

Risk Stratification of Patients With IgA Nephropathy

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In this review, we summarize recent advances in the risk stratification of patients with immunoglobulin A (IgA) nephropathy. Several clinical variables have consistent and independent associations with worse kidney prognosis, including blood pressure, proteinuria, and baseline kidney function. Although one-time cross-sectional assessments of blood pressure and proteinuria are important, a more thorough understanding of risk can be achieved when these variables are considered over a follow-up period. IgA nephropathy is unique compared with other glomerular diseases in that a much lower threshold of proteinuria (protein excretion, 1 g/d) is associated with glomerular filtration rate (GFR) loss. Controlling proteinuria and blood pressure over time is important to reduce the risk of future loss of kidney function. The recently described Oxford classification has helped standardize the pathologic characterization of IgA nephropathy using a scoring system that is readily reproducible and associated with increased risk of GFR loss independent of clinical variables. We suggest an approach to risk stratification in IgA nephropathy when considering potential treatment with immunosuppression. Despite our current understanding of risk stratification in IgA nephropathy, the ability to accurately predict individual patient-level risk currently is limited, and further research into additional biomarkers or risk prediction tools is needed to improve the care of patients with IgA nephropathy.

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INDEX WORDS: Immunoglobulin A nephropathy; prognosis; risk factor; proteinuria; pathology.

Immunoglobulin A (IgA) nephropathy is the most common cause of glomerulonephritis worldwide, yet since its initial description by Berger in 1968, the optimal approach to its treatment remains a significant challenge.¹ As a consequence, IgA nephropathy remains a leading cause of end-stage kidney disease.¹⁻³ Ideally, early identification of patients at high risk of future loss of kidney function would facilitate timely therapeutic interventions to prevent progression to end-stage kidney disease. Recently, several research findings have contributed to our ability to identify such “high-risk” patients, and these new data can be integrated into both the evaluation of patients and therapeutic decisions.

IMPORTANCE OF RISK STRATIFICATION IN IgA NEPHROPATHY

It is not surprising that risk stratification remains a challenge in patients with IgA nephropathy because the natural history of IgA nephropathy ranges from persistent asymptomatic microscopic hematuria to progressive kidney failure.^{1,4,5} Further complicating our understanding of the natural course of IgA nephropathy is the variation created by different biopsy practices. This introduces potential lead-time bias in estimates of kidney survival.⁶

The development of a framework for risk stratification serves several important purposes. First, the information can help physicians inform patients regarding prognosis. As summarized in Box 1, there are several well-established risk factors that identify patients with IgA nephropathy who are likely to develop progressive disease. A second important application of risk

stratification is defining goals of therapy. For example, the knowledge that proteinuria with protein excretion of 3 g/d in a patient with IgA nephropathy is associated with a high risk of progressive loss of kidney function helps inform the decision of whether to expose a patient to the risks of immunotherapy. The threshold for immunotherapy also will be clarified and may differ in IgA nephropathy compared with other forms of glomerulonephritis.⁷ An appreciation of the goals of treatment can assist physicians in quantitatively evaluating the impact of therapy on risk of kidney failure and also provides a framework for patients to be engaged in their own disease monitoring and therapy. Finally, in-depth understanding of risk stratification is essential for the interpretation and design of clinical trials. For example, by understanding the natural history of the disease, one should not be surprised to find a favorable short-term prognosis in patients with low-grade proteinuria treated with

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Box 1. Variables Associated With Higher Risk of Loss of Kidney Function in IgA Nephropathy and That Can Be Used Clinically for Risk Stratification

Cross-sectional Clinical Data at Presentation

- Proteinuria >1 g/d
- Decreased GFR
- Presence of hypertension

Clinical Data During the Follow-up Period

- Persistent proteinuria >1 g/d
- Decreasing GFR
- Persistent hypertension

Pathology

- Oxford pathologic classification

Abbreviations: GFR, glomerular filtration rate; IgA, immunoglobulin A.

immunotherapy.^{8,9} Similarly, the degree of decreased glomerular filtration rate (GFR) and proteinuria may explain the lack of efficacy of a particular intervention.¹⁰

It would be ideal if risk stratification could occur at the time of diagnosis. This might involve integration of kidney biopsy results with cross-sectional clinical data, such as patient demographics, proteinuria, blood pressure, and kidney function. Given the potentially important role of risk stratification in the care of patients with IgA nephropathy, a review of recent developments regarding prognostic tools, clinical variables, and pathology classification is merited.

