The Korean Journal of Internal Medicine
Vol. 5, No. 1, January, 1990

Serum Levels of Soluble Interleukin-2 Receptor in Pulmonary Tuberculosis

Soo Jeon Choi, M.D., Young Soo Moon, M.D., Bong Choon Lee, M.D. and Dong Soon Kim, M.D.

Department of Internal Medicine, College of Medicine, Inje University, Seoul, Korea

It is well known that the activation of cell mediated immunity has an important role in the pathogenesis of pulmonary tuberculosis and the production of the protective immunity against Mycobacterium tuberculosis. During the activation of T-cell by Interleukin-1 released from the macrophage, not only Interleukin-2 but also the soluble Interléukin-2 receptor (sIL-2R) molecule is released into the extracellular fluid. In vitro study reveals that the level of this sIL-2R is well correlated with the degree of activation of the T-cell. We therefore carried out this study to evaluate the significance of the serum IL-2R level in determining the disease activity of pulmonary tuberculosis.

The level of sIL-2R was measured by sandwich ELISA method.

The level of sIL-2R in 42 patients with bacteriologically -proven active pulmonary tuberculosis (29 far and moderately advanced pulmonary tuberculosis, age: 30.3±10.3 yrs; 13 minimal pulmonary tuberculosis, age: 34.4±15.3 yrs) was 1111±424 u/ml, which was significantly higher than the normal control group (age: 31.0±9.9 yrs) (365±143 u/ml) and inactive pulmonary tuberculosis group (age:37.3±16.9 yrs) (465±131 u/ml).

But there was no significant difference between 29 patients with advanced pulmonary tuberculosis (1138±405 u/ml) and 13 patients with minimal pulmonary tuberculosis (1051± 474 u/ml).

More than three months after the initiation of antituberculosis chemotherapy, the follow-up level of serum sIL-2R in 21 patients with active pulmonary tuberculosis (advanced pulmonary tuberculosis 15, minimal pulmonary tuberculosis six) was 533±182 u/ml, which was markedly lower than the pretreatment level (1020±323 u/ml).

In conclusion, the high level of sIL-2R (especially over 1000 u/ml) can be used as a marker of disease activity in pulmonary tuberculosis even though not diagnostic.

Key Words: *Soluble Interleukin-2 receptor, Pulmonary tuberculosis, Disease activity*

INTRODUCTION

According to the 5th National Tuberculosis Survey in Korea in 1985, the prevalence rate of pulmonary tuberculosis in Korea by chest X-ray was about 2.2%, with many new patients developing annually[1]. Detection of Mycobacterium tuberculosis is the most confirmative test in the assessment of disease activity of pulmonary tuberculosis. But AFB staining of sputum is less sensitive in paucibacillary tuberculosis and frequently impossible in cases of pediatric patients and sputum nonproductive patients with tuberculosis. The culture and sensitivity test of Mycobacterium tuberculosis takes two months to evaluate. Tissue biopsy reveals relatively specific findings of tuberculosis, but it is an invasive method and does not exclude other causes of granulomatous diseases, such as fungal diseases, pulmonary sarcoidosis, and beryl-liosis by itself. Radiological test (chest X-ray) is also easily available and can detect minor changes in tuberculous lesions but it is often difficult to differentiate between active and inactive lesions.

This study was supported by a grant from the Inje Research Foundation.

Address reprint request: Dong Soon Kim, Department of Internal Medicine, College of Medicine, Inje University, Paik Hospital, 85 Jur-Dong, Choong-Ku, Seoul, Korea.

So many investigations have been carried out looking for better methods to detect early changes and asses disease activity of pulmonary tuberculosis easily and rapidly. Among these, the detection of antibodies against tuberculous antigens, specific antigens of Mycobacterium tuberculosis, specific chemical structures or DNA sequences of M. tuberculosis in serum or body fluids or sputum[2~11] were tried. In addition, a Gallium scan of the lung[12], the activity of leukocyte acid phosphatase[13], urinary Neopterin[14], the serum activity of angiotensin converting enzyme (ACE)[15] and the serum level of adenosine deaminase (ADA)[16] were studied for their usefulness in the assessment of disease activity of pulmonary tuberculosis.

