Modulation of Chronic Excessive Interleukin-6 Production in Multiple Myeloma Does Not Affect Thyroid Hormone Concentrations

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Interleukin-6 (IL6) is believed to be involved in alterations of thyroid hormone metabolism in acute nonthyroidal illness. To evaluate the effects of IL6 on thyroid hormone metabolism in a chronic IL6-mediated disease, we measured thyroid hormone concentrations in multiple myeloma patients treated with intravenous anti-IL6 chimeric monoclonal antibodies ([cMabs] $K_d = 6.25 \times 10^{-12}$ mol/L). Twelve patients were studied, receiving at least one complete treatment cycle of 14 days (daily dose: 5 mg, n = 3; 10 mg, n = 3; 20 mg, n = 3; and 40 mg, n = 3). Eight of them also completed a second treatment cycle of 14 days. Thyroid hormone concentrations were measured before, during, and after treatment with the anti-IL6 cMab. Even in the group with the lowest dosage, IL6 activity measured by the B9 bioassay was blocked completely. Compared with the reference ranges, 10 of 12 patients had one or more abnormal pretreatment values for thyroid hormone concentrations. Thyroid autoantibodies were negative in all patients. There was no correlation between thyroid hormone concentrations and IL6 levels, although plasma IL6 levels were increased in all but one subject. Moreover, neutralization of free IL6 by the anti-IL6 cMab did not affect thyroid hormone concentrations, although IL6-dependent C-reactive protein (CRP) levels decreased to undetectable levels in 11 of 12 patients. Two patients developed infectious complications resulting in increased free IL6 and CRP levels and in profound alterations of thyroid hormone levels consistent with an acute euthyroid sick syndrome. We conclude that IL6 is not a major determinant of thyroid hormone abnormalities in a chronic disease like multiple myeloma, but IL6 may be involved in thyroid hormone metabolism in acute diseases (probably in combination with other factors).
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IN PATIENTS WITH NONTHYROIDAL ILLNESS, changes in plasma concentrations of thyroid hormones are frequently found. These alterations in thyroid hormone plasma concentrations in otherwise euthyroid patients are referred to as the euthyroid sick syndrome.[1-4] Although the pathogenesis of this euthyroid sick syndrome has not been completely elucidated, several lines of evidence indicate that inflammatory mediators like interleukin-6 (IL6) may be involved.[5]

The relationship between IL6 and the euthyroid sick syndrome has been addressed in a number of studies. The serum IL6 concentration was correlated inversely with the triiodothyronine (T_3) level, as well as the T_3 to thyroxine (T_4) ratio. In patients with acute illness, a positive correlation between IL6 and reverse T_3 (rT_3) was found, whereas no correlations between tumor necrosis factor alpha (TNF-α) or IL1 and thyroid hormone levels were found.[6-9] In accordance with this, administration of IL6 to patients with renal carcinoma induced a euthyroid sick syndrome within several hours.[10] However, IL6 also induced a flu-like syndrome with a number of other biological effects. Therefore, it was uncertain whether the effects of IL6 on thyroid hormone metabolism were a direct consequence of IL6. In this respect, the recent study by Boelen et al[11] is of interest, wherein they describe the effects of acute inflammation induced by endotoxin, turpentine oil, or *Listeria* infection in IL6 knockout mice. These mice showed a smaller decrease in T_3 levels during the 48 hours after the three inflammatory challenges. These data suggest that IL6 is involved in the pathogenesis of the acute euthyroid sick syndrome.

Although administration of IL6 induced an acute euthyroid sick syndrome within hours in humans, long-term IL6 administration for several weeks was associated with a disappearance of the alterations in thyroid hormone concentrations in the same humans.[10] Therefore, it still remains uncertain whether chronically increased IL6 production is also involved in the alterations of thyroid hormone metabolism in chronic diseases.

