REVIEW

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IgA nephropathy: Challenges and opportunities

ABSTRACT

Immunoglobulin A (IgA) nephropathy poses many challenges to investigators and physicians in its etiology, pathogenesis, prevention, and treatment. But at the same time, opportunities abound for new tests and treatments that may eventually lead to control of this common form of chronic kidney disease.

KEY POINTS

IgA nephropathy tends to progress slowly, and in only about half of patients does it progress to end-stage renal disease within 25 years.

At present, the factors that predict an accelerated course and progression to end-stage renal disease are persistent proteinuria, elevated serum creatinine at diagnosis, persistent microscopic hematuria, poorly controlled hypertension, and extensive glomerulosclerosis or interstitial fibrosis, or both, on renal biopsy.

Needed are better diagnostic and prognostic tests and therapies that address the mechanism of the disease.

The value of treatment with an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, or both is well established. If protein excretion does not decrease with this therapy, one can consider adding immunosuppressive therapy in selected patients, but this strategy is still empiric and unproven.

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Much progress has been made in the 40 years since immunoglobulin A (IgA) nephropathy was first described. We now have a reasonably complete understanding of the pathogenesis and mediation of this disease, but its etiology remains obscure and mysterious. New data on its epidemiology continue to emerge that will undoubtedly have clinical significance. We are beginning to perceive—but only dimly—the genetic predisposition to the disease.

Prognostication remains an imperfect science, but we are clearly making progress. The role of pathology in estimating prognosis in individual patients needs to be thoroughly reexamined, based on a uniformly agreed-upon classification scheme. Such work is currently in progress.

Therapy has certainly advanced, and we now have the rudiments of an evidence-based approach to management. However, much more needs to be done to refine these strategies so that they can be better matched to the characteristics of the patients, and there is a great need for novel therapeutic approaches and more information on multidrug regimens in selected patients. Many opportunities exist for improvement in the control of this common cause of chronic kidney disease, but we should not underestimate the challenges that present themselves in the field of IgA nephropathy in 2008 and beyond.

THE SCOPE OF THE PROBLEM

IgA nephropathy, also called Berger disease, is the most common form of primary glomerular disease in the developed world.[1,2]

Morphologically, it is characterized by diffuse deposition of IgA in the glomerular mesangium and by various degrees of damage of the glomerular capillary network seen on light microscopy[3,4] By some estimates, as many as 5% to 15% (averaging about 10%) of the general population may have IgA deposits in the glomerular mesangium, but only about 1 in 50 people with IgA deposits will actually have some abnormal clinical manifestation (principally recurring bouts of hematuria, with or without accompanying proteinuria) that brings them to the attention of a physician.[5]

Although not all patients with IgA nephropathy have progressive renal disease, IgA nephropathy is a significant contributor to the incidence of end-stage renal disease (ESRD) in many countries.[1–4]

DIAGNOSTIC AND PROGNOSTIC CHALLENGES

Since 1968, when IgA nephropathy was first described,[6] great strides have been made in clarifying its epidemiology, its pathogenesis, the prognostic factors involved in its progression to ESRD, and its treatment. However, many gaps in our knowledge remain, particularly regarding its etiology, the genetic factors predisposing to it, its therapy, and the problem of recurrent disease in renal transplant recipients.

IgA nephropathy is often initially mistaken for urinary tract infection or urolithiasis

Can IgA nephropathy be diagnosed without a renal biopsy?

While renal biopsy and immunochemical analysis of renal tissue remain the gold standard for diagnosing IgA nephropathy, new sensitive and reasonably specific noninvasive tests are emerging and may provide another diagnostic approach. One of the most promising new tests is for abnormal circulating levels of abnormally glycosylated IgA subclass 1 (IgA_1), which appears to be involved in the pathogenesis of the disease (see below).[7] If noninvasive diagnostic techniques can be simplified and their accuracy validated across diverse populations, they offer great promise for use in epidemiologic and genetic studies, in which routine renal biopsy for diagnosis is impractical.

