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Plasma Soluble Interleukin-2 Receptor Levels in Patients With Idiopathic Thrombocytopenic Purpura

Erol Erduran,* Yakup Aslan, Yüksel Aliyazıcıoğlu, Hilal Mocan, and Yusuf Gedik

Department of Pediatrics and Biochemistry, School of Medicine, Karadeniz Technical University, Trabzon, Turkey

Soluble interleukin-2 receptor (sIL-2R) was measured in the plasma of 31 patients with idiopathic thrombocytopenic purpura (ITP) and 22 normal controls. When thrombocytopenia persisted longer than 6 months, the diagnosis of chronic ITP was made. Twenty patients had acute ITP, 11 patients had chronic ITP, and all patients received high-dose methylprednisolone (HDMP) (30 mg/kg/d for 3 days, 20 mg/kg/d for 4 days). The sIL-2R levels of the patients were determined before being giving HDMP and 14 days after the end of HDMP therapy. Platelet counts were determined before administration of HDMP, one day after the end of HDMP therapy, and once every 28 days for 7 months thereafter.

There was not a significant difference between the mean pre-treatment plasma sIL-2R levels of both acute and chronic ITP groups ($P > 0.05$), and these were higher than that of the control group ($P < 0.001$). The mean post-treatment sIL-2R level of the chronic ITP group was significantly higher than those of both the control and post-treatment acute ITP groups ($P < 0.001$). There were negative correlations between the plasma sIL-2R levels and platelet counts of both group patients in the pre-treatment period and between post-treatment sIL-2R levels and platelet counts in chronic ITP group ($P < 0.05$).

We think that there was a good correlation between prognosis of ITP and sIL-2R levels after HDMP therapy, and platelet counts in patients with ITP are linked to sIL-2R levels. Am. J. Hematol. 57:119–123, 1998.

Key words: soluble interleukin-2 receptor; idiopathic thrombocytopenic purpura; HDMP therapy

INTRODUCTION

Thymocyte and T-cell activation by antigens and phytohemaglutinin (PHA) stimulates interleukin-2 (IL-2) production [1]. IL-2 has been demonstrated to be important in lymphocyte activation and mobilization [2]. Lymphocytes express maximal levels of high-affinity IL-2 receptors (IL-2R) for only a brief period following exposure to a specific antigen [3]. IL-2R is composed of at least three distinct subunits, designed alpha (α 55 or Tac), beta (β or p 70/75), and gamma (γ). In addition to a cell-associated receptor, a soluble IL-2R (sIL-2R) also exists. The receptors have been assembled on an antibody surface and are held by an epitope engineered into the C-terminus of each of the soluble extracellular domains of IL-2R subunits [4].

Soluble IL-2R levels have been found elevated in diseases associated with T- and B-cell activation. Such conditions include systemic lupus erythematosus (SLE), juvenile chronic arthritis, and multiple sclerosis [5–7]. In addition, sIL-2R also has been found at increased levels in patients with hemotologic diseases associated with lymphocyte activation including chronic lymphocytic leukemia, hairy cell leukemia, acute myeloid leukemia, primary myelofibrosis, hypereosinophylic syndrome, myelodysplastic syndrome, and Hodgkin's lymphoma [8–14].

Immune thrombocytic purpura (ITP) in childhood is a heterogeneous clinical disorder characterized by immune-mediated platelet destruction. Although generally it is considered to involve autoreactive B-lymphocytes, which produce antiplatelet antibodies, there is increasing evidence that T-lymphocytes also play an important role in this autoimmune process [15,16]. The responsible factor for ITP is an immunoglobulin of the IgG class that is species specific. Increased quantities of IgG against gly-

*Correspondance to: Erol Erduran, KTÜ Lojmanları 35/2, 61080, Trabzon, Turkey.