Multiple myeloma is a malignant proliferation of plasma cells in the bone marrow. With respect to IL6 production, multiple myeloma is an interesting disease. IL6 plays a key role in the pathogenesis of the disease,[12-19] and we recently found that IL-6 production rates were two to 30 times higher in these patients than in healthy controls. Moreover, anti-IL6 chimeric monoclonal antibodies (cMabs) strongly suppressed endogenous IL6 production in these patients, probably by blocking a positive feedback loop between IL6 and myeloma cell–induced IL6 production by bone marrow stromal cells.[20] Therefore, the patients from that trial are of interest with respect to the relation between chronic IL6 overproduction and thyroid hormone concentrations. To evaluate the effects of increased IL6 production on thyroid hormone metabolism, we measured thyroid hormone concentrations before, during, and after inhibition of IL6 production and IL6-dependent effects by anti-IL6 cMabs in these patients with multiple myeloma.

SUBJECTS AND METHODS

We studied 12 weight-stable patients (median age, 61.5 years; median body mass index, 25 kg/m^2) during 14 days of treatment with the cMab. Clinical characteristics are shown in Table 1. All patients had multiple myeloma according to the criteria of Durie and Salmon,[21] and were either relapsing after or resistant to second-line chemotherapy (vincristine, adriamycin, and dexamethasone [VAD] or VAD-like regimens, high doses of melphalan with or without autologous bone marrow or peripheral stem cell support). Exclusion criteria were as follows: age

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Table 1. Clinical Characteristics of the Subjects

Subject No./ Parameter	Sex	Age (yr)	Creatinine (μmol/L)	BMI (kg/m²)
1	M	53	67	21.6
2	F	70	59	20.9
3	F	58	64	26
4	F	71	108	24.3
5	F	74	123	25.6
6	F	63	40	27.3
7	F	60	92	27.1
8	F	58	72	20
9	F	54	49	39.5
10	F	53	41	22.5
11	M	69	82	24.2
12	F	64	83	26.3
Median		61.5	70	25
Range		53-74	40-123	20-39.5

Abbreviations: M, male; F, female; BMI, body mass index.

less than 18 or greater than 75 years, life expectancy less than 3 months, Karnofsky score less than 60, diabetes mellitus, hypercalcemia requiring treatment, recent allogeneic bone marrow transplantation, kidney and/or liver functional abnormalities, coexisting malignancies, and active infection. None of the patients had a history of thyroid or other endocrine diseases. The patients did not receive any treatment for multiple myeloma at least 1 month before the start of the study.

The subjects did not take any medication known to interfere with thyroid hormone metabolism. The study protocol was approved by the institutional medical ethics committee.

Anti-IL6 cMab

To circumvent possible induction of human antimouse antibodies, a murine-human anti-IL6 cMab (chimeric CLB IL6/8) was developed. It was constructed of the antigen-binding variable region of the murine anti-IL6 antibody (CLB IL6/8) and the constant region of a human IgG1-κ immunoglobulin. This cMab has a high affinity for recombinant and native IL6 ($K_d = 6.25 \times 10^{-12}$ mol/L).[20,22] The cMab (chimeric CLB IL6/8) was developed at Centocor (Malvern, PA) and manufactured by Centocor Europe (Leiden, The Netherlands).

Treatment Schedule

Anti-IL6 cMabs were administered daily by 2-hour infusions for 14 days. Before treatment, a test dose of the cMab (10 μg intravenously) was given over 5 minutes. Since none of the patients developed an immediate hypersensitivity reaction, treatment was started 15 minutes later. The first three patients received the cMab 5 mg/d intravenously, the next three patients received 10 mg/d, patients no. 7 to 9 received 20 mg/d, and the last three patients received 40 mg/d. Eight of 12 patients received a complete second treatment of 14 days' duration with a similar dosage as in the first treatment cycle of anti-IL6 cMab, starting 14 days after the end of the first treatment cycle.