We investigated the availability of the serum level of soluble IL-2R, which was known as the indicator of activiation of cell mediated immunity[17], to determine the disease activity of pulmonary tuberculosis and follow up during antituberculosis chemotherapy.

MATERIALS AND METHODS

Table 1 summarizes the age and sex distribution of the subjects. Forty-two patients with active pulmonary tuberculosis (far and moderately advanced tuberculosis 29, minimal tuberculosis 13) were confirmed by AFB staining and mycobacterial culture of sputa.

The control groups included 16 patients with inactive pulmonary tuberculosis, eight patients with other lung diseases (pneumonia two, bronchiectasis three, lung cancer three), and 15 persons of a healthy control group who had no history of respiratory diseases.

The sera were obtained from venous blood and stored in −70℃ till measurement of sIL-2R. In cases of active pulmonary tuberculosis, samplings were done before and during antituberculosis chemotherapy.

The level of sIL-2R was measured using Cellfree® ELISA kit prepared by T-cell Sciences Company (Cambridge, Mass, USA). This is a sandwich ELISA test using monoclonal antibodies against two different epitopes of IL-2R molecule, and processes of the test were as follows:

1) Anti-IL-2R was adsorbed onto the microtiter well.

2) Specimen IL-2R was bound to the antibody-coated microtiter well.

3) Enzyme (Horseradish peroxidase) conjugated anti-IL-2R was bound to a different IL-2R epitope.

4) Enzyme-substrate interaction resulted in color development proportional to IL-2R level, and the optical density of the specimen was measured by photometry at 490 nm.

5) The IL-2R level correlated with the optical density of the specimen gotten from standard curve, and when IL-2R level surpassed the reliable range of standard curve (1600 u/ml), the specimen was tested again after dilution two or three times. The serum level of sIL-2R was determined as average of the duplicate values on the same plate.

Results were expressed as Mean±Standard deviation, and statistical analysis was done by a two-tail Student t test.

RESULTS

The levels of sIL-2R of patients with active pulmonary tuberculosis and control groups are summarized in Table 2.

The level of sIL-2R of the normal control group was 365±143 u/ml, and of patients with inactive pulmonary tuberculosis it was 465±131 u/ml; there was no significant difference between these two groups ($p>0.05$). The level of sIL-2R of patients with other lung disease was 540±232 u/ml, in

Table 1. Characteristics of the Subjects

	Number	Age (year)	Sex (M:F)
Normal control	15	31.0 ± 9.9	8 : 7
Pulmonary tuberculosis			
Minimal	13	34.4 ± 15.3	7 : 6
Far and moderately advanced	29	30.3 ± 10.3	16 : 13
Inactive tuberculosis	16	37.3 ± 16.9	8 : 8
Other lung diseases*	8	46.4 ± 17.5	6 : 2

* Pneumonia 2, Bronchiectasis 3, Cancer 3

Table 2. Soluble IL–2 Receptor Levels in Patients and Control Group

	Number	sIL–2R(u/ml)
Normal control	15	365±143
Pulmonary tuberculosis*	42	1111±424
Minimal**	13	1051±474
Far and moderately advanced***	29	1138±405
Inactive tuberculosis****	16	465±131
Other lung diseases	8	540±232

* P < 0.01, ** P < 0.01, *** P < 0.01, **** P > 0.05, compared to the control group

