Effect of Prednisolone Therapy on Serum Concentrations of Soluble Interleukin-2 Receptor in Patients with IgA Nephropathy

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Background: It is not known whether steroid therapy affects the serum level of soluble interleukin-2 receptor (sIL-2R) in patients with glomerulonephritis. We therefore examined the relationship between serum level of sIL-2R and indicators of disease activity in patients with immunoglobulin (Ig) A nephropathy, and serum levels of sIL-2R in patients before and after prednisolone therapy.

Methods: Serum sIL-2R levels were determined using an immunoenzymatic technique in 97 patients with IgA nephropathy, and the effects of prednisolone therapy on sIL-2R levels were assessed in 15 patients with IgA nephropathy.

Results: An increased level of serum sIL-2R was shown at the time of renal biopsy in all patients with IgA nephropathy. Moreover, the serum sIL-2R levels were positively correlated with urinary protein excretion ($P<0.01, r=0.32$) and negatively correlated with creatinine clearance ($P<0.01, r=-0.42$) in all patients with IgA nephropathy. Prednisolone therapy (0.8 mg/kg per day) caused a significant reduction in the serum sIL-2R level in accordance with the decrease in daily proteinuria in 15 patients with IgA nephropathy.

Conclusions: These results suggest that the measurement of serum sIL-2R would be useful in evaluating the degree of disease activity, and the serum sIL-2R levels may be a useful indicator for estimating the effect of prednisolone therapy in patients with IgA nephropathy.

Key words: soluble interleukin-2 receptor, IgA nephropathy, prednisolone, creatinine clearance, urinary protein excretion

Immunoglobulin A (IgA) nephropathy has a wide variety of clinical and pathologic features, particularly mesangial IgA deposition. The presence of circulating immune complexes in IgA nephropathy supports the role of an altered humoral immune response to unknown foreign antigens. Moreover, it is now generally held that cellular immunity is hyperactivated in IgA nephropathy.

Interleukin 2 (IL-2) is a polypeptide, produced by activated T cells, that plays a central role in the proliferation of T-effector lymphocytes after antigenic stimulation. The activated T cells express high-affinity receptors for IL-2 (IL-2R). IL-2R is not only expressed on the cell membrane, but is also released into the extracellular fluid as a soluble form of the IL-2R protein (sIL-2R). The release of sIL-2R appears to be a characteristic marker of T-cell activation and seemingly plays a regulatory function during normal and abnormal cell growth and differentiation.

It seems that IL-2 might participate in the pathogenesis of IgA nephropathy. Several authors have reported increased serum levels of sIL-2R in chronic renal failure and various types of glomerulonephritis, including IgA nephropathy. However, it has not been reported whether or not steroid therapy affects the serum level of sIL-2R in patients with glomerulonephritis. We therefore examined the serum levels of sIL-2R in patients with IgA nephropathy before and after prednisolone therapy.

PATIENTS AND METHODS
We studied 97 patients (45 men, 52 women) with a clinical and renal immunopathologic diagnosis of IgA nephropathy, but without clinical or biologic evidence of hepatic or systemic disease. The diagnosis of IgA nephropathy was based on evidence of mesangial proliferative glomerulonephritis with prominent mesangial IgA deposits and the presence of electron-dense deposits in the mesangial area under electron microscopy. The mean patient age was 32.9 ± 8.8 years. Mean daily proteinuria was 1.4 ± 1.2 g/day, and mean number of urinary red blood cells were 44.4 ± 36.8 per high-power
microscopic field. Mean creatinine clearance was 79.3 ± 21.7 mL/min. No patient had renal insufficiency. All patients were clinically quiescent and had been free from infections or macroscopic hematuria for at least 4 weeks before the study. Fifteen patients were taking prednisolone at an initial dose of 0.8 mg/kg body weight per day. Forty healthy individuals, 26 men and 14 women (mean ages; 36.5 ± 6.8 years), were chosen as control subjects. All patients provided informed consent before starting the study.

Patient serum was collected in polypropylene tubes at the time of renal biopsy and stored at −70°C until analysis. Serum sIL-2R concentrations were determined by using the Cell Free IL-2R Test Kit (T Cell Sciences, Cambridge, MA, USA). This kit is a sandwich enzyme-linked immunoassay containing 2 kinds of monoclonal antibodies against Tac epitope on the 55kD IL-2-binding protein (IL-2R). The results are expressed in units per milliliter. The 1000 unit is defined as the amount of sIL-2R present in 1 mL of a T Cell Science's reference preparation of serum for phytohemagglutinin-stimulated pooled peripheral blood mononuclear cell lines.

To determine the clinical significance of the high serum sIL-2R levels observed in patients with IgA nephropathy, we performed a comparative study. We first examined whether or not serum sIL-2R levels could be positively correlated with the grade of daily urinary protein excretion in the entire IgA nephropathy patient group.

All data are expressed as means ± SE. The statistical significance of the results was determined by using either the Mann-Whitney U test or linear regression analysis.

**RESULTS**

The results of this study showed a significantly increased mean serum level of sIL-2R in the 97 patients with IgA nephropathy, compared with the mean serum level in normal subjects (508.5 ± 147.3 U/mL vs. 168 ± 54.2 U/mL, respectively; P < 0.01). Serum sIL-2R levels tended to increase in tandem with the rise in urinary protein excretion in all patients with IgA nephropathy, and a significant positive correlation was found, as shown in Fig. 1 (r = 0.32, P < 0.01). However, there was no correlation between the serum sIL-2R levels and the grade of hematuria (r = 0.21). A negative correlation was observed between serum sIL-2R levels and creatinine clearance at the time of renal biopsy, as shown in Fig. 2 (r = −0.42, P < 0.01).

After 6 months of continuous prednisolone therapy, the 15 patients' serum sIL-2R levels were significantly reduced (P < 0.05), and this change remained constant after up to 12 months of therapy (P < 0.01), as shown in Fig. 3.

In addition, we compared the reduction in serum sIL-2R levels and the change of urinary protein excretion in response to prednisolone therapy (Δ urinary protein excretion), and found a positive correlation, as shown in Fig. 4 (r = 0.68, P < 0.01).