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Research report

Effects of symptomatic severity on elevation of plasma soluble interleukin-2 receptor in bipolar mania

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Abstract

Background: Circulating soluble interleukin-2 receptors (sIL-2Rs) and soluble interleukin-6 receptors (sIL-6Rs) are stable immune measures. Elevated plasma sIL-2R levels are present in patients with schizophrenia, major depression, and bipolar mania, but not with minor psychiatric disorders. The increased plasma sIL-2R levels are state-dependent in bipolar mania. However, altered production of plasma sIL-6R and the effects of clinical characteristics on plasma sIL-6R and sIL-2R levels in bipolar disorder remains uncertain. *Methods:* Plasma sIL-2R and sIL-6R levels were measured in 31 Taiwanese bipolar manic (DSM-IV) patients with Young Mania Rating Scale (YMRS) scores of ≥ 26 as well as during the subsequent remission (YMRS ≤ 12), and equal numbers of age- and gender-matched healthy controls. The relationships of clinical variables such as age, age of onset, smoking, medication status, coexisting psychotic features, number of prior episodes, duration of illness, presence of depression before or following the manic episode, and manic severity to plasma sIL-2R and sIL-6R levels in acute mania along with remission were examined. *Results:* Plasma sIL-2R but not sIL-6R levels were significantly higher in acute mania than in subsequent remission ($P < 0.05$) and controls ($P < 0.0005$). In acute mania, the plasma sIL-2R levels were significantly correlated to YMRS scores ($r = 0.34$, $P < 0.05$). The remaining clinical variables had no effect on plasma sIL-2R and sIL-6R levels in acute mania or remission. There was a significantly positive relationship between the reduction of plasma sIL-2R levels from the acute to follow-up measurements (ΔsIL-2R) and symptomatic improvement of acute mania (ΔYMRS) ($r = 0.61$, $P < 0.001$). *Limitations:* Our sample included medicated and unmedicated patients in acute mania. The psychotropic medication may have divergent effects on the plasma sIL-2R levels in acute mania and subsequent remission. *Conclusions:* Elevation of plasma sIL-2R but not sIL-6R levels in bipolar mania supports the idea that the immunomodulatory mechanism may vary in different psychotic disorders. In contrast to being a trait marker in schizophrenia and depressive disorder, plasma sIL-2R levels may be considered a biological indicator of manic severity in a group of bipolar affective patients. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Bipolar disorder in Taiwan; Severity of mania; Soluble interleukin-2 receptors (sIL-2R); Soluble interleukin-6 receptor (sIL-6R)

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1. Introduction

A pathophysiological role of the immune system has been suggested in various psychiatric disorders. There is increasing evidence that schizophrenia (Ganguli and Rabin, 1989; Rapaport et al., 1994a; Hornberg et al., 1995; Maes et al., 1995a; Müller et al., 1997b), major depression (Maes et al., 1995b; Sluzewska et al., 1996), and bipolar mania (Maes et al., 1995a; Tsai et al., 1999a) are characterized by activation of the inflammatory response system (IRS) with increased levels of plasma soluble interleukin-2 receptor (sIL-2R). Likewise, major depression may be accompanied by an increased secretion of interferon-gamma (IFN-γ) (Maes et al., 1994b). Decreased production of IFN-γ was observed in different subtypes of schizophrenia (Wilke et al., 1996), and bipolar affective patients in acute mania along with their subsequent remission (Leu et al., 1998). However, increased plasma soluble interleukin-6 receptor (sIL-6R) levels are found in schizophrenia (Maes et al., 1995a) as well as major depression (Maes et al., 1995b; Sluzewska et al., 1996), but not in bipolar mania (Tsai et al., 1999a). Though plasma levels of sIL-2R may vary with race and environmental influences such as smoking in healthy humans (Tollerud et al., 1994), the circulating sIL-2Rs and sIL-6Rs are more stable immune markers and are readily measured in plasma. Thus, it has been suggested that these immune modulators may vary in different psychotic disorders (Tsai et al., 1999a).

