Editorial

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KIDNEY RESEARCH AND CLINICAL PRACTICE

Biomarker for recurrent immunoglobulin A nephropathy in kidney allografts: promising but still a long way to go

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Immunoglobulin A (IgA) nephropathy (IgAN), the most common primary glomerulonephritis worldwide, frequently leads to end-stage renal disease, which requires renal replacement therapy, including kidney transplantation (KT). Recurrence of IgAN after KT was reported to range from 35% to 60%, with a graft loss rate of 7%–10 % [1]. Diagnosis of recurrent IgAN is dependent upon a pathologic diagnosis by an invasive allograft biopsy, and no effective noninvasive methods have been successfully proposed. In this regard, the KDIGO guidelines for care of KT recipients recommend screening for IgAN recurrence using urinalysis and kidney function tests [2]. KT recipients await serological biomarkers for a noninvasive determination of recurrence or severity of IgAN in kidney allograft. To discuss the possibility of biomarkers for recurrent IgAN in kidney allograft, we need to understand the proposed mechanism of development of IgAN. IgAN is characterized by IgA deposits in the kidney, resulting in mesangial cell proliferation, extracellular matrix expansion, and inflammation, finally progressing to fibrosis. Although the origin of the disease is under investigation, aberrantly glycosylated IgA1 might be a key element in the pathogenesis of the disease [3]. Defective galactosylation can lead to self-polymerization of IgA1 and facilitate its deposition in the kidney. An autoimmune response against the galactose-deficient (Gd) IgA1 molecule is initiated, with production of glycan-specific immunoglobulin G (IgG) or IgA autoantibodies. Therefore, IgAN can be caused by immune complex deposition resulting from generation of IgG and IgA antibodies to aberrant nonglycosylated IgA1 [3]. Based on this information, serum levels of "Gd-IgA1," "Gd-IgA1-specific IgG and IgA," and "its related immune complexes" have been proposed as biomarkers for progression of IgAN in the native kidney [4]. A study by Berthoux et al. [5] analyzed serum samples from 97 patients with IgAN, 30 healthy volunteers, and 30 patients with non-IgAN disease. The study found that the level of the putative antigen anti-glycosylated IgA1 correlated with the disease process in the native kidney.

It has been suggested that this hypothesis for pathogenesis of IgAN can be adapted to an allograft [6]. Therefore, these serological biomarkers might be suitable for characterization of the stage of recurrent IgAN in kidney allografts. To date, four reports (including the current study [7]) investigated the role of serum Gd-IgA1 or its related autoantibody/immune complexes for prediction of recurrent IgAN in a kidney allograft (Table 1). Berthelot et al. [8] reported the predictive

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Table 1. Published reports of serologic biomarkers for recurrent IgAN after KT

Study	Year	Patient group	Measured biomarker	Sampling time	Observation period (yr)	Result
Berthelot et al. [8]	2015	38 KTRs (recurrence)	Serum Gd-IgA1	At transplant	8.7 ± 2.5	All three markers predicted recurrence of IgAN
		22 KTRs (non-recurrence)	IgG anti-IgA autoantibodies			
		17 HCs	IgA-soluble CD89 complexes			
Berthoux et al. [9]	2017	96 KTRs	Serum Gd-IgA1	At diagnosis of IgAN (pretransplant),	12.4 ± 6.1	Only IgG predicted clinic-pathologic recurrence of IgAN
		30 HCs	IgA1-specific IgG and IgA autoantibody	At transplant		
Temurhan et al. [10]	2017	18 KTRs (recurrence)	Serum Gd-IgA1	Posttransplant	7.0 ± 3.0	Serum Gd-IgA1 predicted recurrence of IgAN
		23 KTRs (non-recurrence)				
		44 non-KT IgAN patients				
		11 HCs				
Park et al. [7]	2021	14 KTRs (recurrence)	Serum Gd-IgA1	Posttransplant	12.8 ± 7.0	Serum Gd-IgA1 predicted recurrence of IgAN
		13 KTRs (non-recurrence)				

Gd-IgA1, galactose-deficient immunoglobulin A1; HC, healthy controls; IgAN, immunoglobulin A nephropathy; IgG, immunoglobulin G; KT, kidney transplant; KTR, KT recipient.