Plasma samples for IL6, cMab, and C-reactive protein (CRP) were taken five times per week and stored at −80°C until the patient completed the study. Routine samples for thyroid hormone concentrations were taken on days 0, 7, 14, 28, and 41 and analyzed immediately. The samples were drawn before starting infusion of anti-IL6.

Assays

IL6 levels were determined by the B9 bioassay as described previously.[20,23] One unit of B9-stimulating activity was defined as the amount inducing half-maximal proliferation, and it corresponded to 1 pg IL6. To determine the total IL6 level (ie, free IL6 plus IL6 complexed to Mab), an excess (10 μg/mL) of a second anti-IL6 Mab (CLB IL6/14) was added to each well to displace IL6 from binding with the in vivo administered, neutralizing chimeric CLB IL6/8. CLB IL6/14 and CLB IL6/8 Mabs recognize partly overlapping sites of IL6. However, CLB IL6/14 is not capable of inhibiting IL6 activity in the B9 bioassay.[24]

During treatment with the cMab, actual free IL6 levels cannot be measured, because dilution of the samples necessary for testing in the B9 bioassay or enzyme-linked immunosorbent assay (ELISA) immediately influences the equilibrium between the IL6-cMab complex, free IL6, and free cMab. Therefore, free IL6 levels were calculated using the Henderson-Hasselbach equation, with the K_d, serum cMab levels, and total IL6 levels as known parameters.

Levels of the CLB IL6/8 cMab were determined using a radioimmunoassay (RIA) as described previously.[20] The threshold of this assay is 0.5 ng/mL Mab. IL1 was determined using the D10 bioassay[25] (normal value, undetectable) and TNF by ELISA (Central Laboratory Bloodtransfusion, Amsterdam, The Netherlands; normal value, <50 pg/mL).

Thyroid hormones were determined by the following assays: thyrotropin (TSH) by TSH-ICMA (Behring, Marburg, Germany; normal value, 0.4 to 4.0 mU/L; intraassay variation, 6.8%; interassay variation, 5.7%); T_3 by in-house RIA (normal value, 1.3 to 2.9 nmol/L; intraassay variation, 4.0%; interassay variation, 6.3%); rT_3 by in-house RIA (normal value, 0.11 to 0.44 nmol/L; intraassay variation, 4.6%; interassay variation, 4.6%); T_4 by in-house RIA (normal values, 70 to 150 nmol/L; intraassay variation, 3.0%; interassay variation, 5.1%); free T_4 (fT_4) by SPAC fT_4-fraction (Byk-Sangtec Diagnostica, Dietzenbach, Germany; normal value, 10.0 to 20.0 pmol/L; intraassay variation, 2.8%; interassay variation, 5.7%); T_3 uptake by a commercial kit (T_3-uptake (MAA) kit; Kodak Clinical Diagnostics, Amersham, England; normal value, 0.84 to 1.11; intraassay variation, 2.7%; interassay variation, 2.3%); thyroid peroxidase (TPO) autoantibodies (anti-TPO) by a commercial luminescence immunoassay (LIA; Lumitest anti-TPO; Brahms, Berlin, Germany); and antithyroglobulin antibodies by a homemade assay using ^{125}I-TG and IgG antibodies.

C-reactive protein (CRP) was determined by nephelometry (Behring; normal value, <5 mg/L).

Statistical Analysis

The effect of treatment with anti-IL6 cMab was evaluated by ANOVA for randomized block design and Fisher's least-significant difference test, when appropriate, or the Wilcoxon rank test. Significance was set at P less than .05.

RESULTS

Twelve patients (three per dosage group) completed at least one treatment cycle of 14 days, and eight of them also completed a second treatment cycle. Patient no. 1 received only 2 days of the second treatment cycle, because he needed radiotherapy for myeloma-related neurological complications. His thyroid hormone concentrations were determined and remained within normal limits until day 100. Patient no. 5 (dosage group 10 mg/d) and patient no. 9 (20 mg/d), only completed the first treatment cycle because of infectious complications, and patient no. 12 (40 mg/d) received anti-IL6 from days 1 to 4 and 16 to 29 because she had a fever of unknown origin on day 5.