Interestingly, elevation of plasma sIL-2R levels is not present in minor psychiatric disorders, such as panic disorder (Rapaport and Stein, 1994a), social phobia (Rapaport and Stein, 1994b), obsessive compulsive disorder (Maes et al., 1994a), post-traumatic stress disorder (Spivak et al., 1997), anorexia nervosa (Nagata et al., 1999), or stress-induced anxiety (Song et al., 1999). The significant elevation of sIL-2R levels represents a state-dependent effect in bipolar disorder (Rapaport, 1994; Tsai et al., 1999a). Therefore, following our previous report that PHA-induced lymphocyte proliferation in acute mania is significantly higher than that in remission (Tsai et al., 1999a), more data are needed to explore the relationships between plasma sIL-2R levels and bipolar disorder.

Gender, age, and medication status may not affect the plasma levels of sIL-2R and sIL-6R levels in bipolar disorder (Rapaport, 1994; Maes et al., 1995a; Tsai et al., 1999a), yet little is known about the effects of the clinical characteristics of bipolar disorder such as age of onset, presence of psychotic features, length of illness, number of prior episodes, and symptomatic severity on plasma sIL-2Rs and sIL-6Rs. Furthermore, the results of studies investigating plasma sIL-6R levels in bipolar mania are not consistent (Maes et al., 1995a; Tsai et al., 1999a). It is hypothesized that the immune-modulators play a role in bipolar mania. The purposes of this study were: (1) to re-investigate plasma sIL-2R and sIL-6R levels in acute mania along with remission of bipolar disorder with a larger sample size of patients and (2) to examine the influences of the aforementioned clinical characteristics of bipolar disorder on these two immune modulators. The present sample is independent from our prior work (Tsai et al., 1999a) and represents an attempt to replicate and extend the findings of that study.

2. Methods and materials

2.1. Subjects

Acute in-patients meeting the DSM-IV diagnostic criteria for bipolar disorder, manic with Young Mania Rating Scale (YMRS, Young et al., 1978) scores of ≥ 26, and aged ≤ 45 years were invited to participate. They were rated and diagnosed by two senior psychiatrists with a well-validated semi-structural schedule for Taiwanese psychiatrists, the Psychiatrist Diagnostic Assessment (PDA) (Hwu and Yang, 1988) that has been successfully used in bipolar research and described extensively elsewhere (Tsai et al., 1997, 1999b). Clinical data were obtained to make a diagnosis for patients by evaluating all available information, including family members' confirmation and review of medical records. Patients with mixed episode or comorbid with other Axis I psychiatric disorders (e.g., substance abuse) were excluded. After written informed consent was obtained, blood samples were taken the next morning. Follow-up blood samples of the same manic patients were collected while in subsequent remission

(YMRS scores of ≤ 12 and free from any sign of depression), usually before their discharge. During the index hospitalization, all patients were treated with lithium, and typical antipsychotics (haloperidol or chlorpromazine) were given when clinically indicated.

Age- and gender-matched healthy control subjects were recruited from our hospital staff, medical students, and a youth fellowship of a Presbyterian church. All healthy controls were personally interviewed and screened by a well-validated Chinese version of the General Health Questionnaire to detect current cases of psychiatric disturbance, with those scoring greater than four being excluded (Cheng and Williams, 1986).

Patients and control subjects were screened by physical examination, complete blood counts with differentials, serum enzyme and metabolite screening, urine analysis, and thyroid function tests. All subjects had shown no symptoms of chronic or acute infection, allergies, past history of autoimmune diseases, or any other condition known to affect the immune system for at least 2 weeks before the study.

2.2. Clinical variables

Clinical features well recognized in the history of the illness were collected for analysis including continuous variables (age, age at onset, length of illness, number of prior episodes, length of psychotropic medication before blood sampling, plasma lithium level, CPZ equivalents [mg chlorpromazine/day], and YMRS scores); and categorical variables (sex, past history of major depression, smoking, presence of depression before or following the index manic episode, co-existing psychotic features [delusions or hallucinations], and smoking.)

2.3. Assays

Following an overnight fasting from 2400 h the preceding night, venous blood samples were withdrawn between 0830 and 0930 h to control for circadian rhythms. Heparinized blood was drawn by venous puncture. Plasma was collected and frozen at -70°C until use.

According to the manufacturer's instructions, the plasma levels of sIL-2R and sIL-6R were measured in duplicate using commercial enzyme-linked immunosorbent assays purchased from BioSource International (Camarillo, CA, USA) and R&D Systems, (Minneapolis, MN, USA), respectively. Assays of sIL-2R and sIL-6R levels in bipolar individuals during acute mania as well as remission and healthy controls were carried out at the same time and in the same run. The limits of detection were 125 pg/ml for sIL-2R and 31.2 pg/ml for sIL-6R. The intra- and inter-assay coefficients of variation (CV) according to the manufacturer for sIL-2R were lower than 6 and 9%; and the intra- and inter-assay CV values for sIL-6R were lower than 9 and 7%, respectively.