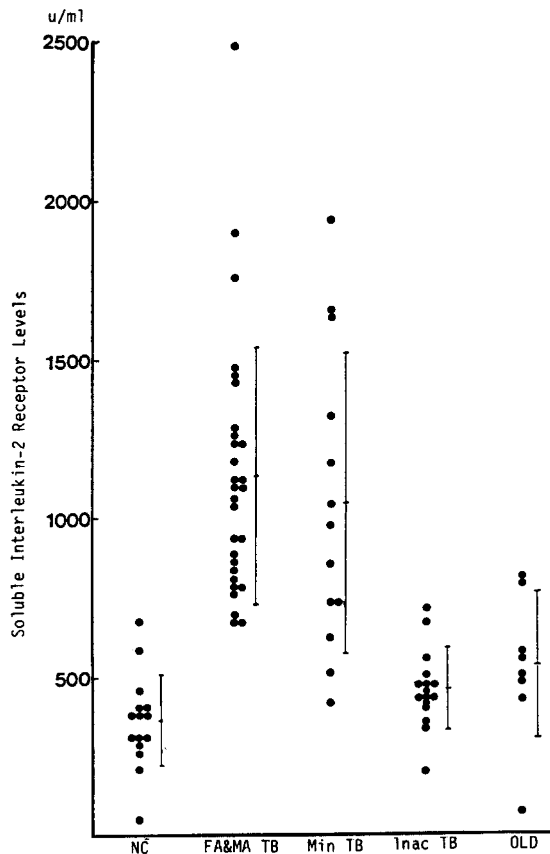

Fig. 1. *Levels of serum soluble interleukin-2 receptor (sIL-2R) in patients and control groups. NC: Normal control: FA & MA TB: Far advanced and moderately advanced pulmonary tuberculosis: Min TB: Minimal pulmonary tuberculosis: Inac TB: Inactive pulmonary tuberculosis: OLD: Other lung diseases (pneumonia, bronchiectasis, cancer)*

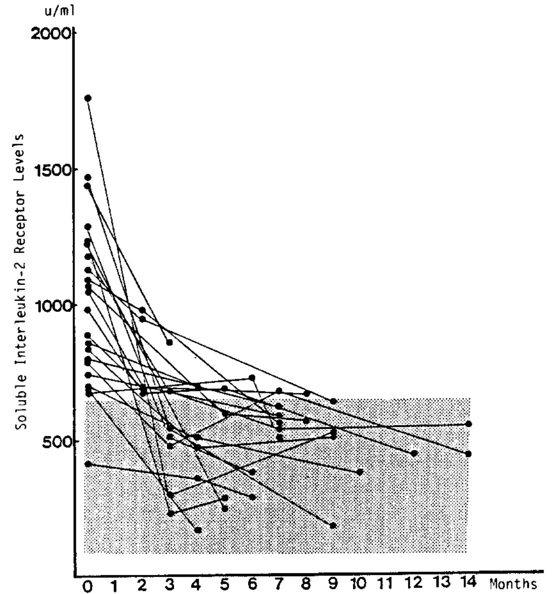

Fig. 2. *Serial observations of the serum sIL-2R levels in patients with active pulmonary tuberculosis during antituberculosis chemotherapy. Shaded area shows mean±2 SD of normal control group.*

which the number of cases was small (n=8), but the level of sIL-2R was similar to the control groups.

The level of sIL-2R in 42 patients with active pulmonary tuberculosis was 1111±424 u/ml, which was significantly higher than the level of the normal control group and patients with other lung diseases ($P<0.01$, $P<0.01$ respectively). It also showed a significant difference compared with the level of patients with inactive pulmonary tuberculosis ($P<0.01$).

The level of sIL-2R of 29 patients with far and moderately advanced pulmonary tuberculosis was compared with that of 13 patients with minimal pulmonary tuberculosis in order to detect differences according to the severity of the tuberculous lesions, but there was no significant difference ($P>0.5$) between them (1138±405 u/ml vs 1051±474 u/ml). Even the level of sIL-2R of patients with minimal pulmonary tuberculosis (1051±474 u/ml) showed a significant difference from the normal control group, patients with other lung diseases and patients with inactive pulmonary tuberculosis ($p<0.01$, $p<0.02$, $p<0.01$, respectively).

