Immunosuppression in IgA Nephropathy: Guideline Medicine Versus Personalized Medicine

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Summary: The role of immunosuppression in IgAN remains controversial despite a growing evidence base of randomized controlled trials (RCTs). In IgAN with nephrotic syndrome the role for corticosteroids is limited to cases with minimal change on light microscopy. In crescentic IgAN, the use of immunosuppression is supported only by anecdotal data, and outcome may be poor especially when glomerular filtration rate is impaired severely at presentation or there are pathologic features of chronic injury. In slowly progressive IgAN, prediction of outcome now is based both on clinical and pathologic features. Most RCTs have studied patients with urine protein levels greater than 1 g/24 h and only a minority have enrolled patients with a glomerular filtration rate less than 60 mL/min. The Supportive versus immunosuppressive Therapy of Progressive IgA nephropathy (STOP) IgAN study emphasized the efficacy of supportive therapy (including blood pressure control and renin-angiotensin system blockade) in decreasing proteinuria to less than the usually accepted threshold for the use of corticosteroids. Earlier RCTs of corticosteroids usually did not deploy supportive therapy optimally. The recent Therapeutic Evaluation of STeroids in IgA Nephropathy Global (TESTING) study closed prematurely because of excess toxicity, but the high dose of corticosteroids seemed to provide benefit. Guidelines provide valuable information about the quality and limitations of available evidence that needs to be personalized in application to the individual patient's medical and nonmedical circumstances to ensure wise clinical decision making.

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DEFINITION OF IgAN

The defining criterion that was used in the original report of IgAN by Berger and Hinglais[1] in 1968 remains as follows: the dominant or co-dominant diffuse mesangial deposition of IgA (detected by immunofluorescence or immunohistochemistry). Electron microscopy identifies electron-dense deposits corresponding to the mesangial IgA deposits. IgAN is unique among the recognized patterns of glomerular injury being defined by the identifiable glomerular immune reactants independent of any histologic features recognizable by light microscopy.

Primary IgAN also is defined further by the absence of any associated clinical features that are thought to provide a specific etiology for IgAN, which therefore might provide an alternative mechanistic explanation of mesangial IgA deposition and subsequent injury, and therefore may offer different therapeutic opportunities (eg, by focusing on treatment of the associated condition and looking for improvement in the glomerular disease).[2] Many such associations have been reported for IgAN, some so uncommon that they likely are coincidental rather than causative associations. Among those most reported are alcoholic liver disease, celiac disease, and ankylosing spondylitis. The management of IgAN secondary to these and other conditions will not be discussed here further.

Another group that is excluded is patients with IgAN who have overt evidence of an accompanying IgA-mediated, small-vessel vasculitis. This condition has been known since the 19th century as Henoch-Schönlein purpura, and the glomerular lesions (often indistinguishable from primary IgAN) are known as Henoch-Schönlein nephritis. Recent nomenclature recommendations favor the term *IgA vasculitis* instead of *Henoch-Schönlein purpura*. Patients with IgA vasculitis typically are excluded from almost all published treatment trials in IgAN, and there is a separate evidence base of treatment options for IgA vasculitis that is even more limited than that for primary IgAN, including mostly observational data. The treatment of IgA vasculitis will not be discussed here further.

I therefore have limited the discussion in this review to the treatment of primary IgAN, which for convenience I will simply call *IgAN*.

It should not be forgotten that in many parts of the world, IgAN cannot be diagnosed either because renal biopsy as a diagnostic technique is unavailable, or because only analysis of a biopsy light microscopy can

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This article reviews the clinical management of primary IgAN, with a specific focus on the role of immunosuppressive therapy. This will be discussed within a spectrum of treatment decision making that sometimes is polarized as two distinct approaches: on the one hand as guideline medicine, and on the other hand as personalized medicine.

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be provided, and there is no expertise to prepare immunofluorescence or immunohistochemistry to detect IgA. This article restricts discussion to management of patients with biopsy-proven IgAN.