2.4. Statistical analyses

Immune parameters were compared between mania and subsequent remission in bipolar individuals by using the analysis of variance (ANOVA) for repeated measures followed by paired *t*-test, as appropriate; with *t*-test for bipolar patients and normal controls. Among bipolar patients in mania and subsequent remission, Pearson's product–moment correlations were used to examine the relationship of continuous clinical features to plasma levels of sIL-2R and sIL-6R. Furthermore, Wilcoxon's nonparameteric test or *t*-test was used to compare plasma sIL-2R and sIL-6R levels with each categorical clinical feature as the independent variable. Finally, to investigate the contribution of clinical variables to plasma sIL-2R and sIL-6R levels, stepwise multiple regression analyses were undertaken. Pearson correlations and stepwise multiple regression were also used to assess the association of clinical variables to changes of sIL-2R values (ΔsIL-2R, Δ = mania − remission values) as well as ΔsIL-6R during the current episode.

3. Results

Fifteen male and 16 female manic patients with a mean age of 31.9 years (S.D. = 10.0) and 31 (15 male and 16 female) healthy controls with a mean age of 33.1 years (S.D. = 8.7) participated in the study. Table 1 displays continuous variables of clinical characteristics in the acute mania and subsequent remission. The plasma sIL-2R levels in

Table 1
The clinical characteristics of bipolar subjects

Continous variables	Mean (S.D.)
Age at illness onset (years)	24.0 (8.8)
Number of prior episodes	4.7 (3.1)
Length of medication (days)	
Acute mania	11.4 (16.9)
Subsequent remission	62.3 (30.6)
Scores of YMRS in blood sampling	
Acute mania	33.6 (4.5)
Subsequent remission	3.8 (3.9)
CPZ equivalent (mg chlorpromazine/day)[a]	
Acute mania	313.8 (306.4)
Subsequent remission	168.7 (224.7)
Plasma Li level (mEq/l)[b]	
Acute mania	0.19 (0.27)
Subsequent remission	0.65 (0.36)

[a] $Z = 2.12$, $P < 0.025$.
[b] $Z = 5.67$, $P < 0.0005$.

subgroups with various categorical variables of clinical characteristics are given in Table 2.

In acute mania, plasma sIL-2R levels in 74.2% (18 medicated and 5 drug-free patients) of bipolar subjects were detectable. There were five patients (16.1%) whose plasma sIL-2R levels in subsequent remission were higher than in acute mania; four of them had detectable plasma levels of sIL-2R in acute mania. The mean plasma sIL-2R levels of bipolar patients in acute mania (210.7±212.8 pg/ml) was significantly higher than that in subsequent remission (170.4±200.8 pg/ml) (paired $t = 2.05$, df = 30, $P < 0.05$) and was also higher than that of the control subjects (75.6±123.3 pg/ml) ($Z = 3.81$, $P < 0.0005$).

In acute mania, there were 13 patients free of any psychotropic agents for at least 2 weeks whose mean plasma sIL-2R levels (87.0±111.2 pg/ml) were similar to that of normal controls (75.6±123.3 pg/ml) and significantly lower than that (300.1±225.8

Table 2
Plasma levels of soluble interleukin-2 receptor (sIL-2R) in subgroup with various clinical characteristics in bipolar patients

Categorical variables	Acute mania sIL-2R (S.D.) (pg/ml)	Subsequent remission sIL-2R (S.D.) (pg/ml)
Drug-free for 2 weeks		
Yes ($N = 13$)	87.2 (111.2)	–
No ($N = 18$)	75.6 (123.3)	–
Sex		
Male ($N = 15$)	194.1 (39.8)	169.9 (231.0)
Female ($N = 16$)	219.2 (66.3)	160.9 (175.0)
Coexisting delusion or hallucination		
Yes ($N = 16$)	187.1 (178.0)	172.7 (176.5)
No ($N = 15$)	230.7 (257.0)	157.7 (237.0)
History of major depression		
Yes ($N = 13$)	243.5 (270.9)	174.0 (248.8)
No ($N = 18$)	183.4 (174.0)	160.1 (174.4)
Smoking		
Yes ($N = 9$)	200.4 (143.1)	165.9 (160.9)
No ($N = 22$)	210.5 (243.3)	165.6 (222.7)
Depressive symptoms before or following the index mania		
Yes ($N = 7$)	343.6 (252.1)[a]	252.5 (244.5)
No ($N = 24$)	159.1 (190.4)[a]	139.3 (187.3)

