_progression.php) (31), although it is critical to note that this risk score has not yet been validated across diverse populations.

Genetic Risk

Much evidence supports a significant genetic contribution to the risk of IgAN. Recently completed genome-wide association studies (GWAS) have identified at least seven susceptibility loci for IgAN, with the strongest signal seen in the MHC coding region of chromosome 6 (32,33). Among the non-MHC loci are genes related to the regulation of mucosal immunity (*HORMAD2*, *DEFA*, and *TNFSF13* loci) and complement system (*CFHR1* and *CFHR3* genes). Loci discovered in the first GWAS were subsequently confirmed in eight independent cohorts of varied ancestry (5). Geospatial analysis of IgAN genetic risk was performed across 85 populations worldwide. The very low genetic risk for IgAN in Africans rises steadily with increasing eastward longitude, with the highest risk among East Asian populations (those from Japan, China, Cambodia, and Siberia). Inhabitants of Nordic countries carry a greater burden of risk alleles compared with southern Europeans. Analyses of epidemiologic data across European populations reveal a corresponding South to North increase in the incidence and prevalence of ESRD from IgAN. These results demonstrate how genetic analyses may provide new insights into disease epidemiology and pathogenesis. However, the clinical utility of genotyping individual patients with IgAN remains to be determined.

Studies of gene expression and post-transcriptional regulation may provide fertile ground both for deepening the understanding of disease pathogenesis and identifying novel disease biomarkers. One example is the profiling of microRNAs, small RNA molecules involved in post-transcriptional gene regulation. One genome-wide microRNA analysis identified 85 microRNAs differentially expressed in the tissue of patients with IgAN compared with controls, although much additional work is needed to validate such findings and demonstrate clinical or pathophysiologic importance (34).

Serum Gd-IgA1 Levels

Although patients with IgAN have on average higher circulating levels of total IgA, this is neither sensitive nor specific for the disease. The subsequent identification of specifically elevated serum levels of Gd-IgA1 in patients with IgAN made it a logical candidate for noninvasive diagnosis. Moldoveanu *et al.* assayed Gd-IgA1 in adult patients with IgAN and controls and found that using the 90th percentile among controls as a cutoff, the test identified IgAN with sensitivity of 77% and specificity of 94% (14). Test performance was almost identical in children with IgAN but was less sensitive for Henoch-Schönlein purpura nephritis (17,35). However, many nondiseased relatives of patients with IgAN also have elevated levels of Gd-IgA1 compared with healthy and unrelated controls, limiting its usefulness as a purely diagnostic test (16).

Gd-IgA1 levels hold greater promise for disease prognosis. Zhao *et al.* prospectively measured Gd-IgA1 levels in 275 Chinese patients with IgAN followed for a median of 4 years (36). Higher levels of Gd-IgA1 at diagnosis were independently associated with greater risk of renal deterioration, even after adjustment for proteinuria, hypertension, estimated GFR, steroid therapy, and histologic classification. Compared with patients in the first quartile of Gd-IgA1 level, those in the fourth quartile had a hazard ratio for kidney failure of 4.76 (95% confidence interval, 1.61 to 14.09). These findings will require prospective validation in additional cohorts of different ethnicities.

Circulating Antiglycan Antibodies

Autoantibodies formed against Gd-IgA1 are another logical target for measurement. Berthoux *et al.* examined serum levels of IgG and IgA antiglycan autoantibodies as predictors of disease progression in 97 patients with IgAN (37). Normalized IgG autoantibody serum levels and total IgA autoantibody serum levels at diagnosis were associated with higher estimated risk of death or dialysis. Kaplan-Meier survival analysis confirmed a significant difference in survival from death or dialysis between patients with IgAN who have high versus low levels of normalized IgG autoantibody. In the high antibody group, 5- and 10-year survival rates were 76% and 56%, respectively, compared with 94% and 80% in the low antibody group.