In 21 patients with active pulmonary tuberculosis (far and moderately advanced tuberculosis 15,

minimal tuberculosis six), the level of sIL-2R could be followed up during antituberculosis chemotherapy (Fig. 2). The pretreatment level (1020±303 u/ml) markedly decreased to 533±182 u/ml more than three months after the initiation of antituberculosis chemotherapy. After six or seven months of treatment, the level showed the tendency of recovery to the arbitrary normal range (mean±2SD of normal control group).

DISCUSSION

It is well known that the activation of cell mediated imunity has an important role in the pathogenesis of pulmonary tuberculosis and the production of protective immunity against Mycobacterium tuberculosis[18~20]. Several years or decades after primary infection of M. tuberculosis the remaining mycobacteria proliferate and make a hypersensitivity reaction with sensitized T-cells and develop tubercule or cavity formations when defense mechanisms of the host become weak[19]. In addition, upon reintroduction of antigens to a primed cell population, IL-2receptors are expressed more synchronously[21]. In such a cell mediated immune reaction, macrophages have a very important role because activated macrophages are the most important cells that can kill mycobacteria[22]. Thus macrophages phagocytize and process the antigens, which can be presented to T-cells, and when highly specific receptors of T-cells recognize the antigens in the context of HLA-DR glycoproteins on the membranes of macrophages, then full activation of T-cells can occur[18]. But activation of T-cells requires synthesis and the release of Interleukin-1 from macrophages, and activated T-cells produce IL-2, and IL-2 stimulates proliferation of other T-cells.

Once T-cells are activated, IL-2 receptors are expressed on the surface of activated T-cells and also those are released into the extracellular fluid in vitro, and the level of sIL-2R is known as an indicator of the activation of T-cells[17]. Also sIL-2R was released and detected in vivo[23].

Among IL-2R, high affinity receptors and low affinity receptors are known[24], and high afinity receptors are supposed to have an affinity with IL-2R about 1000 times more than low affinity receptors[25], while IL-2R is composed of alpha chain (p55, Tac) and beta chain (p70-75). High affinity receptor is composed of both alpha and beta chain and binding to its ligand, IL-2 is rapid, but dissociation from IL-2 is slow. The low affinity receptor is composed of the alpha chain only, and binding to and dissociation from IL-2 are rapid. The intermediate affinity receptor is known to be composed of beta chain only, and binding to IL-2 is slow, but dissociation from IL-2 is rapid[26~30]. The high affinity receptor and low affinity receptor are known to be encoded in the genes of the human chromosome 10[31]. Two kinds of sIL-2R are known to exist: 55 kDa sIL-2R, which is the same size with cell surface low affinity IL-2R and smaller 45 kDa sIL-2R[29]. Three hypotheses have been supposed as mechanisms of release of sIL-2R: 1) release of molecules lacking transmembrane domain derived from alternate sliced mRNA, 2) release by proteolytical cleavage of the surface expressed IL-2R and 3) degradation product of released 55-kDa sIL-2R. This is still controversial[29,30,32]. In addition, released sIL-2R is known to bind to IL-2R with low affinity (K_D=30 nM)[30,33], and so sIL-2R has been supposed to have an immunoregulatory role by competing with cell surface IL-2R[17].

The range of sIL-2R in the serum of the normal individual is between 100 and 500 u/ml, which reflects the lymphocyte activation normally occurring upon physiological stimuli[34]. Abnormally increased sIL-2R may result either from an increased release rate by activated cells or from release by neoplastic cells constitutionally expressing the IL-2R molecule[34].