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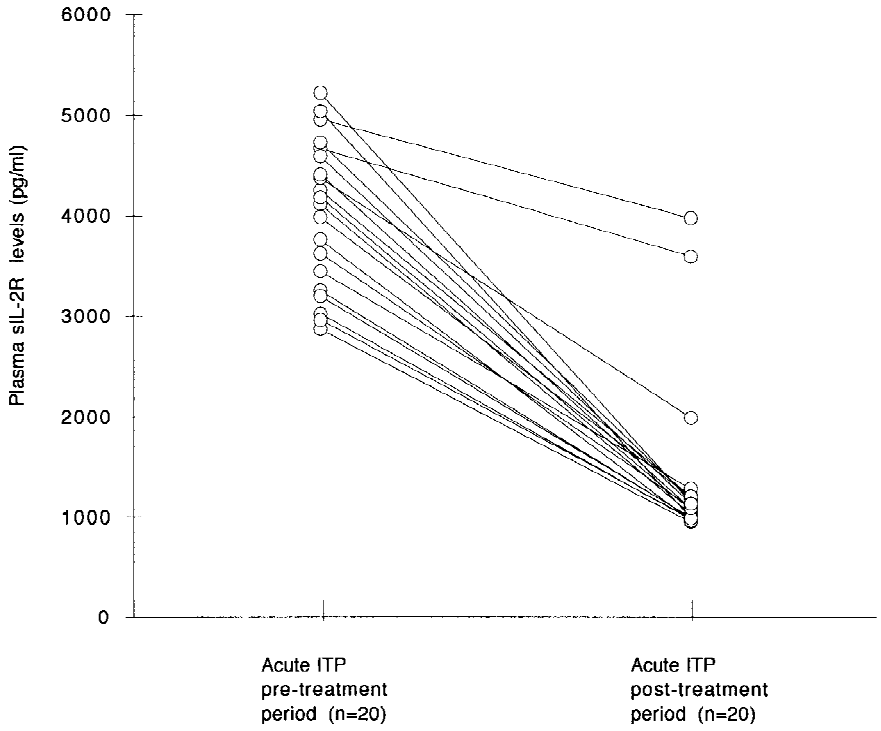

Fig. 1. Plasma sIL-2R (soluble interleukin-2 receptor) levels of the acute ITP group in the pre- and post-treatment periods.

coprotein IIb/IIIa have been demonstrated on the platelet surface (platelet-associated IgG) [17].

In this study, plasma sIL-2R levels were measured in patients with ITP in which lymphocyte activation is responsible for the aetiopathogenesis, and their results were compared to controls without ITP.

MATERIALS AND METHODS

Patient and Diagnostic Criteria

From June 1994 to May 1996, 31 patients with ITP and 22 normal controls were studied. The patients were aged between 3 months and 17 years old, 19 girls and 12 boys. The controls' ages were similar to those of the patients. A diagnosis of ITP was made by physical signs (petechial, purpuric, and ecchymotic skin eruptions), thrombocytopenia (<50,000/μl), increased megakaryocyte in bone marrow, and negative throat culture, LE cell, anti-double stranded DNA (ds-DNA), anti-nuclear antibody (ANA), and direct Coombs test. High-dose methylprednisolone (HDMP) therapy as described by Özsoylu (30 mg/kg/d for 3 days, 20 mg/kg/d for 4 days, before 9 A.M. after breakfast, perorally [18]) was given to the patients for 7 days.

Assay Procedures

Patient and control plasmas were obtained from heparinized blood, after informed consent was obtained, and stored at −70°C until assay. Soluble IL-2R assays were performed using the cytoscreen sIL-2R immunoassay kit (Catalog no: KHR 0022, Lot: 100496, CA). All samples were determined in duplicate. Assay results were expressed as pg/ml. Plasma sIL-2R levels of the patients were determined before giving HDMP therapy and 14 days after the end of HDMP therapy. Platelet counts of the patients were determined at initial period (before administration of HDMP therapy) and one day after the end of HDMP therapy, once every 28 days for 7 months thereafter. When thrombocytopenia persisted longer than 6 months in a patient, the diagnosis of chronic ITP was made.

None of the patients received any thrombocytopenic agent or had malignant or chronic inflammatory or collagen tissue or hematologic disease except for ITP, and viral or bacterial infections.