[a] Wilcoxon rank-sum test, $Z = 1.93$, $P = 0.055$.

pg/ml) of medicated patients (Wilcoxon rank-sum test, $Z = 2.65$, $P < 0.01$). The plasma levels of sIL-2R were undetectable in 23 (74.2%) normal controls and 7 drug-free manic patients in acute mania along with subsequent remission.

During the index manic episode, 29 patients (93.5%) were treated with lithium and antipsychotics. Analyses were conducted to examine the possible relationship between medication status and plasma sIL-2R levels in all bipolar patients. No significant correlation was found between plasma sIL-2R levels and length of medication (acute mania: $r = 0.32$, $P = 0.18$; remission: $r = 0.10$, $P = 0.65$), lithium levels (acute mania: $r = 0.10$, $P = 0.59$; remission: $r = 0.07$, $P = 0.78$), or CPZ equivalents (acute mania: $r = 0.51$, $P = 0.13$; remission: $r = 0.35$, $P = 0.15$). There was no significant relationship between YMRS scores and lithium levels (acute mania: $r = 0.17$, $P = 0.37$; remission: $r = 0.01$, $P = 0.97$), or CPZ equivalents (acute mania: $r = 0.01$, $P = 0.50$; remission: $r = 0.09$, $P = 0.97$). In the acute mania, the medicated patients were divided into three groups based on the length of medication: ≤ 7 days ($N = 2$), 8–14 days ($N = 8$), and ≥ 15 days ($N = 8$). Mean plasma sIL-2R levels (415.4±269.1 pg/ml) in the 8–14-day medication group were higher than those in the other two groups (≤ 7-day group: 205.1±132.7 pg/ml; ≥ 15-day group: 208.5±146.7 pg/ml), but this increase did not reach statistical significance ($F = 2.16$, df = 2/15).

Out of the other continuous variables including age, age at onset, length of illness, number of prior episodes, and YMRS scores, only symptomatic severity of mania (YMRS scores) was positively correlated with plasma sIL-2R levels in acute mania ($r = 0.34$, $P < 0.05$) (Fig. 1). None of these variables was correlated to plasma sIL-2R levels in subsequent remission. Moreover, out of the categorical variables (Table 2), patients ($N = 7$) with depressive symptoms before or following the manic episode had non-significantly higher mean plasma sIL-2R levels in acute mania than those ($N = 24$) without depression. With plasma sIL-2R levels in acute mania as the dependent variable, the YMRS scores and the presence of depression before or following the index mania were entered into a multivariate regression. However, stepwise multiple regression analyses revealed that plasma sIL-2R levels in acute mania were not significantly predicted by any clinical variable.

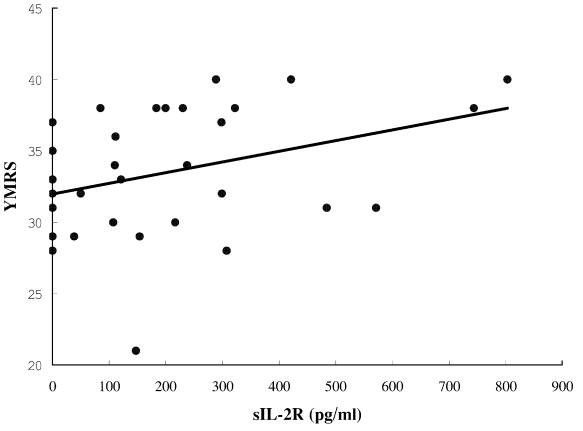

Fig. 1. Relationship between plasma sIL-2R levels and manic severity (YMRS scores) in bipolar mania ($\gamma = 0.34$; $P < 0.05$).

The plasma sIL-6R levels, in either acute mania (45.1±9.6 ng/ml) or remission (45.3±10.5 ng/ml), showed no significant difference between bipolar patients and control subjects (43.6±6.3 ng/ml). There was no significant difference in mean plasma sIL-6R levels between medicated patients (46.0±9.8 ng/ml) and unmedicated ones (43.7±9.2 ng/ml) in acute mania, neither was there between manic patients with (45.4±9.9 ng/ml) and without (44.6±9.2 ng/ml) psychotic features. Furthermore, the sIL-6R plasma levels in either acute mania or subsequent remission had no significant association with any clinical variable.