CLINICAL VARIABLES

Proteinuria

Proteinuria has a particularly strong association with poor kidney prognosis in IgA nephropathy. The association between proteinuria at the time of biopsy and risk of progression is well described in diverse geographic cohorts, including those followed up in Italy,^{11,12} Australia,¹³ France,¹⁴⁻¹⁶ the United States,¹⁷ Japan,^{18,19} Canada,²⁰ and China.^{21,22} The consistency across different countries of origin, eras of care, and biopsy practices further confirms the robust association between proteinuria and poor kidney prognosis.

Unlike other types of primary glomerulonephritis in which subnephrotic proteinuria at presentation is not associated with a measurable increase in risk of GFR loss, much lower levels need to be considered in IgA nephropathy.^{7,14,17,23,24} In a cohort of 148 patients with IgA nephropathy followed up at the Mayo Clinic, patients were stratified for risk of end-stage kidney disease by proteinuria at presentation. The risk of end-stage kidney disease at 10 years was ~10% for those with protein excretion <1 g/d, but the risk substantially increased with increasing proteinuria at presentation, up to 30%-40% for those with protein

excretion of 1-3 g/d and 60% for those with protein excretion >3 g/d.¹⁷ Therefore, it appears that a threshold proteinuria at presentation of protein excretion of 1 g/d identifies a high-risk group of patients, an observation that has been confirmed in several other studies.^{7,14,23,24} It is important to note that not all studies suggest that low-grade proteinuria at presentation necessarily is associated with a favorable outcome: as many as one-third of patients will have a progressive increase in proteinuria with protein excretion beyond 1 g/d and the subsequent development of hypertension.²⁵ This highlights the need to expand proteinuria evaluation beyond 1-time cross-sectional assessments at the time of diagnosis to include longitudinal measurements of proteinuria for improved quantification of disease activity and risk of progression.

Although proteinuria at presentation is an important consideration, our work suggests that proteinuria over time more closely correlates with disease outcome. If proteinuria is maintained over time at protein excretion <1 g/d, the 10-year risk of end-stage kidney disease is <5%. This risk increases to 20% with sustained proteinuria with protein excretion of 1-2 g/d, to 40% with protein excretion of 2-3 g/d, and to 60% with protein excretion >3 g/d.²³ Repeated measurements of proteinuria averaged over time have been shown to predict GFR loss better than proteinuria at presentation in several cohort studies and a prospective randomized trial.^{20,23,26} This may require modification of prognosis in a patient with worsening proteinuria. Our data suggest that regardless of the peak level of proteinuria, partial remission to protein excretion <1 g/d is associated with a decrease in risk of end-stage kidney disease similar to that for patients who are without grossly elevated proteinuria at presentation.²³ These results are supported by evidence from therapeutic randomized controlled trials.^{8,9,26,27} In the original trial by Pozzi et al,⁸ median proteinuria at 6 months decreased to protein excretion <1 g/d in the prednisone group, but not in the placebo group. Achievement of partial remission of proteinuria to protein excretion of 1 g/d was associated independently with a lower risk of GFR loss during long-term follow-up.²⁷ Therefore, a reasonable therapeutic target appears to be achieving a consistent level of proteinuria with protein excretion <1 g/d.