Pretreatment Thyroid Hormone Concentrations

Pretreatment thyroid hormone levels showed multiple abnormalities (Table 2). Both plasma T_4 and T_3 concentrations were decreased in patients no. 3 and 7. In patient no. 3, this was associated with a decreased fT_4 concentration. Nonetheless, in

Table 2. Pretreatment IL6 and Thyroid Hormone Concentrations

Subject No./ Parameter	IL6 (<3 pg/mL)	T_4 (70-150 nmol/L)	fT_4 (10-20 pmol/L)	THBI (0.84-1.11)	T_3 (1.3-2.7 nmol/L)	TSH (0.4-4.0 mU/L)	rT_3 (0.11-0.44 nmol/L)
1	50	85	11.1	0.96	1.1	1.0	0.14
2	3	145	15.9	ND	2.5	2.6	0.25
3	7	65	8.5	0.94	1.25	1.4	0.08
4	22	150	27	1.24	1.6	0.57	0.31
5	17	90	14.4	0.98	1.25	2.7	0.18
6	13	75	9.0	0.87	1.4	17.6	0.12
7	10	60	10.8	1.18	0.95	2.1	0.21
8	41	80	9.6	0.93	1.05	10.6	0.13
9	7	125	12.5	0.92	2.15	1.9	0.15
10	5	105	13.7	ND	1.5	2.4	0.09
11	33	150	21.6	0.98	2.9	1.8	0.34
12	9	135	17.8	1.0	2.35	2.0	0.59
Median	11.5	97.5	13.1	0.97	1.45	2	0.17
Range	3-50	60-150	8.5-27	0.87-1.24	0.95-2.9	0.57-17.6	0.08-0.59

NOTE. Anti-TPO and antithyroglobulin antibodies were negative in all patients. Values in parentheses in column headings are the normal range. Abbreviations: ND, not determined; THBI, thyroid hormone binding index.

both subjects, plasma TSH concentrations were not increased. In patients no. 6 and 8, plasma fT_4 concentrations were decreased despite normal total T_4 concentrations. This was associated with a decreased T_3 concentration and a decreased T_3/T_4 ratio in patient no. 8 (13.1×10^{-3}; normal range, 14.9 to 21.9×10^{-3}). In both patients no. 6 and 8, plasma TSH levels were increased. In patients no. 1 and 5, only plasma T_3 concentrations were decreased compared with the normal range.

In patient no. 11, fT_4 concentration was slightly increased, with normal T_4 and TSH levels. Plasma rT_3 concentration was increased only in patient no. 12. Only two of 12 patients had thyroid hormone concentrations that were all within the normal reference range of our laboratory. Anti-TPO and anti-TG autoantibodies were not detectable in any of the patients.

The median pretreatment IL6 level was 11.5 pg/mL in these patients, and only one (no. 2) had a normal IL6 level (Table 2). There was no significant correlation between pretreatment serum IL6 and thyroid hormone concentrations in these patients (rT_3/IL6, $r = -.06$; T_3/IL6, $r = -.22$; TSH/IL6, $r = .08$; and T_4/IL6, $r = -.08$).

Effects of Infusion of Anti-IL6 cMabs

There were no toxicities or allergic reactions related to the cMab. During treatment with the cMab, IL6 circulates as a biologically ineffective complex with the cMab. The median serum half-life of the cMab was 17.8 days, resulting in an accumulation and high serum levels of the cMab. Mean peak serum levels of the cMab were between 6.7 μg/mL in patient no. 1 (5 mg/d anti-IL6 cMab) and 288 μg/mL in patient no. 11 (40 mg/d).[26]