The possible influences of age, age of onset, number of episodes, length of illness, length of medication, change of daily antipsychotics dose (ΔCPZ equivalent), the improvement of symptomatic severity (ΔYMRS), and length from the first investigation to reinvestigation on the change of sIL-2R values (ΔsIL-2R) were also examined. Among these variables, only ΔYMRS was significantly correlated with ΔsIL-2R ($r = 0.61$, $P < 0.001$) (Fig. 2). There was no correlation between ΔsIL-6R and any one of those clinical variables. Furthermore, a stepwise multiple regression analysis showed that ΔYMRS accounted for 36.8% of the variance in

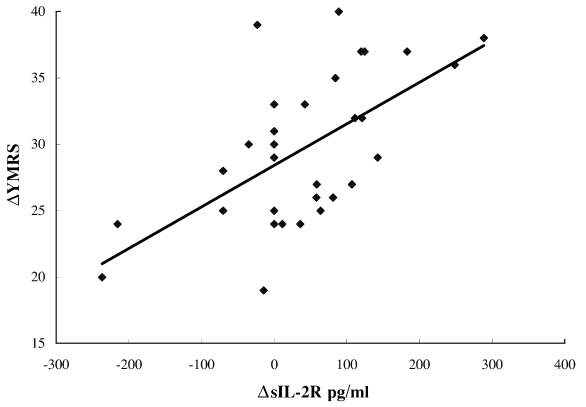

Fig. 2. Relationship between the change of plasma sIL-2R levels (ΔsIL-2R) and the reduction of YMRS scores (ΔYMRS) in remission of bipolar disorder ($\gamma = 0.61$; $P < 0.001$).

ΔsIL-2R (standardized beta = 4.109, $F = 16.88$, $P < 0.001$).

4. Discussion

To our knowledge, this is the first study to examine the influence of clinical characteristics on plasma levels of sIL-2R along with sIL-6R in bipolar mania and subsequent remission. In contrast to schizophrenia (Hornberg et al., 1995) and depressive disorder (Maes et al., 1995b; Sluzewska et al., 1996) with increased sIL-2R levels as a trait marker, one major finding is that there is an association between plasma sIL-2R levels and severity of mania in bipolar disorder. However, the increased plasma sIL-2R levels are present independently of symptomatic severity in major depression (Maes et al., 1995b; Sluzewska et al., 1996) and are not associated with the severity of positive or negative symptoms in schizophrenia (Hornberg et al., 1995; O'Donnell et al., 1996). It is estimated by the existing literature that about one third of schizophrenic patients show increased plasma sIL-2R levels. However, the plasma sIL-2R levels were detectable and increased in approximately 75% of these bipolar patients during acute mania. We observed that the plasma sIL-2R and sIL-6R levels in bipolar mania along with subsequent remission were not influenced by age, gender, age of onset, length of illness, number of previous episodes, smoking, or medication status. These clinical characteristics without influence on plasma levels of sIL-2R and sIL-6R have been reported in depressive disorder (Maes et al., 1995b,c) and schizophrenia (Hornberg et al., 1995; Maes et al., 1995c; Müller et al., 1997b). However, since patients with depression before or following manic episodes have higher plasma sIL-2R levels, this may show that symptomatic severity of opposite polarity in bipolar disorder may also increase the plasma sIL-2R levels. Although individual plasma sIL-2R levels may fluctuate and have a wide range, the population mean value of sIL-2R measurement is quite stable over a 3-month interval in physically healthy persons (Maloney et al., 1997).