Two important questions remain about proteinuria over time: what duration of follow-up should be considered, and what are the risk-modifying effects of antiproteinuric therapies? Shorter periods of observation would facilitate prompt therapeutic decisions and earlier patient education, but it is not clear how long patients should be observed before a sufficient risk assessment has been achieved. In one study, clinical

data averaged over progressively longer periods up to 2 years of follow-up explained increasing variability in GFR loss, with no additional benefit to adding data thereafter.²⁰ Furthermore, to the extent that proteinuria may be directly nephrotoxic and contribute to irreversible fibrosis (instead of simply being a marker of more aggressive disease),^{28,29} it would be reasonable to consider the level of proteinuria after maximum antiproteinuric measures for purposes of prognostication. This is supported by several small randomized trials of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in IgA nephropathy and the observation that these medications result in improved kidney outcomes in patients with nondiabetic glomerular disease.^{23,30-35} The REIN (Ramipril Efficiency in Nephropathy) study showed that a reduction of proteinuria with ramipril significantly lowered the rate of GFR loss in the subgroup of patients with primary glomerular diseases independent of blood pressure effects.^{30,31,35} Therefore, we consider patients to be at significantly increased risk of GFR loss if their proteinuria persistently has protein excretion >1 g/d after optimization of conservative measures, including blood pressure control and inhibition of the renin-angiotensin system.

Blood Pressure

Hypertension at presentation, defined as blood pressure >140/90 mm Hg, has a strong association with increased risk of GFR loss in IgA nephropathy. This is a consistent observation across cohorts of different ethnicities covering a wide range of treatment eras.^{6,11-17,20-23,36} A recent study of 332 patients from France showed that from the onset of symptoms, the 20-year risk of death or dialysis was 6% for those who were not hypertensive at baseline compared with 41% for those who were.¹⁶ These results highlight the important association between increased blood pressure and GFR loss in IgA nephropathy.

Fortunately, blood pressure is modifiable. The beneficial effect of blood pressure lowering is demonstrated by the fact that when analyzed together, blood pressure averaged over time is a better predictor of prognosis than that measured at presentation.^{20,23} In a Dutch study of 75 patients with IgA nephropathy, those who were hypertensive at presentation but well controlled during the follow-up period did not have an increased risk of GFR loss. However, there was a substantial increase in risk in persistently hypertensive patients. In the previously mentioned French study, the 20-year risk of death or dialysis was 19% in hypertensive patients with well-controlled blood pressure at the end of follow-up, but 42% in hypertensive patients with poorly controlled follow-up blood pressure.¹⁶ Unfortunately, there are no randomized con-

trolled trials in IgA nephropathy that have investigated different blood pressure targets, but both the MDRD (Modification of Diet in Renal Disease) Study and AASK (African-American Study of Kidney Disease and Hypertension) suggest beneficial effects of blood pressure control on long-term kidney function in nondiabetic kidney disease, particularly in patients with increased proteinuria.^{37,38} One recent systematic review suggests that blood pressure of 125/75 mm Hg is associated with favorable prognosis in patients with chronic proteinuric kidney disease.³⁹ Therefore, in the absence of clinical trials specific to IgA nephropathy, we suggest a reasonable therapeutic target for blood pressure of 130/80 mm Hg as advised by the KDOQI (Kidney Disease Outcomes Quality Initiative) guidelines for general chronic kidney disease.⁴⁰ It also is important to recognize that blood pressure and proteinuria are not entirely independent parameters, and moderation of blood pressure likely will impact on proteinuria.²³

Baseline Kidney Function

Most studies that have investigated risk factors for end-stage kidney disease in patients with IgA nephropathy have found strong associations with baseline kidney function.^{6,12-14,17-19,21,22,24,36} A large cohort of more than 2,000 Japanese patients shows the 7-year risk of dialysis to be 2.5% for patients with baseline creatinine level <1.24 mg/dL (<110 μ mol/L), but this risk increases dramatically to 90% for patients with creatinine levels >2.49 mg/dL (>220 μ mol/L).¹⁹ However, these studies used survival analysis techniques that model the time to end-stage kidney disease. In such models, it is not clear whether baseline kidney function is associated with a more rapid rate of GFR loss or simply represents a more impaired starting point with less kidney reserve. Nonetheless, the consistent association across multiple cohort studies emphasizes the high risk for dialysis in patients who present with decreased kidney function.