Diseases which show increased levels of sIL-2R are as follows: lymphoreticular malignancies[34,35], such as hairy cell leukemia, Hodgkin's disease, non Hodgkin's lymphoma, B-chronic lymphocytic leukemia, acute myeloid leukemia, acute lymphocytic leukemia, angioimmunoblastic lymphadenopathy, adult T-cell leukemia and Sezary's syndrome; autoimmune diseases[36~39], such as rheumatoid arthritis, systemic lupus erythematosis, primary Sjögren's syndrome, atopic dermatitis, psoriasis, chronic progressive multiple sclerosis and type I diabetes; and viral infections, such as measles[40], HIV infection and infectious mononucleosis[34]; and viral hepatitis[41], rejection reaction of transplantation[42], burn patient[43], administration of IL-2[44] and systemic or local granulomatous diseases[45,46], such as sarcoidosis and fungal infections. In tuberculosis, increased levels of sIL-2R were reported in pulmonary or extrapulmonry tuberculosis[47] and in the fluid of suction-induced blisters in vivo after injection of PPD[48].

In this study we can observe a markedly increased level of sIL-2R in patients with far and

moderately advanced pulmonary tuberculosis (1138±405 u/ml) and minimal pulmonary tuberculosis (1051±474 u/ml). But levels of sIL-2R in patients with inactive pulmonary tuberculosis (465±131 u/ml) was not significantly different from that of the normal control group (365±143 u/ml) and patients with other lung diseases (540±232 u/ml). These results could be interpreted as the reflection of disease activity of pulmonary tuberculosis. But there was a broad overlapping range in the distribution between the level of patients with active pulmonary tuberculosis and the control groups (Fig. 1). which did not guarantee the diagnostic value of sIL-2R. So if we would determine 1000 u/ml as the cut-off value in the assessment of disease activity of pulmonary tuberculosis, the sensitivity and specificity were 55% and 100%, respectively. Therefore, a higher level of sIL-2R (1000 u/ml) could be used as an indicator of disease activity in patients with pulmonary tuberculosis. However, the level of sIL-2R increases in patients with many other diseases, such as lymphoreticular malignancies, viral infections, autoimmune diseases, sarcoidosis and fungal diseases. So the level of sIL-2R cannot be suspected to be valuable in the differential diagnosis with those diseases. Concerning the level of sIL-2R in extrapulmonary tuberculosis, Brown et al[47], reported 921 u/ml in eight patients of extrapulmonary tuberculosis (tuberculous lymphadenitis six, genitourinary tuberculosis one, spine tuberculosis one), which were slightly lower than 1192 u/ml in 12 patients with pulmonary tuberculosis, but showed significant differences from the level of the control group. We observed an increased level of sIL-2R in three patients with tuberculous lymphadenitis, 1440, 1221, 736 u/ml, respectively. These observations suggest the possible value of sIL-2R in assessing the disease activity of extrapulmonary tuberculosis. Furthermore, a higher increase of sIL-2R can be expected in tuberculous pleural effusion, which is immunologically more active than pulmonary tuberculosis. Further study in this field will be necessary.

Another known indicator of activation of cell mediated immunity, adenosine deaminase (ADA), was reported to be valuable in the diagnosis of miliary tuberculosis and tuberculous pleural effusion[16], but in the assessment of disease activity of pulmonary tuberculosis, ADA had a wider overlapping range with other lung diseases than sIL-2R. So sIL-2R may be a more valuable indicator of disease activity of pulmonary tuberculosis than ADA, but this will require control study.

In addition, the follow-up level of sIL-2R in 21 patients with active pulmonary tuberculosis, three or more months after initiation of antituberculosis chemotherapy showed a marked decrease of the level (533±182 u/ml) compared with the pretreatment level (1020±323 u/ml) (Fig. 2). which could be interpreted as the result of loss of mycobacterial burden and a subsequent decrease of T-cell activation due to lack of persistent antigen stimulation.

But Brown et al.[47] reported a persistent high level of sIL-2R after two or three months of antituberculosis chemotherapy, which could be due to the short period of observation. If they could have been followed longer, they might have been able to recognize recovery to nearly normal range as in our study. Rapid decline of sIL-2R during the first three months of antituberculosis chemotherapy (Fig. 2) showed a better reflection of the course of treatment than the gradual decline of other reports[49~51].