Signs and symptoms of IgA nephropathy are nonspecific

The most common clinical presentation of IgA nephropathy is recurring bouts of macroscopic hematuria, often but not invariably accompanied by proteinuria.[2] Persistent asymptomatic hematuria without any detectable proteinuria (so-called isolated hematuria) affects a minority of patients. The red cells in the urine are typically dysmorphic (altered in size and shape compared with normal red cells), as they are in many other glomerulonephritic diseases.

Because low-grade fever and pain in the loins may accompany these bouts of hematuria, the disorder is often initially mistaken for urinary tract infection or urolithiasis. Careful microscopic examination of the urinary sediment for the characteristic dysmorphic erythrocytes that indicate a glomerular disease often provides the crucial clue that a glomerular disorder is the cause of the hematuria.[8]

However, a somewhat similar presentation may also be seen in thin basement membrane nephropathy, Alport syndrome (hereditary nephritis), and membranoproliferative glomerulonephritis,[2] although these disorders can be readily distinguished from IgA nephropathy on examination of renal biopsy material under light, immunofluorescence, and electron microscopy. In addition, serum complement levels are typically reduced in membranoproliferative glomerulonephritis, and a family history of nephritis (without father-to-son transmission), often with deafness, can be obtained in the X-linked form of Alport syndrome. IgA nephropathy can be reliably distinguished from thin basement membrane nephropathy only by renal biopsy and electron microscopy.

Can we better predict which patients with IgA nephropathy will develop renal failure?

Although the rate of progression is very slow, and in only about 50% (or less) of patients does IgA nephropathy progress to ESRD within 25 years of diagnosis, the risk varies considerably among populations.[9] Spontaneous clinical remissions are relatively uncommon in adults but much more common among children.

Several factors, if present at the time of discovery or developing within a relatively short time thereafter (usually within 6 months to 1

year), appear to predict a progressive course and, eventually, ESRD.[9,10] We need to characterize and validate these risk factors in detail to be able to design and carry out appropriately powered, randomized, controlled clinical trials of treatment.

Unfortunately, cumulatively, the risk factors identified so far explain less than 50% of the variation in observed outcome of IgA nephropathy. Many of the risk factors identified so far are primarily indicators of the extent of disease at a particular time, and it is therefore not surprising that they would have some ability to predict the later behavior of the disease.

Clinical and pathologic risk factors in IgA nephropathy

Although imperfect, the major risk factors auguring a poor prognosis are:

- Proteinuria (> 500 mg/day) that persists for more than 6 months
- Elevated serum creatinine at diagnosis
- Microscopic hematuria that persists for more than 6 months
- Poorly controlled hypertension
- Extensive glomerulosclerosis or interstitial fibrosis or both on renal biopsy.[7,10]

Extensive crescentic disease also confers a worse short-term prognosis, often accompanied by a rapidly progressive loss of renal function.

Are clinical risk factors more useful than pathologic risk factors in IgA nephropathy?

Of importance, clinical factors, such as persistent proteinuria or declining renal function on follow-up appear to have greater predictive power than pathologic factors for long-term outcome.[9–12] Clinical factors, such as decreasing estimated glomerular filtration rate (GFR) after short-term follow-up, persistent moderate to marked proteinuria (500–1,000 mg/day, or more), hyperuricemia, hyperlipidemia, concomitant obesity, poorly controlled hypertension, absence of treatment with angiotensin II inhibitors, and, possibly, persistent microhematuria are the most consistent factors independently associated with a poor prognosis in multivariate analysis. Pathologic changes noted in the original diagnostic renal biopsy do not consistently add greatly to the precision of prognosis beyond the analysis of these clinical and laboratory factors.[11]

A detailed and uniform immunologic and morphologic approach to classifying the pathology of IgA nephropathy may yet uncover some new and very useful prognostic factors, independent of those generated by simple clinical assessment. Efforts are under way, and such a development would greatly improve the accuracy and precision of outcome prediction and reduce the amount of unexplained variation in prognosis observed in groups of patients with IgA nephropathy.