An inconsistent but intriguing observation is that the rate of GFR loss also may be dependent on baseline kidney function. A large study of 711 patients from 4 different centers showed that baseline creatinine clearance was an important determinant of the rate of kidney function decrease, even when analysis was restricted to patients with decreased kidney function at presentation.⁶ This suggests that the rate of GFR loss may change or accelerate,^{6,20,41} and this has physiologic plausibility. It is possible that compensatory glomerular hyperfiltration maintains overall clearance in the earlier stages of disease, so that the rate of GFR loss (measured by currently available clinical tests) is moderated until this compensatory function is lost. Although this remains an area of uncertainty, it

should be appreciated that serum creatinine levels during a period of compensatory hyperfiltration may not be reflective of the amount of kidney injury that has occurred. Furthermore, when kidney function has started to decrease, there may be irreversible structural and functional changes with a substantial risk of progression to end-stage kidney disease.⁴² For these reasons, we do not advocate delaying treatment decisions until kidney function starts to decrease.

Other Clinical Variables

Inconsistent associations with outcome are seen with age, sex, and isolated macroscopic hematuria.^{5,43,44} Although there is prominent geographic variability in the prevalence and incidence of IgA nephropathy, it is unclear from the current literature if racial background affects kidney outcome. IgA nephropathy is the cause of 40% of biopsy-proven cases of glomerulonephritis in Asian countries, but <10% in the United States.^{1,45-47} This difference may be due to a combination of varied rates of disease susceptibility and progression. Furthermore, not all diagnoses in end-stage kidney disease registries are biopsy proven; many cases attributed to IgA nephropathy may be presumptive based on the local prevalence of disease.^{45,47,48} Differences in biopsy thresholds and treatment patterns may explain some of the regional variation in the observed rates of kidney progression in IgA nephropathy.^{6,49} Despite these significant geographic differences in the incidence and prevalence of IgA nephropathy, it is unknown whether race or geography directly impact on either the immunopathogenesis or progression of this disease.

CONSIDERING CLINICAL VARIABLES TOGETHER

The most important clinical variables for risk stratification in IgA nephropathy appear to be proteinuria, hypertension, and baseline kidney function (Box 1). However, these variables should not be considered in isolation. In practice, the treating physician will have access to all 3 variables simultaneously and must understand how each behaves in the context of the others. Although not all studies that considered these 3 variables together have shown independent statistical significance for each, it can be seen in Table 1 that the overall trend across all studies is that proteinuria, hypertension, and baseline kidney function are each associated with an independent risk of GFR loss in IgA nephropathy. It should be emphasized that although proteinuria, blood pressure, and kidney function may vary similarly with the severity of disease, these results suggest that each individually contributes to the risk of GFR loss independent of the values of the other 2. For example, persistently elevated blood pressure in the context of proteinuria with

protein excretion <1 g/d and normal kidney function nonetheless is associated with worse GFR loss.

Although multivariable models provide important information about associations in the larger population, they do not apply directly to risk prediction at the patient level. To this end, several groups have attempted to develop scoring systems for risk prediction in IgA nephropathy.^{16,19,20,41,50,51} Bartosik et al²⁰ used the first 2 years of follow-up blood pressure and proteinuria values to predict the rate of change in estimated creatinine clearance using a cohort of 298 patients with IgA nephropathy from Toronto. The prediction model subsequently was validated in a cohort of 169 patients from Scotland, but the accuracy of the model was poor, with only 44% of patients having predicted rates of change of creatinine clearance within 2 mL/min per year of observed values.⁴¹ For any prediction model to be widely applicable, it must be validated in cohorts outside that in which it was derived and similar to the population in which it is intended to be applied. It must use reproducible clinically available variables, and it must have sufficient discrimination and accuracy to meaningfully affect clinical decisions. Unfortunately, there are no current risk prediction models that satisfy all these criteria and no validated predictive models including kidney pathology data.