A major shortcoming in interpreting the alternation of plasma sIL-2R levels is the effects of medication. Typical antipsychotics are reported to have no significant effects on plasma sIL-2R in schizophrenia (Rapaport et al., 1994a; Maes et al., 1995a; Müller et al., 1997b; Pollmächer et al., 1997) and bipolar disorder (Maes et al., 1995a; Tsai et al., 1999a). Lithium has long been known to have immunomodulatory effects, but its influence on circulating sIL-2Rs is not conclusive. Healthy subjects treated with lithium for 28 days had a slight but significant increase in serum sIL-2R levels (Rapaport et al., 1994b). However, plasma sIL-2R levels in rapid cycling bipolar patients seem to decrease with 30 days of lithium treatment (Rapaport et al., 1999). Non-significant changes in plasma sIL-2R levels are observed in lithium-treated bipolar patients during the euthymic state (Rapaport, 1994) and upon hospital admission (Haack et al., 1999). The plasma sIL-2R levels in a portion of acute manic patients might increase, but might not reach our limit of detection. About a half of drug-free patients without detectable levels of plasma sIL-2R showed a weak trend towards presence of lithium and other psychotropic agents increasing the sIL-2R levels in early phase of mania. By comparing bipolar subjects at two points in time, if the psychotropic agents increase plasma sIL-2R levels, the significantly higher lithium levels and dosage of typical antipsychotics taken by patients while follow-up blood sampling could not

account for the decreased plasma sIL-2R levels in subsequent remission. Thus, this finding shows the divergent effects of psychotropic medication on bipolar patients in acute mania and subsequent remission.

Our findings are consistent with previous reports that treatment may normalize immune activation in bipolar patients (Maes et al., 1997; Hornig et al., 1998; Rapaport et al., 1999). Immune activation in bipolar disorder is state-dependent (Rapaport, 1994; Tsai et al., 1999a). Moreover, we did not identify a relationship between medication status (e.g., length of medication, lithium levels, and CPZ equivalents) and plasma sIL-2R levels in either acute mania or remission, but a significant reduction of plasma sIL-2R levels in remitted bipolar patients with medication correlated with symptomatic improvement. Accordingly, we suggest that the influence of lithium alone or with antipsychotics on the IRS of bipolar disorder may depend on manic severity. In acute mania, the IRS of bipolar patients might be activated and more sensitive to psychotropic agents. Although the direction of the cause-and-effect relationship remains unclear, reducing manic severity through psychopharmacological treatment may be accompanied by decreasing plasma sIL-2R levels in subsequent remission.

Müller et al. (1997a) found significant correlations between the paranoid–hallucinatory syndrome and sIL-6R levels both in serum and in cerebrospinal fluid. Thus, it is suggested that IL-6 plays a role in the paranoid–hallucinatory symptomatology of schizophrenia. Moreover, neuroleptic treatment has a down-regulating effect on plasma sIL-6R levels of schizophrenic patients (Maes et al., 1995a; Müller et al., 1997b). However, the present data replicate our previous findings that plasma sIL-6R levels of bipolar mania with or without coexisting psychotic features are comparable to those of normal controls. Our results reveal no relationship between plasma sIL-6R levels and any clinical characteristic of bipolar disorder. Interleukin-6 and sIL-6Rs are part of the early pro-inflammatory cascade that is activated when the immune system is challenged. Interleukin-2 and sIL-2Rs represent a component of the immune activation cascade, associated with T-helper cell type 1 (TH-1) cellular immune activation. Another major finding of this study is that our results support various immunomodulatory mechanisms in different psychotic disorders.

There are some methodological limitations to this study that must be acknowledged. Plasma sIL-2R levels have been reported to increase among the elderly. However, there are controversial results showing that the increased sIL-2R production in schizophrenic patients is associated with young age (Rapaport et al., 1994a; Müller et al., 1997b). Our sample excludes people of more than 45 years-of-age. Thus, the exact influence of age on the plasma levels of sIL-2R and sIL-6R in bipolar patients remains unsolved. Another limitation of this study is that some biological variables possibly affecting sIL-2R levels were not examined, such as body temperature (Pollmächer et al., 1996), body mass index (Haack et al., 1999), and physical activity (Bøyum et al., 1996). Perhaps, manic patients have altered circadian rhythms of sIL-2R (Maes et al., 1995a). Ideally, using several points in time spread over a manic episode to assess the immune parameters would provide more information on trends and stability of sIL-2R as well as immunity in bipolar patients. Additionally, since the plasma sIL-2R levels in a small portion of our subjects were undetectable in acute mania or increased in subsequent remission, the interpretation and generalisability of the data may be limited.

In conclusion, bipolar mania is probably characterized by elevation of plasma sIL-2R but not sIL-6R levels. Increased plasma sIL-2R levels are not influenced by many clinical characteristics except severity of mania. The symptomatic improvement in subsequent remission through lithium alone or with typical antipsychotics is accompanied by reduction of plasma sIL-2R levels. It is suggested that the mean plasma sIL-2R level might be an indicator of manic severity in a group of bipolar affective patients.

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