Soluble Interleukin-2 Receptors in the Serum of Patients with Chronic Renal Failure

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Recently, a soluble form of the interleukin-2 receptor (sIL-2R), which binds to IL-2 (Rubin et al. 1986), was found to be released by activated lymphocytes (Rubin et al. 1985). The level of sIL-2R has also been found to be high in the serum of hematologic malignancies such as ATL, hairy cell leukemia, CLL, lymphoma (Greene et al. 1986; Chilosi et al. 1987; Pizzolo et al. 1987b; Semenzato et al. 1987). The high level of sIL-2R has been reported to be linked to poor prognosis of the disease (Pui et al. 1987; Wagner et al. 1987). The sIL-2R of elevated level may block the normal immune system by binding effective IL-2 in these diseases (Pizzolo et al. 1987a). The elevated level of sIL-2R has been presumed to be due to production by malignant cells or enhanced production by activated T-lymphocytes. However, little is known about the catabolism of sIL-2R. To elucidate the influence of renal function on the sIL-2R level, we studied the sIL-2R level in patients with chronic renal failure (CRF).

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PATIENTS AND METHODS

Patients and controls

The serum level of sIL-2R was determined before and after hemodialysis in 29 patients with CRF (chronic glomerulonephritis or chronic pyelonephritis). They included 11 females and 18 males, between 79 and 31 years old (mean 52 years). Most of them had been on dialysis for 5 hr thrice weekly using cellulose dialyzers. The sera from 12 individuals with a normal blood urea nitrogen (BUN) level (10.6–19.0 mg/100 ml) were used as normal controls.

Measurement of sIL-2R, creatinine, BUN and β2-microglobulin

The values of sIL-2R were measured with a sandwich enzyme immunoassay available as the CELLFREE Interleukin-2 Receptor Test Kit (T-cell Science, Inc., Cambridge, MA, USA). At first, a mouse monoclonal antibody to human IL-2R was adsorbed onto a polystyrene microtiter well. Patient’s samples and standard were added to the antibody-coated well and reacted at 37°C and then washed. A second horseradish peroxidase-conjugated murine monoclonal antibody to a distinct epitope of the human IL-2R was added to the well and reacted. After removal of unbound enzyme-conjugated anti-IL-2R by washing, a substrate solution was added to the well. After terminating the reaction by a stop solution (2 N H2SO4), the absorbance was measured. Then the values were plotted on a standard curve. Serum levels of IL-2R are expressed in units per milliliter. A reference preparation of 1,000 U/ml of supernatant from phytohemagglutinin-stimulated peripheral blood lymphocytes was used as a standard.

The serum creatinine, BUN and β2-microglobulin levels were evaluated by using a routine clinical laboratory method.

Statistics

The results were expressed as the mean ± s.d. and the significance of the differences between means was evaluated by the paired and unpaired Student’s t-test for paired and unpaired observations, respectively. The correlation coefficient (r) for each parameter was calculated and significance was evaluated using a t-test. Values of p exceeding 0.05 were not considered to be statistically significant.

RESULTS

In patients with CRF, the serum creatinine value before the hemodialysis was 11.7± 2.9 mg/100 ml and was correlated with the BUN level, 80.9±22.4 mg/100 ml (r=0.42). The serum β2-microglobulin level in these patients was 35.6±11.3 μg/ml (normal range, 0.5–2.0 μg/ml). All the patients had a high sIL-2R level (633–1576 U/ml) and the mean value, 1146±258 U/ml, was significantly higher than the control mean, 288±118 U/ml (p=0.01) (Fig. 1). After hemodialysis the mean creatinine level significantly decreased to 4.9±1.4 mg/100 ml (p=0.01), but the change in sIL-2R level (1163±280 U/ml) was not significant (p >0.05). In the patients with CRF, the correlation between sIL-2R level and creatinine level and that between sIL-2R level and β2-microglobulin level (Fig. 2) were not significant (r = –0.33, p >0.05, r = 0.07, p >0.05, respectively).
Fig. 1. sIL-2R levels in patients with chronic renal failure.
Control, individuals with normal BUN levels; CRF, chronic renal failure;
The difference between means (——) was significant (p = 0.01).

Fig. 2. Correlation between sIL-2R and β2-microglobulin. r = 0.07, p > 0.05.
DISCUSSION

To date the level of sIL-2R has been reported to be elevated mainly in the hematologic malignancies (Pizzolo et al. 1987a). Recently Colvin et al. (1987) reported the elevation of the sIL-2R level in CRF. In this study, we confirmed the increase of sIL-2R in the sera of patients with CRF, and studied further the correlations between the sIL-2R level and other parameters. All patients in this study had undergone hemodialysis. Therefore, to estimate the influence of hemodialysis, we measured the sIL-2R level in the serum before and after the hemodialysis, but found no significant differences. The renal clearance of substance depends on its molecular radius (Arturson and Wallenius 1964; Hulme and Hardwicke 1968). Judging from its molecular weight, 45,000 (Rubin et al. 1985), the glomerular permeability of sIL-2R is not supposed to be so high. However, the elevation of the sIL-2R level in CRF suggests that sIL-2R may be normally catabolized in the kidneys to some degree. The elevation of serum \( \beta_2 \)-microglobulin level in renal failure is well known (Bernier et al. 1968). In this study, no correlation was observed between the levels of sIL-2R and \( \beta_2 \)-microglobulin in patients with CRF. This discrepancy may be due to difference in productive mechanism on the one hand and to the difference in renal clearance between the two substances caused by the difference in molecular weight between \( \beta_2 \)-microglobulin and sIL-2R (11,800 vs. 45,000; Peterson et al. 1969; Rubin et al. 1985) on the other hand. The relation between the disease process of the CRF and the elevation of sIL-2R is unclear. The T-cell activities in renal failure have been reported to be suppressed (Touraine et al. 1975; Kay and Raji 1986). The elevated sIL-2R level may be responsible for the compromised immunoregulation in CRF by binding to effective IL-2, although the demonstration of this hypothesis needs more study about the IL-2 binding capacity in the sera of patients with CRF.

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References