KIDNEY PATHOLOGY

Until recently, the most commonly used grading systems for IgA nephropathy were those developed by Haas⁵² and Lee et al.⁵³ Although providing a valuable resource for standardizing qualitative biopsy descriptions, these grading systems show variable results with respect to internal and external validation. This may be attributable in part to inconsistent inter-rater reproducibility.⁵⁴ Furthermore, the ability of any grading system, including more simplified scales,¹² to provide prognostic value beyond that explained by clinical parameters has been limited.^{12,20,21} Histologic grades reflect a combination of active proliferative changes, glomerular sclerosis, and interstitial fibrosis. To the extent that sclerosis and fibrosis are irreversible, this may limit the utility of these grading systems to predict response to immunotherapy. A common theme emanating from all studies involving grading systems is that more severe interstitial fibrosis, tubular atrophy, and glomerular sclerosis are associated with worse kidney outcomes. However, this may be a reflection of the short follow-up periods in most studies, resulting in measurable kidney outcomes being captured in patients with only the most severe histologic disease at baseline.⁵⁴

The recently developed Oxford histologic classification of IgA nephropathy has overcome many of

Table 1. Select Studies in IgA Nephropathy Investigating Independent Associations of Proteinuria, Hypertension, and Baseline Kidney Function With Risk of GFR Loss in Multivariable Models

Study	N	Outcome	Follow-up (y)	Risk Factors Significant in Multivariable Models			
				Hypertension	Proteinuria	Kidney Function	Pathology
Beukhof et al, ³⁶ 1986	75	ESRD	5	Yes	Yes	Yes	NA
D'Amico et al, ¹¹ 1986	365	ESRD	5	No	Yes	NA	Yes
Alamartine et al, ¹⁵ 1991	282	Creatinine > 135 μ mol/L	8	Yes	Yes	NA	Yes
Ibels & Gyory, ¹³ 1994	121	% Change in creatinine	7	No	No	Yes	Yes
Frimat et al, ¹⁴ 1997	270	ESRD	6	No	Yes	Yes	NA
Radford et al, ¹⁷ 1997	148	ESRD	4	No	No	Yes	Yes
Koyama et al, ¹⁸ 1997	502	ESRD	12	No	Yes	Yes	No
Bartosik et al, ²⁰ 2001	298	Rate of CCr decrease	6	Yes	Yes	No	No
Donadio et al, ²⁴ 2002; IgAN 1 Trial	91	ESRD	6	No	Yes	Yes	No
Donadio et al, ²⁴ 2002; IgAN 2 Trial	63	ESRD	2	No	Yes	Yes	No
Li et al, ²² 2002	168	ESRD	7	Yes	Yes	Yes	Yes
Geddes et al, ⁶ 2003	711	ESRD & rate of CCr decrease	4-10	No	Yes	Yes	NA
Manno et al, ¹² 2007	437	ESRD	9	No	Yes	Yes	Yes
Reich et al, ²³ 2007	542	Rate of CCr decrease	7	Yes	Yes	Yes	NA
Lv et al, ²¹ 2008	204	ESRD	6	Yes	No	Yes	Yes
Prakash et al, ⁴⁹ 2008; Thailand group	76	Rate of CCr decrease	2	No	No	NA	Yes
Prakash et al, ⁴⁹ 2008; Canada group	152	Rate of CCr decrease	3	No	No	NA	No
Goto et al, ⁵¹ 2009	2,283	ESRD	7	Yes	Yes	Yes	Yes
Berthoux et al, ¹⁶ 2011	332	Death or dialysis	13	Yes	Yes	NA	Yes

Note: The study by Goto et al⁵¹ was based on the extended follow-up of the cohort by Wakai et al¹⁹; therefore, only the Goto et al⁵¹ study is presented.