The CRP level, which is IL6-dependent,[27] was below detection level during treatment with the cMab.[20] In accordance, free IL6 levels decreased rapidly to less than 0.3 pg/mL in all patients (Fig 1). No difference in the efficacy of blocking IL6 activity between the different dosage groups was found, and already in the lowest dosage group, the high-affinity cMab was

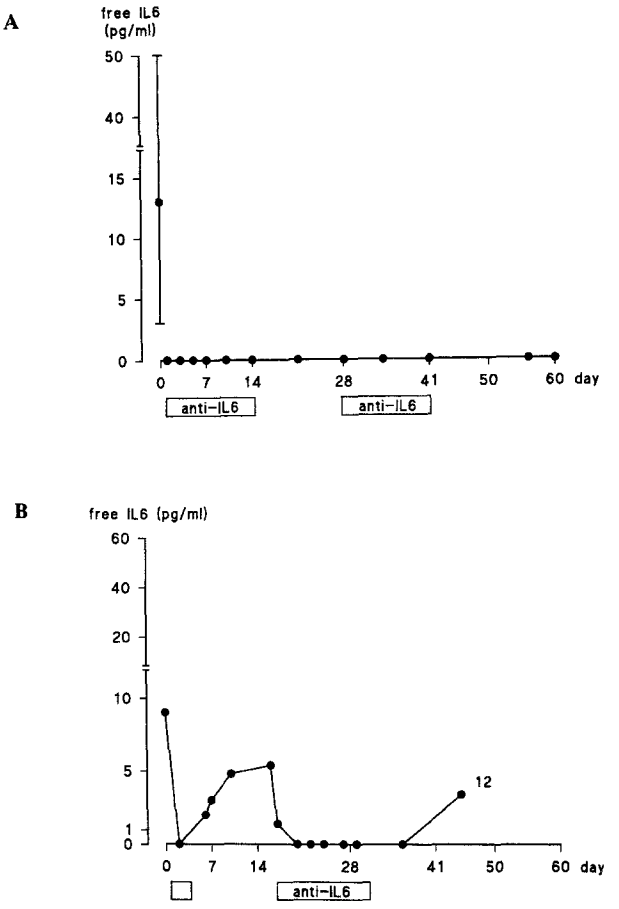

Fig 1. (A) Median (and range) free IL6 levels during anti-IL6 treatment in 9 patients (no. 1 to 4, 6 to 8, 10, and 11). Free IL6 levels decreased immediately after starting anti-IL6 treatment, to <0.3 pg/mL in all patients. (B) Free IL6 levels in patient no. 12. She completed 1 treatment cycle from days 16 to 29. The first treatment cycle was interrupted because of fever of unknown origin. Thyroid hormone concentrations remained normal.

circulating in excess. Thus, no dose-response relation between the different dosage groups was found.

Despite these profound changes in IL6 levels, there were no significant changes in thyroid hormone concentrations during cMab treatment (Fig 2). This was also true for the five patients with low pretreatment T_3 levels when analyzed as a separate group (data not shown). Eight of 12 patients received a second complete treatment cycle. Their thyroid hormone levels before the second treatment cycle were not different from the pretreatment values for the first treatment with the anti-IL6 cMab.