Oxidative Stress

Systemic oxidative stress is an important mediator of the inflammatory damage triggered by nephritogenic immune complexes in IgAN (38). Camilla *et al.* found elevated levels of advanced oxidation protein products in the sera of patients with IgAN, which correlated both with time-averaged proteinuria and with the rate of

decline in eGFR (38). The association was strengthened by combining measurement of advanced oxidation protein products (AOPPs) with Gd-IgA1. This study highlights the potential prognostic value of measuring the activity of pathogenic mediators, as well as the value of combining markers from different steps along the disease pathway.

Proteomics

The characterization of proteins present in urine or serum holds promise for many kidney diseases. Significant progress has been made in identifying individual polypeptides associated with IgAN (39). Wu *et al.*, using a form of mass spectrometry, identified a uromodulin fragment that in receiver-operating characteristic analysis showed areas under the curve of 0.998 for distinguishing patients with IgAN from healthy controls and 0.815 for distinguishing patients with IgAN from those with other glomerular diseases (40). Obara *et al.* developed an ELISA for a urinary complex of IgA with uromodulin and found a sensitivity of 82% and specificity of 73% in differentiating IgAN from other kidney diseases (41).

Before such tests can achieve routine clinical use, affordable assays not requiring specialized laboratories or techniques must be developed, standardized, and validated in diverse racial and geographic populations against both healthy controls and glomerular disease controls.

Treatment

General Recommendations

Some therapeutic interventions appear beneficial in all patients with IgAN. Hypertension, a consistent risk factor for progression, should be controlled. Recent recommendations from Kidney Disease Improving Global Outcomes (KDIGO) suggest targeting <130/80 mmHg in most patients and perhaps <125/75 for proteinuric (>1 g/d) patients (42). Additionally, KDIGO guidelines recommend renin-angiotensin system (RAS) blockade when proteinuria is >1 g/d titrated to achieve maximal reduction in proteinuria as tolerated. Blockade of the RAS with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers reduces proteinuria in IgAN. Randomized trials also support the treatment of hypertension with RAS blockade to slow disease progression. For example, one randomized trial studied patients with IgAN with >500 mg/d proteinuria and serum creatinine <1.5 mg/dl. Despite equivalent BP control over 75 months, serum creatinine increased 50% in 13% of ACEI-treated patients versus 57% of those treated with other antihypertensive agents (43). This trial highlights the fact

Table 2. Approach to the treatment of IgA nephropathy

Patient	Clinical Features	Interventions
All patients		BP control <130/80 mmHg Strongly consider ACEI or ARB Consider statin Consider tonsillectomy if recurrent tonsillitis +/− Fish oils, per patient preference
Mild disease	Normal GFR Proteinuria <500 mg/d Benign histology Normal BP	Watchful waiting Enrollment into prospective observational studies
Moderate or severe disease	Proteinuria >1 g/d or proteinuria 0.5–1 g/d with other features suggesting risk of progression Histologic signs suggesting risk of progression (mesangial hypercellularity, endocapillary proliferation, segmental sclerosis)	Glucocorticoids × 6 months (note: trials showing benefits from steroids treated patients with relatively preserved GFR and proteinuria >1 g/d) Consider cytotoxics (*i.e.*, cyclophosphamide) Enrollment into clinical trials
"Point of no return"	Low GFR, typically <30 ml/min per 1.73 m^2 Biopsy with severe global glomerulosclerosis and tubular atrophy/interstitial fibrosis	No immunosuppression Prepare for transplant or renal replacement therapy
Crescentic IgAN	Rapidly progressive GN >30%–50% cellular or fibrocellular crescents on biopsy	Pulse + high-dose oral glucocorticoids Consider cyclophosphamide
IgAN with minimal-change disease	Sudden-onset nephrotic syndrome Mesangial IgA deposits on biopsy without sufficient sclerosis to explain proteinuria	Glucocorticoids, akin to treatment of minimal-change disease

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; IgAN, IgA nephropathy.

that the exact proteinuria cutoff below which RAS blockade is no longer beneficial has not been determined (if one even exists). Our own practice is to use an RAS blocker as first-line therapy for hypertensive patients with IgAN and to generally consider it whenever macroalbuminuria is present. In addition, optimal lipid control and a low-salt diet may be beneficial (44,45).