Statistical Analysis

All values were expressed as mean ± SD (standard deviation). Statistical analyses were performed by using the correlation coefficients test, one-way analysis of variance, Mann-Whitney U-Wilcoxon Rank Sum W, and Wilcoxon Matched-Pairs signed-ranks tests.

RESULTS

Twenty cases had acute ITP, and 11 cases had chronic ITP. Plasma sIL-2R levels of the acute ITP group in both

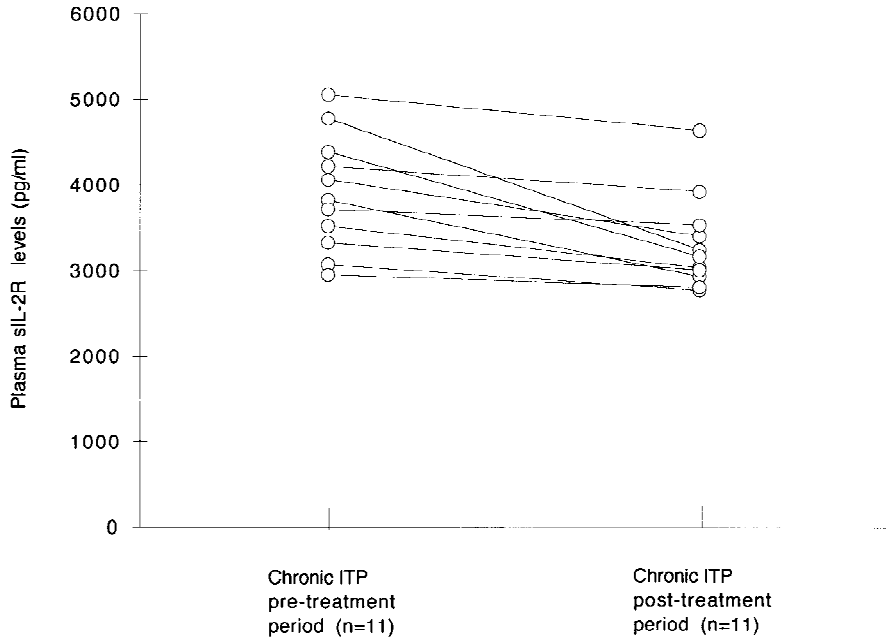

Fig. 2. Plasma sIL-2R (soluble interleukin-2 receptor) levels of the chronic ITP group in the pre- and post-treatment periods.

pre- and post-treatment periods are given in Figure 1. Plasma sIL-2R levels of the acute ITP group in pre- and post-treatment periods ranged from 2,870 to 5,220 pg/ml with a mean ± SD of 4,032 ± 732 pg/ml and ranged from 952 to 3,975 pg/ml with a mean ± SD of 1,395 ± 850 pg/ml, respectively. Plasma sIL-2R levels of the chronic ITP group in both pre- and post-treatment periods are given in Figure 2. Plasma sIL-2R levels of the chronic ITP group in pre- and post-treatment periods ranged from 2,954 to 5,050 pg/ml with a mean ± SD of 3,897 ± 674 pg/ml and ranged from 2,780 to 4,650 pg/ml with a mean ± SD of 3,322 ± 556 pg/ml, respectively. In the control group, sIL-2R levels ranged from 925 to 1,475 pg/ml with a mean ± SD of 1,148 ± 127 pg/ml. Plasma sIL-2R levels of controls and patient groups in the pre- and post-treatment periods are shown in Table I. Three patients in the acute ITP group had higher sIL-2R levels than controls in the post-treatment period. Two weeks later, blood samples of these three patients were drawn again and it was indicated that sIL-2R levels returned to the normal levels.

The mean pre-treatment plasma sIL-2R levels of both acute and chronic ITP groups were not different ($P > 0.05$), and these were higher than that of the control group ($P < 0.001$). Although there was not any significant difference between the mean post-treatment sIL-2R levels of the acute ITP and control groups ($P > 0.05$), the mean post-treatment sIL-2R level of the chronic ITP group was significantly higher than those of both the control and post-treatment acute ITP groups ($P < 0.001$). There were significant decreases in the mean sIL-2R levels in the post-treatment period compared to the pre-treatment period of both acute ITP and and chronic ITP groups ($P < 0.001$ and $P < 0.05$, respectively).