In tuberculosis, the level of serum sIL-2R is the reflection of antigen nonspecific T-cell activation at the disease sites and may be a useful auxilliary method to the conventional bacteriological and radiological methods in diagnosis of pulmonary tuberculosis and its role in immunoregulation was suggested by Rubin et al,[17] but still is not clear.

REFERENCES

1. Status of Tuberculosis in Korea (1985). *Yearbook of health and social statistics Vol 33. Ministry of Health and Social Affairs. Republic of Korea*
2. Daniel TM, Debanne SM: *The serodiagnosis of tuberculosis and other mycobacterial disease by enzyme-linked immunosorbent assay. Am Rev Respir Dis 135:1137, 1987*
3. Ma Y, Wang YM, Daniel TM: *Enzyme-linked immunosorbent assay using Mycobacterium tuberculosis antigen 5 for the diagnosis of pulmonary tuberculosis in China. Am Rev Respir Dis 134: 1273, 1986*
4. Kalish SB, Radin RC, Levitz D, Zeiss CR, Phair JP: *The enzyme-linked immunosorbent assay method for IgG antibody to purified protein derivative in cerebrospinal fluid of patients with tuberculous meningitis. Ann Intern Med 99:630, 1983*
5. Yong AJ, Grange M, Tee RD, Beck JS, Bothamley GH, Kemeny DM, Kardjito T: *Total and anti-mycobacterial IgE levels in serum from patients with tuberculosis and leprosy. Tubercle 70:273, 1989*