Abbreviations: CCr, creatinine clearance; ESRD, end-stage renal disease; GFR, glomerular filtration rate; NA, not assessed.

these earlier limitations.^{55,56} The study included 265 patients with IgA nephropathy and protein excretion >500 mg/d who were followed up for at least 12 months. Patients were recruited from 17 centers across a variety of geographic regions, including Asia, Europe, and North America. Demographic and clinical data were collected at the time of biopsy and over a median follow-up of 5 years. The authors developed this system by first selecting histologic parameters that showed good inter-rater correlation between pathologists. Subsequent analyses showed that mesangial hypercellularity, glomerular sclerosis, and interstitial fibrosis and tubular atrophy were each independently associated with GFR loss, after adjusting for baseline and longitudinal clinical data. The evaluation of the independent relationship between endocapillary hypercellularity and outcome was confounded because a substantial proportion of patients with this lesion had received prednisone. In patients who had not received immunotherapy, endocapillary proliferation was associated with worse kidney prognosis compared with

those without this lesion. Ultimately, the MEST classification scheme was developed (Table 2), each component of which is highly reproducible across pathologists and accounts for additional risk of GFR loss beyond that explained by clinical data. The utility of this scoring system recently has been confirmed in several independent populations, including a validation cohort of 187 patients from 4 centers in North America. This suggests that a robust pathologic classification can help risk-stratify patients at the time of diagnosis.⁵⁷⁻⁵⁹

The Oxford classification potentially has broad application; however, further studies are required to understand how to apply the MEST score in the context of clinical variables to provide patients with an individual risk of GFR loss. Both the original and validation studies show that each component of the MEST score is associated with more rapid GFR loss independent of each other, proteinuria, blood pressure, and baseline kidney function.⁵⁷⁻⁵⁹ Properly validated prognostic models that include the MEST score,

Table 2. Oxford MEST Classification

Variable Name	Definition	Score
Mesangial hypercellularity (M)	<4 mesangial cells/mesangial area = 0; 4-5 mesangial cells/mesangial area = 1; 6-7 mesangial cells/mesangial area = 2; >8 mesangial cells/mesangial area = 3	M0 if score ≤0.5; M1 if score >0.5
Endocapillary hypercellularity (E)	Increased no. of cells within the glomerular capillary lumina, recorded as present or absent	E0 if absent; E1 if present
Segmental glomerulosclerosis (S)	Presence of an adhesion or any segment of the tuft involved in sclerosis	S0 if absent; S1 if present
Tubular atrophy/interstitial fibrosis (T)	Percentage of cortical area involved with tubular atrophy or interstitial fibrosis (whichever is greater)	T0 if 0%-25%; T1 if 26%-50%; T2 if >50%

Adapted from Cattran et al⁶⁵ with permission of Macmillan Publishers Ltd.

clinical variables, or combinations of MEST markers have not yet been developed, and it remains to be seen if the addition of the Oxford classification can improve the ability to provide individual patients with information regarding risk of GFR loss. It is likely that risk associated with MEST variables and clinical data will be additive.

Several additional questions about the implications of pathologic lesions remain unanswered by the Oxford histologic classification. The study was not designed to predict response to immunosuppression. The observed interaction effect between endocapillary proliferation and immunosuppression on rate of GFR loss suggests that this might be a steroid-responsive histologic pattern. Conversely, glomerulosclerosis and tubulointerstitial fibrosis may be advanced lesions that are irreversible. This will need to be confirmed in prospective therapeutic randomized controlled trials, which in the future may include stratified randomization on categories of the MEST classification. Finally, due to the relative infrequency of the histologic lesion and the exclusion of patients with a rapidly progressive clinical course, few patients in the analysis had crescents. Consequently, the significance of these lesions could not be fully evaluated.

FUTURE DIRECTIONS TO IMPROVE RISK STRATIFICATION

The limited ability to predict outcome in individual patients emphasizes the need for identification of new markers of disease activity that will assist in the pursuit to individualize therapy. The search for noninvasive biomarkers of disease activity and adverse kidney prognosis remains an active area of research. The last decade has seen an exponential increase in the number of publications describing novel markers and risk scores for application in patients with IgA nephropathy.⁶⁰ Although an exhaustive review of biomarkers associated with IgA nephropathy prognosis is