At present, the heterogeneity of participants in clinical trials of therapy, the tendency for the disease to progress slowly, and the variation in prognosis due to unexplained factors pose major challenges in designing and carrying out randomized controlled trials of therapy in IgA nephropathy. If we can find new risk factors that can predict progressive disease earlier, the knowledge will help us in designing future clinical trials, which will be vital if progress is to be made towards controlling IgA nephropathy.

Prognosis in individual patients vs populations with IgA nephropathy

Current risk factors explain < 50% of the variation in outcome of IgA nephropathy

At present, we need a way to determine the prognosis more precisely in individual patients rather than in groups of patients. After all, physicians are called upon to determine the likely outcome in single patients, not in a population. Several prediction formulas have been devised, most of them based on relatively simple clinical factors present at discovery or short-term follow-up.[12,13]

Conventional pathologic observations have limited utility in such individualized prognostic formulations.[12] This is not to say that renal biopsy only offers diagnostic utility and has little if any value as a prognostic tool. However, the challenge is to enhance the prognostic usefulness of renal biopsy by refining the examination of the tissue specimens using modern approaches and to conduct the appropriate correlative studies to confirm the value of new pathologic criteria in prognostication, independent of clinical features alone.

For example, the risk of ESRD is greater if the patient has very extensive (> 50%) crescentic glomerular involvement with a rapidly

progressive glomerulonephritic evolution. The risk is less if there are minimal glomerular changes with nephrotic-range proteinuria. Extensive interstitial fibrosis and glomerulosclerosis in the original "diagnostic" renal biopsy merely highlight the existence of prior progressive disease that is likely to continue. The significance of persistent focal necrotizing glomerular lesions (capillaritis) in IgA nephropathy, often associated with persistent microhematuria, is not entirely clear and needs to be specifically explored, especially as it pertains to the need for immunosuppressive therapy added to treatment for hypertension, proteinuria, or both with inhibitors of the renin-angiotensin system (see below).

At present, the most powerful prognostic factor in IgA nephropathy is moderate to severe proteinuria that persists for 6 months or longer.[9,10,12] The relationship between the level of proteinuria and the outcome is continuous, ie, the greater the proteinuria, the worse the prognosis. Compared with some other primary glomerular diseases (such as membranous nephropathy or focal and segmental glomerulosclerosis), progressive disease in IgA nephropathy is associated with lower levels of persistent proteinuria (usually 500 mg to 3 g/day).

The most powerful risk factor in IgA nephropathy is moderate to severe proteinuria for ≥ 6 months

The estimated GFR at the time IgA nephropathy is discovered is a rather weak independent predictor of outcome (up to a point; see below). Many patients have stable (but reduced) renal function in the long term, especially if they receive angiotensin II inhibitor therapy and can keep their systolic blood pressure between 110 and 120 mm Hg.

How can IgA nephropathy be diagnosed and treated before the 'point of no return'?

For patients at risk of developing ESRD, the two most critical goals of treatment are to:

- Control blood pressure rigorously, preferably with an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist (ARB), or both, and
- Reduce proteinuria to less than 500 mg/day.

If these two goals can be met without undue side effects and if the patient remains compliant in the long term, many patients can avoid ESRD. Patients who cannot achieve these goals despite vigorous attempts become candidates for adjunctive therapy, such as pulse intravenous methylprednisolone (Solu-Medrol) combined with oral prednisone, or in some cases a cytotoxic drug combined with prednisone. Small randomized controlled trials suggest these adjunctive treatments are effective and safe.

