RESEARCH

A personalized approach to treatment of IgA nephropathy

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IgA nephropathy (IgAN) is a common glomerular disease with a variable course that ranges from remission of clinical features, indolent and non-progressive course, to rapid progression to end-stage renal disease (ESRD), mimicking vasculitides. At one extreme, these cases are easily identified by minor urinary and pathology changes or, at the opposite extreme, by severe proteinuria, progressive decrease in renal function and hypertension. However, most patients with IgAN have a progressive disease and 10–30 % will reach ESRD by 10 years after diagnosis. Slowly progressive cases have a variable rate of decline in renal function. Hence the diagnosis of IgAN has little significance for the individual patient. Clinicians need a prognosis of the potential progression of the renal disease in each patient so that they can prescribe personalized therapy.

Since the decision about the need for treatment and the choice among various possibilities come after the results of the renal biopsy, much interest has been focused on the identification of pathology features that are associated with risk of progression and are potentially reversible after targeted therapy.

The multicenter VALIGA study, promoted by the Immunonephrology Working Group of the ERA-EDTA, involved 1,147 European patients who were followed up of 4.7 years. In this large cohort, the prognostic value of the lesions identified by the Oxford classification IgAN (the MEST score: mesangial hypercellularity [M], endocapillaryhypercellularity [E] segmental glomerulosclerosis [S], and tubular atrophy/interstitial fibrosis [T]), was confirmed. The strongest predictive value was the presence of irreversible, extensive T lesions in > 25 % of the renal biopsy tissue (T1 and T2), but data also indicated the value of reversible pathology risk factors.

Interest is now being focused on trying to find the way of selecting therapy, not only on the basis of persistent proteinuria, but also on the activity and reversibility of lesions found at renal biopsy. A critical analysis of multicenter collaborative studies and some important recent reports suggest a possible personalized approach to treatment of patients with IgAN that takes into account the pathology features in addition to the classical clinical risk factors.

To sum up the message of the lecture
As demonstrated by the STOP-IgAN randomized controlled trial (RCT), protracted and rigorous supportive care, including blockade of the renin-angiotensin system (RAS) to address blood pressure and proteinuria, and metabolic and lifestyle targets, can be of benefit in one third of patients with IgAN with proteinuria < 0.75–3.5 g/d and who are not at high risk of rapid progression.

Is additional corticosteroid therapy needed?
No, when proteinuria is 0.75–1.5 g/day and MEST scores are negative, as shown in a large multicenter study of 900 patients including VALIGA, Oxford and North America collaborative studies. Yes, when IgAN is progressing with rapid loss of GFR or when crescents are present in > 25 % of glomeruli, as shown by a collaborative study on 3,000 patients from VALIGA, Chinese and Japanese cohorts. Probably yes, when risk factors are present, with persistent proteinuria > 1 g/day or when proteinuria < 1 g/day with M1 or E1 or S1 with podocytopathy, based on the value of risk factors observed in validation studies in young and adult subjects and in untreated cohorts.

The addition of alkylating agents/antimetabolites to corticosteroids is not indicated in non-vasculitis-like progressive forms, particularly when GFR < 50 ml/min/1.73 min. To apply more aggressive therapies, the rapidity of GFR loss over the previous weeks/months must be considered, taking into consideration active and potentially progressive pathology lesions.

The addition of corticosteroids to supportive care induces reduction in proteinuria and possible reno-protective effects in the long term, with an increase in adverse events, which mostly occurs in patients with impaired renal function. Systemic exposure to corticosteroids and their adverse events may be avoided or greatly limited by using the targeted-release, enteric formulation of budesonide, which acts on the intestinal immune system highly expressed at the Peyer's patches near the ileo-cecal junction. A phase 2 RCT showed favorable results without serious steroid side effects. There is interest in this approach for its possible indication for early cases without irreversible sclerotic lesions.

In conclusion, clinical trials often do not consider baseline renal biopsy features. In the era of precision nephrology, pathology lesions – particularly mesangial proliferation, podocytopathy leading to segmental glomerulosclerosis, epithelial crescents and the extent of tubulo-interstitial damage – may represent a useful criterion for designing clinical trials aimed at curbing the risk of kidney failure in IgAN patients with a high risk of progression. ◘

References

01. Coppo R. Corticosteroids in IgA nephropathy: lessons form recent trials. JASN 2017;28:25–33

S 3.2
IgA nephropathy: from genes to therapeutic controversies
Sunday, 08.00–09.30, Hall A2

RESEARCH

From the laboratory to the bedside The role of experimental models in developing new treatment options

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Despite large investments in drug development, the overall success rate of drugs during clinical development remains low, notably for inflammatory renal diseases such as glomerulonephritis. One prominent explanation is flawed preclinical research. Therefore, critical evaluation and selection of a validated and predictive animal model are essential to address clinical questions. For many years, limitations of animal models of IgA nephropathy (IgAN) were highlighted by the absence of the IgA1 isotype and of its receptor, the CD89, in the mouse. Indeed, in IgAN patients, several researchers worldwide have identified abnormalities of IgA1 and its receptor, such as galactose deficiency of IgA1 and release of soluble CD89, that participate in nephrotoxic immune complex formation.

To improve the clinical relevance for translation, a humanized mouse model was generated expressing human IgA1 and CD89, the α1KICD89Tg mouse, which spontaneously develops clinical features typical of IgAN, including mesangial IgA1 deposits, hematuria and proteinuria.[1)] This humanized model of IgAN was essential for translation of drug findings from bench to bedside. We have demonstrated, for example, that recombinant IgA1 protease can reverse the disease by clearing IgA1 deposits, thus opening new avenues for future treatment.[2] Similarly, this mouse model allowed us to test whether food antigens (i. e. gliadin) were deleterious for disease development. A gluten-free diet was beneficial in preventing IgAN development in the α1KIC-D89Tg mouse,[3] confirming results obtained in patients with a gluten-free diet in the early 1990s by Professor Coppo's group. They reappraise the efficacy of such treatment by showing that it may have preventive, rather than curative, effects, as it acted mainly on animals with normal renal function by preventing disease development. Thus, excluding gluten from the diet could be a simple therapeutic approach for patients with preserved renal function, especially those with sensitivity to gluten. A new clinical trial is now under way in France. Animal models can also provide new clues on the pathogenesis of the disease. For example, observed prevention of IgAN in the α1KIC-D89Tg mice following oral antibiotic treatment our group, indicating that the microbiota is directly implicated in disease development. This again opens new avenues for understanding the disease pathophysiology and for future treatments by modulating human microbiota.

Although preclinical testing of a drug in an animal model is not a prerequisite for regulatory agencies before entering clinical trials, it unquestionably provides valuable data on the expected clinical performance of the drug. Inclusion of safety parameters in animal models will help to build the required safety data package of drugs in development. Finally, our experience brings encouragement for new procedures seeking to introduce key disease-driven pathogenic factors in the mouse to generate valuable humanized spontaneous models of human diseases. ◘

References

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02. J Am Soc Nephrol 2016;27:2622–9
03. Kidney Int 2015;88:276–85.

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