value of Gd-IgA1 for IgAN recurrence in allograft kidneys for the first time. They analyzed three markers, Gd-IgA1, IgG anti-IgA autoantibodies, and IgA-soluble CD89 complexes, using serum obtained at pretransplant in 38 KT recipients, and their results showed that all three markers significantly predicted disease recurrence. In another study by Berthoux et al. [9] the prognostic significance of the levels of Gd-IgA1 autoantigen and Gd-IgA1–specific IgG and IgA autoantibodies in serum obtained at the time of transplant or native-kidney IgAN diagnosis was assessed for clinicopathologic recurrence, allograft failure, and patient death over 10 years. Compared to healthy controls, the patients had significantly elevated serum Gd-IgA1 level at diagnosis and transplant, but the level was not associated with any outcomes, including IgAN recurrence. In contrast, the level of serum Gd-IgA1–specific IgG autoantibodies at transplant was associated with a higher risk of recurrence. In contrast to previous studies that used samples at pretransplant or at transplant, a more recent study [10] measured serum Gd-IgA1 level at a mean time of 51 ± 29 months after KT. As a result, the level of Gd-IgG1 in recurrent IgAN patients was significantly higher than those in nonrecurrent IgAN patients or healthy controls. In a current study, Park et al. [7] enrolled 27 KT recipients who underwent allograft biopsy and measured the serum Gd-IgA1 level using serum collected at the allograft biopsy. The mean serum Gd-IgA1 level was significantly higher in the recurrent IgAN group than in the nonrecurrent IgAN group, and serum Gd-IgA1 level was an independent factor predicting IgAN recurrence. They concluded that serum Gd-IgA1 could be used as a diagnostic biomarker for recurrent IgAN in KT.

All the above studies found that serum Gd-IgA1 or its related autoantibody level showed significance in predicting recurrent IgAN in kidney allograft. However, many obstacles must be overcome or clarified before these biomarkers can be applied in clinical practice. First, the previous studies used Gd-IgA1 level at specific time points including pretransplant, at KT, or at allograft biopsy. Thus, the dynamics of Gd-IgA1 level during the posttransplant period and their association to IgAN recurrence after KT were not shown. Therefore, it is unclear whether Gd-IgA1 level remained high and induced IgAN recurrence, or whether it was low but became high at the time of recurrence. To clarify this issue, longitudinal assessment in a prospective cohort should determine the prototypical course of Gd-IgA1 level and its association with clinicopathologic recurrence of IgAN in allograft. Second, most studies did not show an association between Gd-IgA1 level and clinical outcomes, such as al-

lograft failure, even though it was useful in predicting IgAN recurrence. Perhaps an association was not demonstrated because previous studies were performed in a relatively small-sized patient group. If there is no correlation with allograft survival, the need for biomarkers will be halved. Furthermore, an effective therapeutic strategy for recurrent IgAN has not been established. Hence, strategies to improve allograft outcomes when recurrent IgAN is suspected based on high Gd-IgA1 level remain unclear. All KT patients receive strong maintenance immunosuppression, so few other treatments can be added in recurrent IgAN. Hence, new therapeutic agents to change the clinical outcomes need to be developed to maximize the effectiveness of biomarkers for recurrent IgAN. Lastly, the assay method needs to be standardized. In earlier studies, serum Gd-IgA1 level was measured by lectin enzyme-linked immunosorbent assay using *Helix aspersa* agglutinin, a lectin that binds to terminal galactosyl-*N*-acetylamine residues [7,8]. In contrast, the current study [7] and the study by Temurhan et al. [10] used a lectin-independent Gd-IgA1 assay (Immuno-Biological Laboratories Co., Ltd., Gunma, Japan). In addition, the significant level associated with IgAN recurrence was different between the studies. Therefore, standardization of measurement methods to overcome inter- or intralaboratory disparity should be achieved.

In summary, theoretically, serum Gd-IgA level has potential as a biomarker for recurrent IgA nephropathy. Areas that require further investigation, however, include an understanding of IgAN recurrence, especially the dynamics during the posttransplant period, and the effectiveness of serum Gd-IgA level for predicting allograft survival. A prospective multicenter study including serial protocol biopsies and measurement of serum Gd-IgA1 level by nephrologists involved in KT should further clarify these issues.

Conflicts of interest

The author has no conflicts of interest to declare.

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