Unfortunately, IgA nephropathy can progress silently, and many patients do not receive the diagnosis until late in its course. In such patients, the disease may relentlessly progress even with optimal therapy. The "point of no return" appears to be an estimated GFR of about 30 mL/min/1.73 m^2 (stage 4 chronic kidney disease).[14]

These observations underscore the need for early diagnosis and treatment based on factors that accurately predict an unfavorable outcome. Finding these factors will not be easy, because it will require detailed observation of homogeneous groups of patients over prolonged periods of time. New findings show great promise for identifying patients earlier in the course of disease who are more or less likely to progress to ESRD. The challenge is to translate these findings into rational, safe, and effective therapies applicable across a broad spectrum of disease.

OPPORTUNITIES: GENETICS, PROTEOMICS, NEW TESTS AND TREATMENTS

Genetic studies may lead to novel treatments for IgA nephropathy

Susceptibility to IgA nephropathy has a genetic component to varying degrees, depending on geography and the existence of "founder effects." Familial forms of IgA nephropathy are more common in northern Italy and in eastern Kentucky. The familial cases may derive from a mutation of a specific gene occurring in a founder many hundreds of years ago. Several genetic loci are strongly associated with IgA nephropathy (usually as an autosomal-dominant trait with highly variable penetrance).[15] Familial IgA nephropathy is most likely genetically heterogeneous, and many cases of IgA nephropathy that are believed to be sporadic may actually have a less apparent genetic basis, with skipped generations, lanthanic (covert) disease, and incomplete penetrance.

At present, genetic testing based on genomic or transcriptosomic analysis does not appear to have much diagnostic value except in clearly familial cases, because many loci are involved. Many asymptomatic people have mesangial IgA deposits that could be detected by renal biopsy but not by genetic analysis, and this inability is a major obstacle for genetic susceptibility studies. Indeed, most current genetic studies actually examine susceptibility to the clinical expression of disease rather than susceptibility to the mesangial IgA deposition that underlies the disease.[5]

The opportunity that lies ahead in genetic testing of IgA nephropathy (including haplotype analysis) appears to be primarily in the elucidation of potential pathogenetic pathways and in the refinement of prognosis and the definition of treatment responsiveness (pharmacogenomics).

If a gene (or group of genes) can be identified that is strongly and consistently associated with IgA nephropathy across diverse populations, its protein product isolated and characterized, and its role in pathogenesis elucidated, then a new era in targeted therapy of IgA nephropathy will be unleashed, much in the same way as the identification of tyrosine phosphatases played a role in the design of targeted therapy in chronic myelogenous leukemia. Early progress is being made in this area, but many obstacles lie in the way.

Proteomics may prove useful in diagnosis and prognosis of IgA nephropathy

Proteomics—the characterization and analysis of the patient's entire complement of serum and urinary proteins—is a new, exciting, and largely unexplored area in IgA nephropathy. Preliminary studies have shown that this technique may provide a novel noninvasive means of diagnosing IgA nephropathy, and it may have additional value as a prognostic tool.[16]

Much work needs to be done to standardize how specimens are collected, stored, and shipped and to verify the precision and accuracy of proteomics in diverse populations of patients with IgA nephropathy, patients with other glomerular diseases, and normal subjects to ascertain this technique's false-negative and false-positive rates.

IgA_1 testing may help detect IgA nephropathy early in its course

Abnormally undergalactosylated and oversialyted epitopes at the hinge region of the IgA_1 molecule play a critical role in the pathogenesis of sporadic IgA nephropathy.[17] This discovery provides a great opportunity for profiling patients suspected of having IgA nephropathy on the basis of sensitive determination of the serum level of these abnormal IgA_1 molecules.[7]

It may be that pathogenic IgA_1 molecules (and autoantibodies to them) arise many months or even years before the onset of clinical manifestations of overt IgA nephropathy, similar to the situation known to occur in systemic lupus erythematosus. It is also possible that an abnormality of the disposal of immune complexes created by the interaction of autoantibodies with the abnormally glycosylated IgA_1 creates the opportunity for preferential glomerular mesangial deposition of polymeric IgA.

