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Editorial

Rituximab can Decrease Proteinuria in Refractory Lupus Nephritis

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Recently, there is good news for the patients with lupus nephritis (LN), which the US Food and Drug Administration approved 2 medications (belimumab and voclosporin) for the treatment of active LN [1]. Two new drugs showed better renal response than placebo in the LN patients in addition to standard therapy (steroids and such as mycophenolate mofetil (MMF) and low-dose cyclophosphamide) with favorable safety profiles [2,3]. However, the primary efficacy renal response (a ratio of urinary protein to creatinine (UPCR) of ≤0.7, preserved estimated glomerular filtration, and no use of rescue therapy) is only 43% in 104 weeks of the belimumab treatment with standard therapy [2] and the complete renal response (a UPCR ≤0.5 mg/mg, stable renal function, and no administration of rescue medication) is 41% in 52 weeks of the voclosporin treatment with standard therapy [3]. Therefore, there is still a need of medication for the treatment of patients with LN.

Considering the key role that B lymphocytes play in the pathogenesis of the LN, the chimeric monoclonal anti-CD20 antibody (rituximab) has been studied in many observational studies and one randomized controlled trial (RCT) of patients with LN. Generally, the metanalysis of observational studies showed consistent clinical benefit with good response rate (40% complete response and 34% partial response) in refractory LN [4]. However, the only large RCT failed to meet primary endpoint [5]. In spite of this discouraging result, rituximab has been recommended for the patients with refractory LN in the guidelines of the joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association [6]. In addition, recent meta-analysis revealed clear beneficial effects of rituximab in patients with refractory LN [7].

A recent article by Choi et al. [8] published in the *Journal of Rheumatic Disease* report the experience of rituximab treatment for the patients with refractory or relapsing LN in a single tertiary referral hospital in Korea. Among 22 patients with LN treated with rituximab, 10 patients (45.5%) and 12 patients (54.5%) achieved renal response (complete or partial) at 6 months and 12 months, respectively. When the patients with LN were compared according to the glomerular filtration rate (GFR), the renal response rate at 12 months was higher in patients with normal GFR (≥90 mL/min/1.73 m^2) than those with decreased GFR (90.9% vs. 18.2%, p<0.001). It is interesting and understandable, however there are several unbalanced findings. First, the refractory LN is more frequent in patients with decreased GFR. Second, although the use of immunosuppressant is not different statistically, cyclophosphamide was used only in patients with decrease GFR, and MMF and Tacrolimus were more commonly used in patients with normal GFR before the start of rituximab. Third, the UPCR is much higher in the patients with decreased GFR than those with normal GFR (3,110 mg/mg vs. 1,275 mg/mg, p=0.008). Fourth, two patients with decrease GFR were treated with lower dose than standard dose of rituximab therapy. Fifth, the concomitant treatments with rituximab therapy were different with more MMF and tacrolimus in patients with normal GFR. Probably, these unbalanced

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characteristics of patients explain the better renal response in patients with normal GFR.

Currently, there are no useful biomarkers that allow us to predict the prognosis of patients with LN [9]. Numerous serum and urine biomarkers have been proposed, however their predictive value is poor because of the vast heterogeneity across studies [10]. Recently, there are reports about the biomarker to predict response to rituximab treatment, which suggest the combination of serum S100A8/A9 and S100A12 or a panel of six urinary proteins (lipocalin-like prostaglandin D synthase, transferrin, alpha-1-acid glycoprotein, ceruloplasmin, monocyte chemoattractant protein-1 and soluble vascular adhesion molecule-1) can predict response to rituximab treatment [11,12]. Choi et al. [8] reported that the positive anti-La antibody was associated with good renal response of rituximab therapy. However, only 3 patients among 22 patients had positive anti-La antibody, which is too small to deliver clinical significance.

Although the development of new medication for the treatment of LN is accelerated with 2 new drugs approved and several promising candidates in the late development stage, old drug like rituximab is effective to decrease proteinuria in the patients with refractory or relapsing LN.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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