TABLE I. sIL-2R Levels of All Patients and Controls*

		sIL-2R level (pg/ml) (min-max)	
		Pre-treatment period	Post-treatment period
Acute ITP (n = 20)		4,032 ± 732[a] (2,870–5,220)	1,395 ± 850[b] (952–3,975)
Chronic ITP (n = 11)		3,897 ± 674[c] (2,954–5,050)	3,322 ± 556[d] (2,780–4,650)
Controls (n = 22)	1,148 ± 127[e] (925–1,475)		

*The values are expressed as mean ± SD. $P < 0.001$: a-b, a-e, b-d, c-e, d-e; $P < 0.05$: c-d; $P > 0.05$: a-c, b-e.

TABLE II. Platelet Counts of All Patients*

	Platelet count/μl (min-max)		
	Pre-treatment period	Post-treatment period	*P*
Acute ITP (n = 20)	14,010 ± 11,245 (1,000–36,000)	325,750 ± 9,363 (190,000–510,000)	<0.001
Chronic ITP (n = 11)	11,109 ± 9,470 (1,000–31,000)	18,572 ± 11,661 (5,000–41,000)	<0.05
P	>0.05	<0.001	

*The values are expressed as mean ± SD.

Platelet counts of the patients with acute and chronic ITP in the pre- and post-treatment periods are shown in Table II. The post-treatment platelet counts of both

groups were significantly higher than those of the pre-treatment platelet counts ($P < 0.05$). Although the pre-treatment platelet counts of both groups were not significantly different ($P > 0.05$), the mean platelet count of the acute ITP group was significantly higher than that of the chronic ITP group in the post-treatment period ($P < 0.001$). There were negative correlations between the plasma sIL-2R levels and platelet counts of both the acute and chronic ITP patients in the pre-treatment period ($r = -0.604$, $P < 0.05$; $r = -0.788$, $P < 0.05$, respectively) and between the post-treatment platelet counts and sIL-2R levels in the chronic ITP group ($r = -0.648$, $P < 0.05$).

DISCUSSION

The results of this study indicate that the mean sIL-2R levels of both group patients in the pre-treatment period were significantly higher than those of the post-treatment period and control.

These data suggest that T-cell activation may play a role in the development of ITP. In previous studies for ITP, it was suggested that patients with ITP might have platelet-reactive T-lymphocytes identifiable at the clonal level, and autoreactive peripheral T-lymphocytes might mediate or participate in the pathogenesis of ITP [19]. Koyanagi et al. [20] suggested that the lymphocyte blastogenic response to PHA pokewood mitogen and conconavalin was depressed in patients with ITP. The increased proportion of CD_5 B-cell in peripheral blood and spleen had been determined and it was suggested that they directly involved in the autoimmune pathogenesis of ITP [21]. We think that T-cell activation in patients with acute ITP was more depressed than those of chronic ITP patients after HDMP therapy because sIL-2R levels in patients with acute ITP were more decreased than those in patients with chronic ITP in the post-treatment period.

The levels of sIL-2R also are found to be correlated with disease activity in patients with rheumatoid arthritis, SLE, Graves' disease, and pulmonary tuberculosis in which diseases had T-cell lymphocyte activation [3,22–24]. It was suggested that sIL-2R levels were significantly correlated to survival of patients with primary myelofibrosis [11] and chronic lymphoid leukemia [8].

In this study, there was a good correlation between prognosis and plasma levels of sIL-2R after HDMP therapy, because chronic ITP had been developed in patients whose sIL-2R levels were not returned to the normal levels after HDMP therapy. We speculate that platelet counts in patients with ITP are linked to sIL-2R levels because there were negative correlations between the plasma sIL-2R levels and platelet counts of both group patients in the pre-treatment period and of chronic ITP patients in the post-treatment period.

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