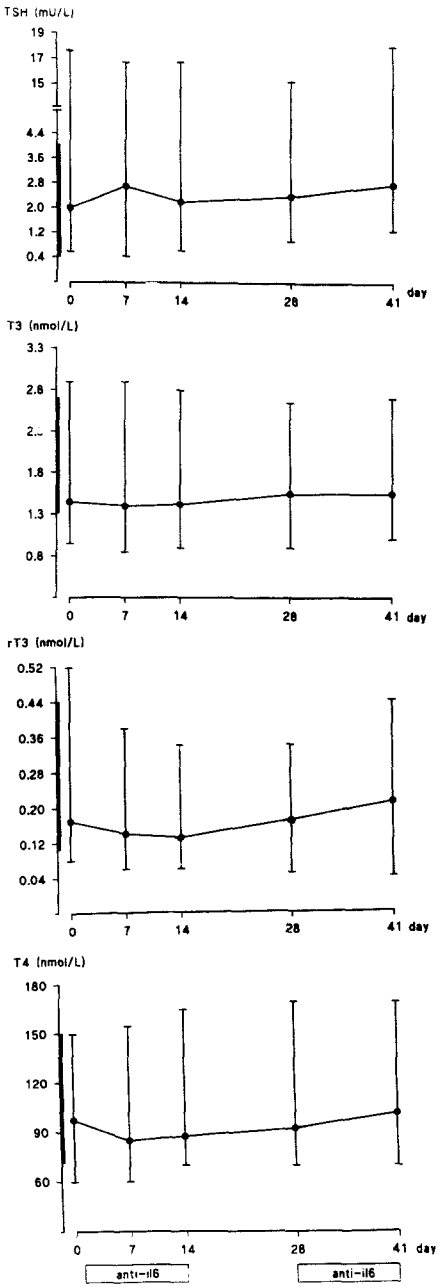

Fig 2. Median (and range) thyroid hormone concentrations in all patients except no. 5 and no. 9 (2 patients with infectious diseases). No significant differences were seen during treatment with anti-IL6 cMab. Normal reference range is shown on the y-axis.

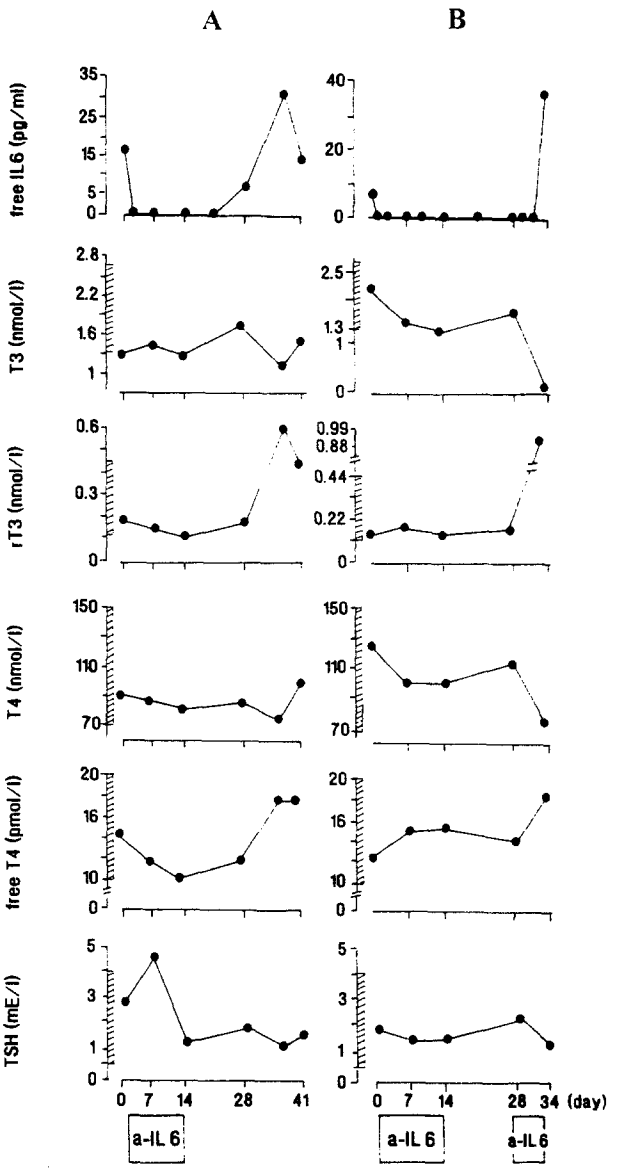

Fig 3. (A) Free IL6 and thyroid hormone levels in patient no. 5. At day 28, she had a urinary tract infection and fever. (B) Free IL6 and thyroid hormone levels in patient no. 9. She developed acute pneumonia and septicemia caused by *Staphylococcus aureus* and died at day 35.