beyond the scope of this article, efforts to identify indicators of progressive IgA nephropathy have focused on evaluating genetic profiles, tissue and leukocyte messenger RNA (mRNA) expression, and urinary proteome profiling. In addition to genome-wide searches for markers of susceptibility to the immunopathogenesis of IgA nephropathy, targeted studies have identified some heritable markers of progression risk. For example, a polymorphism of the MYH9 gene recently was associated with progression in a large cohort of patients in China.⁶¹ Similarly, novel functional mutations in the genes encoding epoxide hydrolase (EPHX2), CD89, and various cytokines also have been implicated in progressive disease.^{62,63} Studies of polymorphisms of the renin-angiotensin system have not consistently shown association with prognosis.⁶⁴ In addition to genome studies, evaluation of tissue mRNA and microRNA expression has identified expression signatures that may be associated with proteinuria and prognosis.⁶⁵⁻⁶⁷ Broad urine proteome patterns show potential to provide prognostic information,⁶⁸ and targeted urine proteome analyses suggest that the balance between trophic and inflammatory markers analyzed in urine may be independently predictive of outcome in IgA nephropathy.⁶⁹ Undoubtedly more candidate biomarkers will appear in the literature; however, it remains to be demonstrated whether these markers inform risk stratification beyond the evaluation of readily available clinical data.

SUGGESTED APPROACH TO RISK STRATIFICATION IN IgA NEPHROPATHY AND IMMUNOSUPPRESSION TREATMENT

The framework described thus far is informative regarding identification of modifiable and nonmodifiable risk factors associated with progressive disease (Box 1). Unfortunately, no targeted therapies exist to modify the susceptibility to IgA nephropathy or halt progression. As a consequence, clinicians must carefully balance the short- and long-term risks of a

limited armamentarium of immunosuppressive therapies in each individual against the potential for moderating the rate of progression. What follows is a suggested approach to identifying patients for whom immunosuppression may be warranted; the evidence supporting specific immunosuppressive strategies is beyond the scope of this article.

As reviewed, persistent proteinuria with protein excretion >1 g/d and decreased GFR are widely accepted as harbingers of progressive loss of kidney function. The role of the MEST score in modifying this risk profile or predicting response to therapy remains to be determined. A period of 6 months of initial therapy is warranted in all patients at increased risk of progression. This includes optimization of blood pressure, directed antiproteinuric strategies (ie, renin-angiotensin system blockade), a potential trial of fish oil, and moderation of the lipid profile according to general chronic kidney disease guidelines.⁷⁰ If proteinuria persistently has protein excretion >1 g/d despite these measures, immunosuppressive therapy should at least be considered because the patient is at substantial risk of further disease progression. The decision to proceed with immunotherapy need not be framed as a 6-month course of treatment. Although within the short term it is unlikely to achieve complete remission of proteinuria, if no measurable improvement is evident after 6–8 weeks of any course of immunosuppression, the treatment plan should be re-evaluated. Furthermore, a decision not to use immunosuppression might be influenced by the presence of diabetes, obesity, advanced age, cardiovascular disease, and other comorbid conditions. Advanced tubulointerstitial injury with significantly impaired kidney function also might reflect a “point of no return” at which the toxicity of therapy outweighs measurable benefit.

There are certain clinical presentations that likely warrant early consideration for immunotherapy. These include rapidly progressive glomerulonephritis with a significant ($>50\%$) number of glomeruli involved with crescents. Although no randomized controlled trials have targeted these 2 rare groups of patients, observational studies suggest benefit.^{71–73}

CONCLUSION

Risk stratification is essential for the care of patients with IgA nephropathy to avoid unnecessary exposure of toxic therapies while reducing the risk of dialysis dependence. To accomplish this goal, the clinician must balance the combined effects of clinical parameters obtained at the time of presentation, clinical parameters repeated during follow-up, and pathologic features seen on kidney biopsy. New insights regarding the relationship between proteinuria and outcome contribute to our ability to provide prognos-

tic information and identify treatment goals. Furthermore, a rigorously defined pathologic scoring system now offers additional independent information regarding disease outcome and may inform therapeutic decisions in the future. Despite these exciting new developments, our ability to reliably risk-stratify patients with IgA nephropathy at the time of diagnosis or during early follow-up remains limited. This emphasizes the need for the identification of new biomarkers of disease activity, therapeutic response, and prognosis.

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