6. French GL, Chan CY, Cheung SW, Oo KT: *Diagnosis of infectary tuberculosis by detection of tuberculostearic acid in sputum by using gas chromatography-mass spectrometry with selected ion monitoring. J Infect Dis 156:356, 1987*
7. Muranishi H, Nakashima M, Ando T, Shigematsu N, Isobe R: *Basic and clinical evaluation of rapid diagnosis of tuberculosis by detecting tuberculostearic acid. Kekkaku 65:39, 1990*
8. Butler WR, Kilburn JO: *Identification of major slowly growing pathogenic mycobacteria and Mycobacterium gordonae by high performance liquid chromatography of their mycolic acids. J Clin Microbiol 26:50, 1988*
9. Roberts MC, McMillan C, Coyle MB: *Whole chromosomal DNA probes for rapid identification of mycobacterium tuberculosis and Mycobacterium avium complex. J Clin Microbiol 25:1239, 1987*
10. Ellner PD, Kiehn TE, Cammarata R, Hosmer M: *Rapid detection and identification of pathogenic mycobacteria by combining radiometric and nucleic acid probe methods. J Clin Microbiol 26: 1349, 1988*
11. Grange JM, Gibson JA, Nassau E, Kardjito T: *Enzyme-linked immunosorbent assay (ELISA): A study of antibodies to Mycobacterium tuberculosis in the IgG, IgA and IgM classes in tuberculosis, sarcoidosis and Crohn's disease. Tubercle 61: 11, 1980*
12. Chung KS, Kim HT, Park SG, Chung JK, Shim YS, Kim KY, Koh CS, Han YC: *Use of 67 Gallium scan in pulmonary tuberculosis. Kor J Tuberc and Resp Dis 34:70, 1987*
13. Kong HH, Woo JH, Han SK, Shim YS, Kim KY, Han YC: *The activities of leukocyte acid phosphatase in pulmonary tuberculosis. Kor J Tuberc and Resp Dis 35:103, 1988*
14. Song JH, Han SK, Shim YS, Kim KY, Han YC: *Neopterin as an activity index in pulmonary tuberculosis. Kor J Tuberc and Resp Dis 33:202, 1986*
15. Kee MD, Woo JH, Shim YS: *A study on angiotensin converting enzyme activity in pulmonary tuberculosis. Kor J Tuberc and Resp Dis 34:240, 1987*
16. Cha SW, Yong SJ, Park JH, Shin KC: *Diagnostic significance of serum ADA activity in miliary tuberculosis. Kor J Int Med 38:68, 1990*
17. Rubin LA, Kurman CC, Fritz ME, Biddison WE, Boutin B, Yarchoan R, Nelson DL: *Soluble interleukin 2 receptors are released from activated human lymphoid cells in vitro. J Immunol 135: 3172, 1985*
18. Edwards D, Kirkpatrick CH: *The immunology of mycobacterial diseases. Am Rev Respir Dis 134: 1062, 1986*
19. Tsuyuguchi I: *Clinical immunology of tuberculosis. Kekkaku 62:253, 1987*
20. Glassroth J, Robins AG, Snider DE: *Tuberculosis in the 1980s. N Eng J Med 302:1441, 1980*
21. Kendal AS: *Interleukin-2. In De Groot ed. Endocrinology. 2nd ed p2459, Phiadelphia, WB Saunders Co, 1989*
22. Walker L, Lowrie DB: *Killing of Mycobacterium microti by immunologically activated macrophages. Nature 293:69, 1981*
23. Nelson DL: *Expression of a soluble form of the interleukin-2 receptor: Normal and abnormal expression in T cells adult leukemics induced by the human T-lymphotropic retroviruses. Greene WC, moderator. Ann Intern Med 105:560, 1986*
24. Robb RJ, Greene WC, Rusk CM: *Low and high affinity cellular receptors for IL-2. J Exp Med 160: 1126, 1984*
25. Smith KA, Cantrell DA: *Interleukin 2 regulates its own receptors. Proc Natl Acad Sci USA 82:864, 1985*
26. Uchiyama T: *IL-2 Receptor Naika 63:1172, 1989*
27. Sharon M, Klausner RD, Cullen BR, Chizzonite R, Leonard WJ: *Novel interleukin-2 receptor subunit detected by cross-linking under high affinity conditions. Science 234:859, 1986*
28. Tsudo M, Kozak RW, Goldman CK, Waldmann TA: *Demonstration of a non-tac peptide that binds interleukin-2: A potential participant in a multichain interleukin-2 receptor complex. Proc Natl Acad Sic USA 8:9694, 1986*
29. Josimovic-Alasevic O, Herman T, Diamantstein T: *Demonstration of two distinct forms of released low-affinity type interleukin 2 receptors. Eur J Immunol 18:1855, 1988*
30. Jacques Y, Le Mauff B, Boeffard F, Godard A, Soulillou JP: *A soluble interleukin 2 receptor produced by a normal alloreactive human T cell clone binds interleukin 2 with low affinity. J Immunol 139:2308, 1987*
31. Leonard WJ, Depper GM, Crabtree GR, Rudikoff S, Pumphrey J, Robb RJ, Kronke M, Svetlik PB, Peffer NJ, Waldmann TA, Greene WC: *Molecular cloning and expression of cDNA for the human interleukin 2 receptor. Nature 311:626, 1984*
32. Loughnan MS, Sanderson CJ, Nossal GJV: *Soluble interleukin 2 receptors are released from the cell surface of normal murine B lymphocytes stimulated with interleukin 5. Proc Natl Acad Sci USA 85:3115, 1988*
33. Rubin LA, Jay G, Nelson DL: *The released IL-2 receptor binds IL-2 efficiently. J Immunol 137: 3841, 1986*
34. Pizzolo G, Chilosi M, Semenzato G: *The soluble*