There were no significant effects of anti-IL6 treatment on thyroid hormone concentrations in these eight patients during the second treatment with anti-IL6 cMab (Fig 2).

Thyroid Hormone Levels in Patients With Infections During Anti-IL6 Treatment

Patient no. 5, who completed the first treatment cycle, had fever due to a urinary tract infection with *Escherichia coli* and negative blood culture results at the time she was admitted on day 28 for the second treatment cycle (Fig 3A). Therefore, a second treatment cycle of anti-IL6 cMab was not given, and she was treated with antibiotics. Free IL6 levels increased to a maximal 32 pg/mL at day 37, at which time T_3 concentrations

were decreased and rT_3 concentrations were increased. Plasma TSH and T_4 levels remained within normal limits. In this patient, TNF-α and IL1 levels remained below the detection limit in all samples. The CRP level increased from less than 3 mg/L (day 21) to a maximum of 130 mg/L at day 37.

In patient no. 9, anti-IL6 cMab was stopped during the second treatment cycle at day 34, because she developed a high fever and low blood pressure due to pneumonia and septicemia caused by *Staphylococcus aureus* (Fig 3B). At day 34 (the day before she died), plasma cMab was 16.3 μg/mL, and total serum IL6 was elevated to 356,000 pg/mL, of which only a minor part (36 pg/mL) was not bound to the cMab. In this patient, plasma T_3 decreased, associated with an increase in plasma rT_3. Plasma T_4, fT_4, and TSH remained within normal limits. CRP increased from less than 3 mg/L (day 33) to 245 mg/L at day 34. TNF-α and IL1 levels were not determined.

DISCUSSION

In this study, we investigated whether IL6 affects thyroid hormone metabolism in multiple myeloma, a chronic IL6-mediated disease. There was no effect on thyroid hormone concentrations when serum IL6 was neutralized and endogenous IL6 production was totally inhibited by the anti-IL6 cMab. Before anti-IL6 treatment, 10 of 12 patients had abnormal thyroid hormone concentrations, and all but one had increased IL6 concentrations. However, there was no correlation between these thyroid hormone and IL6 concentrations. From these observations, we conclude that chronically elevated IL6 concentrations do not seem to play a major role in thyroid hormone metabolism in multiple myeloma.

We studied patients with multiple myeloma who were resistant to second-line chemotherapy. This group appears to have multiple abnormalities in thyroid hormone concentrations. Five of 12 patients had decreased T_3 concentrations consistent with a euthyroid sick syndrome. However, none of these five had increased rT_3 concentrations. Although patient no. 12 had an increased rT_3 level before anti-IL6 treatment, we cannot exclude the possibility of a specific effect of multiple myeloma on rT_3 levels. For instance, the euthyroid sick syndrome in renal disease is also characterized by the absence of an increase in rT_3 concentrations.[8] However, we are not aware of data on thyroid hormone concentrations in patients with multiple myeloma. Two patients (no. 6 and 8) had slightly increased plasma TSH values associated with decreased fT_4 concentrations. Although it is possible that there was mild hypothyroidism in these patients, plasma TSH values can also be increased in the euthyroid sick syndrome.[4] In line with the euthyroid sick syndrome, the T_3/T_4 ratio was decreased in patient no. 8. Moreover, in both patients, no thyroid autoantibodies were detectable. Because treatment with anti-IL6 cMabs did not affect thyroid indices in these two patients with increased TSH levels, and exclusion of these two patients from the analyses did not affect our results (data not shown), our conclusions as to the lack of a correlation between IL6 and thyroid hormone concentrations are not affected by inclusion of these patients.