Clearly, the greatest opportunity lies with understanding the fundamental abnormality leading to defective O-linked galactosylation of the serine/threonine residues at the hinge region of IgA_1 in IgA nephropathy. In addition, it would be very useful to know if this is a generalized and acquired abnormality or whether it is focal in distribution (eg, in the tonsils, bone marrow, or lymphoid tissue in the gut).

If blood pressure and proteinuria can be controlled, many patients can avoid ESRD

Knowledge of secondary mediators may also lead to new treatments for IgA nephropathy

Detailed knowledge of the participation of specific cell types and the "cytokine milieu" (eg, interleukin 4, interferon) in directing the abnormality toward defective glycosylation would also be very important in designing new approaches to diagnosis and therapy.

A better understanding is slowly emerging of the pathways by which pathogenic immune complexes containing IgA are deposited and cleared, and of the secondary mediator systems evoked by their formation and tissue localization. Interference with these secondary mediator processes, such as alternative or mannose-dependent complement activation, platelet-derived growth factor or transforming

growth factor stimulation, also offers a new approach to therapy.

We lack a suitable animal model of IgA nephropathy that mimics all aspects of the human condition, which has impeded progress in this area. A fully humanized mouse model of disease would be a welcome addition to the investigative toolkit.

Prognostic biopsy analysis may be improved in IgA nephropathy

As discussed above, the science of prognostication and stratification of patients with IgA nephropathy into those at high or low risk of ESRD has clearly advanced but is still quite incomplete, especially with respect to individual patients.

Great opportunities lie in refining the value of renal biopsy in prognostication. Although the "snapshot" nature and potential sampling errors intrinsic to diagnostic renal biopsy cannot easily be overcome, at least not without performing multiple and repeated renal biopsies (a very impractical approach to prognostication), refinements in the laboratory seem to offer numerous opportunities for advancement. Much better clinicopathological correlations, especially with respect to outcomes, among well-characterized patients with IgA nephropathy are greatly needed. New nonconventional markers of progression, such as "tubulitis," deposition of fibroblast-specific proteins, and the proteome of the deposited immunoglobulins and complement show much promise.[18]

The point of no return: a GFR of about 30

Immunosuppressive therapy could be added to ACE inhibitors or ARBs in IgA nephropathy

The management of IgA nephropathy has clearly advanced over the last several decades, largely as the result of randomized clinical trials.[3,19] However, these trials had serious limitations: the numbers of patients were relatively small, follow-up was relatively short, and the findings may not apply to the IgA nephropathy population at large or to specific patients having features that diverge from those in the patients enrolled in the studies.

The value of initial therapy with an ACE inhibitor, an ARB, or both in combination appears well established. However, details of dosage, duration of therapy, and the relative values of monotherapy and combined therapy remain uncertain.

Many opportunities for combining angiotensin II inhibition and immunosuppressive therapy are being explored. By and large, all current therapies are empiric and their long-term effects relatively uncertain, owing to small study size and short duration.

Oral and parenteral glucocorticoids,[20] combined regimens of cyclophosphamide (Cytoxan) and azathioprine (Imuran),[21] omega-3 fatty acids,[22] and anticoagulants and antithrombotics[3] each have their advocates and their specified target populations.

Tonsillectomy as a treatment has been particularly controversial. While no controlled studies have been performed yet, observational studies (most of them conducted in some prefectures in Japan) have suggested a higher rate of clinical remission with tonsillectomy than with steroid treatment alone.[5] However, long-term observations have not shown any consistent effect of tonsillectomy on progression to ESRD.

We hope that a better understanding of the fundamental mechanisms of disease and its mediation will provide an impetus for development of more rational targeted therapy. Evaluating potentially promising targeted therapies will be very difficult. Evaluation of safety and efficacy with long-term use will be a key requirement for a successful novel therapeutic agent.