interleukin-2 receptor in haematological disorders. Brit J Haematol 67:377, 1987

35. Chilosi M, Semenzato G, Cetto G, Ambrosetti A, Fiore-Donati L, Zambello R, Mascisrelli M, Dazzi F, Vinante F, Caligaris-Cappio F, Pizzolo G: *Soluble interleukin-2 receptors in the sera of patients with hairy cell leukemia: Relationship with the effect of recombinant alpha-interferon therapy on clinical parameters and natural killer in vitro activity. Blood 70:1530, 1987*
36. Manoussakis MN, Papadopoulos GK, Drosos AA, Moutsopoulos HM: *Soluble interleukin 2 receptor molecules in the serum of patients with autoimmune diseases. Clin Immunol Immunopathol 50: 321, 1989*
37. Kapp A, Piskorski A, Schopf E: *Elevated levels of interleukin 2 receptor in sera of patients with atopic dermatitis and psoriasis. Brit J Dermatol 119:707, 1988*
38. Greenberg SJ, Marcon L, Hurwitz BJ, Waldmann TA, Nelson DL: *Elevated levels of soluble interleukin-2 receptors in multiple sclerosis. N Eng J Med 319:1019, 1988*
39. Giordano C, Galluzzo A, Marco A, panto F, Amato MP, Caruso C, Bompiani GD: *Increased soluble interleukin-2 receptor levels in the sera of type 1 diabetic patients. Diabetes Research 8:135, 1988.*
40. Griffin DE, Ward BJ, Jauregui E, Johnson RT, Vaisberg A: *Immune activation in measles. N Eng J Med 320:1667, 1989*
41. Yamaguchio S, Onji M, Ohta Y: *Increased serum soluble interleukin 2 receptor levels in patients with viral liver diseases. Hepatogastroenterol 35: 245, 1988*
42. Lawrence EC, Holland VA, Young JB, Windsor NT, Brousseau KP, Noon GP, Whisennand HH, Debakey ME, Nelson DL: *Dynamic changes in soluble interleukin-2 receptor levels after lung or heart-lung transplantation. Am Rev Respir Dis 140:789, 1989*
43. Teodorczyk-Injeyan JA, Sparkes BG, Milles GB, Falk RE, Petess WJ: *Increase of serum interleukin 2 receptor level in thermally injured patients. Clin Immunol Immunopathol 51:205, 1989*
44. Lotze MT, Custer MC, Sharrow SO, Rubin LA, Nelson DL, Rosenberg SA: *In vivo administration of purified human interleukin-2 to patients with cancer: Development of interleukin-2 receptor positive cells and circulating soluble interleukin-2 receptors following interleukin-2 administration. Cancer Research 47:2188, 1987*
45. Lawrence EC, Brousseau KP, Berger MB, Kurman CC, Marcon L, Nelson DL: *Elevated concentrations of soluble interleukin-2 receptors in serum samples and bronchoalveolar lavage fluids in active sarcoidosis. Am Rev Respir Dis 137:759, 1988*
46. Lawrence EC, Berger MB, Brousseau KP, Rodriguez TM, Siegel SJ, Kurman CC, Nelson DL: *Elevated serum levels of soluble interleukin-2 receptors in active pulmonary sarcoidosis: Relative specificity and association with hypercalcemia. Sarcoidosis 4:87, 1987*
47. Brown AE, Rieder KT, Webster HK: *Prolonged elevations of soluble interleukin-2 receptors in tuberculosis. Am Rev Respir Dis 139:1036, 1989*
48. Scollard DM, Wagner DK, Nelson DL: *Release of soluble interleukin-2 receptors (Tac peptide) in vivo during human immune response to tuberculin. Clin Immunol Immunopathol 46:450, 1988*
49. Yoon KS, Lee CT, Shim YS, Han YC, Cho MJ, Cha CY, Chang WH: *Antimycobacterial antibody response in patients with pulmonary tuberculosis during chemotherapy. Kor J Tuberc and Resp Dis 33:79, 1986*
50. Cho SH, Lee KY, Kim YW, Hand SK, Shim YS, Kim KY, Hand YC, Son JO: *Antimycobacterial antibody to phosphatide antigen in patients with pulmonary tuberculosis during chemotherapy. Kor J Tuberc and Resp Dis 35:31, 1988*
51. Kusano N: *The serodiagnosis of tuberculosis by enzyme-linked immunosorbent assay with tuberculin purified protein derivative. Kekkaku 65:42, 1990*