Before going beyond these measures, it is important to recognize that some patients with IgAN present with advanced, sclerotic disease not amenable to aggressive intervention (the so-called "point of no return") (7). These patients are best served with conservative management and preparation for renal transplant whenever possible. Table 2 summarizes our clinical approach to the treatment of IgAN.

Tonsillectomy

The tonsils may be a source of antigenic stimulus in driving IgAN, and episodes of tonsillitis often lead to flares of hematuria. This has served as the justification for some practitioners to recommend tonsillectomy to reduce the mucosal immune activation that produces IgAN. Small or nonrandomized retrospective studies of tonsillectomy in IgAN have given conflicting results. One study of 55 patients with IgAN, of whom 16 had tonsillectomy, could find no independent benefit of the procedure >10 years after tonsillectomy (46). Another evaluated 118 patients with IgAN: 48 with prior tonsillectomy and 70 without (47). Renal survival at 240 months was 90% for the tonsillectomy group and 64% for the group without tonsillectomy, but no difference in renal survival was noted between the groups until 10 years from biopsy. A more recent retrospective review of 200 Japanese patients with IgAN, including 70 with tonsillectomy, found greater remissions in proteinuria and hematuria and improved renal survival in the tonsillectomized group (48). However, this group received more treatment with steroids and RAS inhibitors. Given the lack of prospective controlled studies, there are insufficient data to recommend tonsillectomy for most patients with IgAN, although we agree with the KDIGO guidelines that some patients with severe recurrent bouts of tonsillitis may benefit (42).

Fish Oils

The role of fish oils in IgAN is also controversial. Fish oils have cardiovascular benefits, inhibit cell proliferation and renal inflammation, reduce serum lipids, lower BP, and in several animal models of glomerular disease reduce proteinuria and glomerular histologic injury (49). Several small well designed randomized studies found no benefit on renal outcomes, but one large randomized, placebo-controlled study of 106 patients with IgAN did show benefit. These patients, all with >1 g/d proteinuria and 60% with hypertension, received 12 g of fish oil or olive oil per day for 2 years, followed by a 5-year follow-up. The fish oil group had fewer patients with a 50% increase in plasma creatinine (6% versus 33%); a slower decline in GFR; and less death, dialysis, or transplantation (50).

At present, KDIGO guidelines recommend fish oils for persistent proteinuria >1 g/d despite 3–6 months of optimized RAS blockade. Although these supplements are objectively fairly safe, a common complaint limiting adherence is the "fishy" taste that they produce. We feel it is most reasonable to let patients decide for themselves whether the side effects and cost of fish oil therapy outweigh uncertain renal benefits.

Corticosteroid Therapy

Corticosteroids clearly produce remissions of proteinuria in patients with so-called IgA minimal-change disease (*i.e.*, nephrotic patients with normal-appearing glomeruli by light microscopy, diffuse foot process effacement on electron microscopy, and mesangial IgA deposits by immunofluorescence). Until recently the benefit of corticosteroids in more typical IgAN had been uncertain, but recent trials suggest clear benefit in selected patients.