At this time, it remains uncertain whether the clinicopathologic entity now known as IgAN is a single disease or the same disease in all parts of the world. This uncertainty comes in part from variations in clinical features. For example, in East Asia IgAN has much greater incidence, a different gender distribution (equal in males and females compared with most other parts of the world where the male:female ratio typically is approximately 4:1), and more rapid progression toward end-stage renal disease (ESRD)[3]; the basis, genetic or environmental, for these differences still is being studied. The existing evidence base for treatment of IgAN does not specifically take these clinicopathologic variations into account.

PATHOGENESIS OF IgAN AND IMPLICATIONS FOR TREATMENT

Over the past 20 years there has been accelerating understanding of abnormalities in circulating and mesangial IgA in primary IgAN, and of a range of immune and nonimmune mechanisms that contribute to mesangial IgA deposition and subsequent glomerular and extraglomerular injury.[4] These include mechanisms likely to be unique to IgAN, for example, the role of altered glycosylation of IgA1, as well as immune and nonimmune mechanisms that likely are active in other glomerular diseases characterized by mesangial inflammation, and also in a broader range of proteinuric kidney diseases.

However, it cannot be assumed that the entity we now call IgAN is uniform in terms of pathogenesis. It probably includes patients in whom mesangial IgA deposition and the subsequent glomerular injury come about through a range of pathobiological mechanisms, and it is likely that IgAN will be subdivided and redefined over the coming years based on new understanding of these different mechanisms. This in turn would be expected to lead to disease-specific therapeutics based on rational approaches to modifying disease mechanisms There are no such mechanism-specific therapies at present for IgAN, therefore, in this article, nonspecific immunosuppressive therapies, which may interrupt several mechanisms of disease progression, are discussed. Our understanding of the role of such therapies is derived from treatment trials that include all patients with the existing histopathologic definition of IgAN, and therefore may well include patients with a variety of pathogenic disease mechanisms. This heterogeneity makes the outcome of trials less easy to interpret and generalize.

CLINICAL PRACTICE GUIDELINES

The frequent publication of clinical practice guidelines in recent years reflects the emergence and sustained influence of evidence-based medicine as a modifier of traditional opinion-based medicine. As the concept of evidence-based medicine became established, increasing efforts followed across all branches of medicine to provide analysis of the best available evidence base to support the principle.

At first, these efforts typically resulted in guidelines that mainly were opinion-based, developed by expert groups with neither an ideal rigorous scientific approach to the systematic review of evidence, nor defined criteria for guideline presentation or interpretation. This soon was followed by the emergence of international organizations, such as Kidney Disease Improvement in Global Outcomes (KDIGO), whose primary purpose is to develop and publish high-quality, evidence-based guidelines, emphasizing the well-conducted randomized controlled trial (RCT) as the gold standard of evidence.

The best available clinical practice guideline for IgAN is contained within the KDIGO Clinical Practice Guideline on Glomerulonephritis.[5] This usually is regarded as superseding earlier guidelines, which had not approached the evidence base with the same rigor used by KDIGO, although some countries such as Japan continue to publish guidelines for local use.[6] The evidence base used for the KDIGO guideline closed in November 2011.

GUIDELINE MEDICINE, PERSONALIZED MEDICINE, AND EXPERT OPINION

Guideline medicine and personalized medicine sometimes unhelpfully are presented as polarized and mutually exclusive approaches to clinical practice.

Clinical practice guidelines eagerly are awaited and widely read. Sessions at nephrology congresses at which guidelines are presented and discussed typically attract large audiences. The principles by which guidelines can be used by physicians to influence their decision making are sound. Guidelines often particularly are welcomed by those who do not regard themselves as expert in a field, providing an effective and objective way to ensure familiarity with published literature with a balanced interpretation and weighting.

Nevertheless, it is not uncommon that those who read such guidelines overinterpret the strength of the advice that is offered to clinical decision making. KDIGO guidelines are careful in how recommendations and suggestions for different treatments are discussed, and how the weight of evidence is described (Tables 1 and 2). Recommendations within the KDIGO guideline are more circumspect than the users of