Anti-IL6 cMabs were administered well in excess of circulating IL6 concentrations, even in patients who received the lowest dose (cMab 5 mg/d). Almost all free IL6 was complexed by the surplus of antibodies (high-affinity cMab in micrograms per milliliter *v* IL6 in picograms per milliliter). These circulating complexes of IL6-cMab are biologically inactive.[20,26] Neutralization of IL6 by the cMab is also indicated by the sharp decrease of CRP levels to below detection limits in 11 patients and an 87% decrease in patient no. 12. Therefore, the absence of any change in thyroid hormone levels is not the result of ineffectiveness of the anti-IL6 cMab to neutralize IL6 activity. Moreover, we also found that endogenous IL6 production in these myeloma patients was nearly completely inhibited during anti-IL6 treatment.[20]

In a previous study, we documented that IL6 administered as a single dose to patients with renal cell carcinoma induced changes in thyroid hormone concentrations within several hours, mimicking the euthyroid sick syndrome. Plasma T_3 and TSH concentrations decreased, whereas rT_3 levels increased.[10] In contrast, prolonged administration of IL6 resulted in normalization of T_3 and rT_3 concentrations within several weeks. This is in agreement with observations in rodents wherein prolonged administration of cytokines like IL1 and TNF resulted in attenuation of the effects of these cytokines on thyroid hormone metabolism.[28] Thus, the effects of cytokines on thyroid hormone metabolism appear to be dependent on the duration of exposure. Boelen et al[7] observed a correlation between IL6 concentrations and plasma T_3 concentrations in blood samples from patients admitted to a medical ward because of acute illness. In our patients with chronic illness, we did not find this correlation. Although this could be due to the small number of subjects involved, we think that the exposure to chronic rather than to acute elevation of endogenous IL6 production in our patients with multiple myeloma is a more likely explanation. Moreover, Davies et al[9] also postulated that IL6 does not play a role in the pathogenesis of the euthyroid sick syndrome in all types of nonthyroidal illness. In patients with chronic renal disease, they found a high proportion of individuals with low T_3 and T_4 serum levels, whereas IL6 levels were relatively low.

Two patients developed infectious complications during or after treatment with anti-IL6 cMabs. In these two patients, a similar pattern of changes in thyroid hormone concentrations occurred: plasma T_3 decreased and rT_3 increased, reflecting the worsening of a euthyroid sick syndrome. Apparently, high levels of IL6-neutralizing antibodies did not prevent this euthyroid sick syndrome induced by acute infection. In accordance, we have found that infection-induced IL6 production could not be blocked by the anti-IL6 cMab, probably because this endotoxin/TNF-mediated IL6 production by monocytes/macrophages and/or endothelial cells lacks the positive feedback loop, as we have recently described for myeloma cell–induced IL6 production by bone marrow stroma cells.[20] Moreover, in vitro experiments gave support to this assumption, because IL6 production by monocytes could not be blocked by anti-IL6 Mabs (Aarden LA, Rensink HJAM, van Oers MH, unpublished observations, February 1994). Although our Mab was able to bind infection-induced IL6 (reflected in very high total IL6 levels), the amount of IL6 was too high for it to be complexed totally, resulting in a sharp increase of free IL6, associated with the induction of a euthyroid sick syndrome. Nonetheless, the absolute free IL6 levels were relatively low and even within the range of the (chronically elevated) pretreatment IL6 levels. Because rT_3 concentrations increased consider-

ably and were much higher than pretreatment rT_3 concentrations, this suggests that an acute increase in serum IL6 and/or other covarying factors (eg, other cytokines) is important for the pathogenesis of the acute euthyroid sick syndrome.

Our study shows that modulation of IL6 production and activity in a condition with chronic IL6 excess does not influence thyroid hormone concentrations. Although IL6 is probably involved in the pathogenesis of the euthyroid sick syndrome in acute conditions, our present data are in line with previous observations[10] that the acute effects of IL6 on thyroid hormone concentrations disappear during long-term IL6 administration. Therefore, it is likely that the involvement of IL6 in the pathogenesis of the euthyroid sick syndrome is different in acute and chronic diseases.

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