A well designed trial of corticosteroids in IgAN randomly assigned 86 patients with 1–3.5 g/d proteinuria and a plasma creatinine of <1.5 mg/dl to receive six monthly cycles of pulse methylprednisolone followed by every-other-day corticosteroids versus supportive care. At 10 years, renal survival was 97% in the steroid group versus 53% in the placebo group, with improvement favoring steroids regardless of histologic class (51). Few adverse effects from this short course of treatment occurred. One criticism of this trial was that only a minority of patients received RAS blockade. Two subsequent controlled trials of corticosteroids addressed this (52,53). One Chinese trial of 63 patients with biopsy-proven IgAN included patients aged 18–65 years with 1–5 g/d proteinuria (52). They were treated with the ACEI cilazapril alone or cilazapril plus prednisone, 0.8–1 mg/kg per day, for 8 weeks, followed by taper. Kidney survival based on 50% increase in serum creatinine was superior in the combined ACEI-corticosteroid group. A second randomized controlled trial from Italy used the ACEI ramipril in 97 patients with IgAN with >1 g/d proteinuria and GFR >50 ml/min (53). Half also received prednisone, 1 mg/kg per day for 2 months with taper. At 8 years, renal survival was 70% in the ACEI group versus 98% in the combined ACEI-corticosteroid group ($P=0.006$). Thus, corticosteroids appear to preserve renal function over the long term in at least three randomized prospective trials of proteinuric IgAN.

Other Immunosuppressive Regimens

Most studies of other immunosuppressives in patients with IgAN have been small or uncontrolled or had negative results. A recent randomized trial of azathioprine for 6 months plus corticosteroids versus corticosteroids alone in >200 patients with IgAN who had proteinuria >1 g/d and plasma creatinine <2 mg/dl showed no difference in preservation of renal function over 5 years (88% versus 89%) (54). One small randomized trial of 38 patients with progressive IgAN did show a benefit for oral cyclophosphamide plus steroids for 2 months followed by azathioprine for ≥2 years compared with no immunosuppression (55). The treated group experienced a 5-year renal survival rate of 72% versus 5% in the control group. Limitations of the study include inadequate BP control, insufficient use of RAS blockade, and an unusually poor survival rate among controls. Although cyclophosphamide may have a benefit for the rare patient with crescentic IgAN (56), at present it is reasonable to otherwise reserve cytotoxics for patients in whom

standard therapy fails and who have significant proteinuria and deteriorating GFR, being fully aware that the evidence supporting this treatment is weak.

Mycophenolate mofetil (MMF) has been studied in several randomized trials in IgAN, but all studies have been underpowered and the results mixed. For example, one blinded trial randomly assigned patients with progressive IgAN (mean creatinine, 2.4 mg/dl; proteinuria >2.5 g/d) to MMF or placebo (57). All patients had optimal BP control with RAS inhibition. This trial was terminated after 40 patients were enrolled because of the high rate of progression in both study groups. Clearly, MMF does not work in all patients and has no value for patients with severely reduced GFR. Use of MMF in IgAN should currently still be considered investigational. Likewise, immunosuppressives such as rituximab, leflunomide, adrenocorticotropic hormone, and sirolimus should also be considered experimental therapies at present.

Ongoing Clinical Trials

Several important ongoing studies involve patients with IgAN. The STOP-IgAN (Supportive Versus Immunosuppressive Therapy of Progressive IgA Nephropathy) trial is a German multicenter, randomized, open-label study of patients with IgAN. All receive RAS blockade and statins for 6 months. If proteinuria still exceeds 0.75 g/d, patients are randomly assigned to immunosuppression versus supportive care, stratified by GFR. This study is fully recruited, with an estimated completion date of December 2013. The TESTING (Therapeutic Evaluation of Steroids in *IgA Nephropathy* Global) Study in China is a randomized controlled trial of corticosteroids versus placebo with a recruitment goal of 1300 patients. Another Chinese study is comparing MMF with glucocorticoids, and another study is comparing prednisone and cyclophosphamide with prednisone alone. An ongoing trial in the United States is comparing rituximab with standard care for progressive disease. It is hoped that these more robust prospective controlled trials will clarify many key questions about the treatment of IgAN.

Conclusion

Our understanding of the pathogenesis of IgAN has markedly improved in recent years. Advances in immunology and increasingly sophisticated genetic analyses have suggested specific and noninvasive tests for use in diagnosis, prognosis, and monitoring of disease activity. The role of immunosuppression in treatment is increasingly being defined. However, there remains a considerable need to identify safe, effective, and specific therapies that can halt or slow the progression of IgAN early in its course.

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Disclosures

None.

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