FOR NOW, AN EMPIRIC APPROACH TO IGA NEPHROPATHY

Start with an angiotensin II inhibitor

The current body of evidence for choosing a particular therapeutic approach for a given patient with IgA nephropathy cannot be regarded as definitive, owing to limitations in the quality and strength of the trials serving as the basis of the evidence. Nonetheless, patients with IgA nephropathy and abnormal protein excretion (> 500 mg/day) should probably always be given angiotensin II inhibitor therapy (an ACE inhibitor, an ARB, or both) if they have no contraindications to it such as a hypersensitivity reaction or pregnancy, as a base for future monitoring and adjuvant therapy.

A response, tentatively defined as a 30% to 50% decline in proteinuria from baseline levels or a decrease to less than 500 mg/day, would be a reason to continue this conservative approach. Lack of a response after several months of observation at maximal tolerated dosage (plus salt restriction or a diuretic) would be a reason for considering adjuvant therapy.

If the patient does not respond to an ACE inhibitor or ARB and his or her estimated GFR is over 70 mL/min/1.73 m^2, a trial of oral and parenteral glucocorticoids might be undertaken, as suggested by Pozzi and coworkers.[20]

On the other hand, if the estimated GFR is in the range of 30 to 70 mL/min/1.73 m^2 and declining at a rate that predicts that ESRD will develop in less than 5 to 7 years, this would be a possible indication for low-dose oral cyclophosphamide and then azathioprine, as suggested by Ballardie and Roberts.[21] Omega-3 fatty acids (Omacor) could also be considered as add-on therapy, particularly for patients with very heavy proteinuria (> 3.0 g/d) and reduced estimated GFR.[22]

Patients with an estimated GFR of less than 30 mL/min/1.73 m^2 and chronic (irreversible) changes on renal biopsy—the point of no return—probably will not respond to any therapy other than an ACE inhibitor, an ARB, or both.

The role of more aggressive immunosuppression

At present, the evidence for using mycophenolate mofetil (CellCept) or calcineurin inhibitors (such as cyclosporin or tacrolimus) is fragmentary or contradictory.[3,19,23] Similarly, the benefits of long-term azathioprine therapy are based on observational data only and so it cannot be recommended as evidence-based.[24] Opportunities exist for combined therapy (eg, an ACE inhibitor or an ARB or both, combined with omega-3 fatty acids and azathioprine or mycophenolate mofetil), but at present, controlled trials are lacking. Crescentic disease and rapidly progressive glomerulonephritis should probably be treated with combined cyclophosphamide and parental and oral corticosteroids, based on observational data. Patients with IgA nephropathy and minimal change disease with nephrotic syndrome should be treated with oral steroids, but the only data available are observational. Low-protein diets could be tried in the presence of slowly progressive renal disease with estimated GFR less than 30 mL/min/1.73 m^2, but there are no controlled trials demonstrating efficacy for this approach in IgA nephropathy.

Renal transplantation is very successful

Renal transplantation is a very suitable alternative for patients with IgA nephropathy that progresses to ESRD. Overall success rates are as good or better than those in other primary glomerular diseases. Unfortunately, the disease recurs in the majority of renal grafts and may in some cases lead to loss of the graft.[25,26] We need much more information on the factors that predict such recurrences and their undesirable effects on transplantation outcomes.

MUCH WORK TO BE DONE

Much work needs to be done in the field of therapeutics in IgA nephropathy. Much of this effort will hinge on the interests of the pharmaceutical industry in IgA nephropathy as a potential therapeutic market. At present, the prospects for the development of a safe and effective novel therapy for IgA nephropathy (eg, approvable by the US Food and Drug Administration) do not appear great, but this may be overly pessimistic. The nature of the disease mandates long-term observation, agents that are very safe (with low rates of ESRD, death, and transplantation), and dependency on surrogate markers of efficacy. Therefore, designing and executing studies will not be easy.

Patients with IgA nephropathy, protein excretion > 500 mg/day, and no contraindications should get an ACE and/or an ARB

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