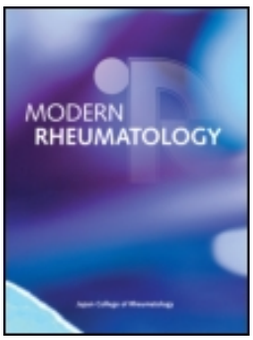

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ORIGINAL ARTICLE

Infliximab treatment reduces the serum levels of interleukin-23 in patients with rheumatoid arthritis

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Abstract In this study, we investigated the effect of the antitumor necrosis factor alpha (anti-TNF-α) antibody, infliximab, combined with methotrexate (MTX) and MTX alone on the serum levels of interleukin (IL)-23 and IL-17 in rheumatoid arthritis (RA) patients. Infliximab combined with MTX was administered to 26 patients with RA (infliximab group), and MTX alone was given to 20 patients with RA (MTX group). We evaluated clinical and laboratory parameters, including the Disease Activity Scores of 28 joints (DAS28) and serum levels of IL-23 and IL-17 at baseline and at 14 and 30 weeks after the initial treatment with these drugs. Single regression analysis was performed between the levels of serum IL-23 and other clinical and laboratory parameters at baseline before the initial treatment with infliximab or MTX. A significant reduction of DAS28 scores was observed in both the infliximab and the MTX group at 14 and 30 weeks after the initial treatment. A significant decrease in serum levels of IL-23 was observed in the infliximab group but not in the MTX group at 14 and 30 weeks after the initial treatment. Serum IL-17 levels did not show a significant change during the follow-up period. At baseline, before the initial treatment with infliximab or MTX, serum IL-23 levels showed a significant correlation with DAS28 and the number of swollen joints. This study indicated that the reduction of serum IL-23 levels in RA patients was a novel action of infliximab.

Keywords Rheumatoid arthritis · Infliximab · Interleukin-23 · Interleukin-17

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Introduction

The highly successful use of a chimeric antibody against tumor necrosis factor alfa (TNF-α), infliximab, for rheumatoid arthritis (RA) patients may suggest that TNF-α plays a key role in the pathogenesis of RA [1, 2]. Although the effect of infliximab is extensively known, the biological mechanism by which the clinical effect is obtained is not clearly understood. Previous study indicated that infliximab reduced the serum levels of interleukin (IL)-6 and D-dimer of coagulation biomarkers [3], IL-8, monocyte chemotactic protein-1, IL-18 [4], and matrix metalloproteinase (MMP)-1,-3, and -9 [5] in RA patients, and soluble adhesion molecules in patients with juvenile idiopathic arthritis [6]. Study results have shown that blockade of TNF-α also inhibits the spontaneous production of granulocyte macrophage colony-stimulating factor [7]. We also previously demonstrated that infliximab reduced the serum levels of IL-15 and human growth-regulated peptide alpha in RA patients [8, 9].

IL-23 has recently been considered to be a cytokine that plays an essential role in the disease process of RA [10, 11]. IL-23p19 concentration in synovial fluid (SF) was higher in RA patients who had bony erosions than in those who did not [12]. IL-23 indirectly stimulates the differentiation of osteoclast precursors by enhancing IL-17, which in turn stimulates osteoclastogenesis in osteoclast precursor cells [13]. In addition, we previously reported that the serum levels of IL-23 in RA patients at posttreatment with a soluble TNF-α receptor, etanercept, decreased.

Although etanercept and infliximab are TNF-α-blocking agents, they do not always show equal effects on the identical RA patients in clinical use. This may result from different mechanisms in TNF-α blocking. For example, infliximab gives reverse signaling through transmembrane

TNF-α on the cell surface [14], but etanercept does not have such a function. Therefore, in this study, we investigated whether infliximab and methotrexate (MTX), respectively, affect the serum levels of IL-23 and IL-17.

Materials and methods

RA patients receiving infliximab combined with MTX, those receiving MTX alone, and control individuals

Twenty-six RA patients receiving infliximab combined with MTX (infliximab group) (23 women and three men; mean age 61.4 ± 10.6 years; mean disease duration 17.6 ± 6.0 years; Steinbrocker's stage I: 1, II: 6, III: 18, IV: 1) were involved in this study between January 2004 and July 2008. Ten patients received a constant dose of prednisolone (mean dose 3.9 ± 1.4 mg/day) during this study. Informed consent was obtained from all patients. Infliximab was injected intravenously at a dosage of 3 mg/kg at baseline, then at 2 and 6 weeks, and after that every 8 weeks. In all patients treated with infliximab, MTX was also administered at a constant dosage (mean dose 5.89 ± 1.75 mg/week). Physical examinations and blood analysis were performed just before infusion of infliximab at baseline and at 14 and 30 weeks after the initial treatment with infliximab.

Twenty RA patients receiving MTX alone (MTX group) (15 women and five men; mean age 59.0 ± 12.3 years; mean disease duration 11.9 ± 7.6 years; Steinbrocker's stage I: 4, II: 2, III: 10, IV: 4) were also included in this study. Ten patients in the MTX group received a constant dose of prednisolone (mean dose:3.9 ± 2.0 mg/day) throughout the study. The control group consisted of five women and two men (mean age 58.0 ± 8.0 years).

To evaluate the disease activity of RA in the infliximab and MTX groups, we measured the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and counted the number of swollen joints and tender joints. The Disease Activity Scores of 28 joints (DAS28) and European League Against Rheumatism (EULAR) response criteria were also evaluated. Serum antigalactosyl immunoglobulin G (IgG) antibody [carbohydrate in rheumatoid factor (CA-RF)] levels were also measured by enzyme-linked immunosorbent assay (ELISA) (Ei test, Eisai, Tokyo, Japan). Clinical and laboratory examinations, including ESR, CRP, CA-RF, number of swollen joints and tender joints, and DAS28 were performed at baseline and at 14 and 30 weeks after the initial treatment with infliximab combined with MTX or with MTX alone. The serum levels of IL-23 and IL-17 were also measured in all patients, as described below.

The serum samples from RA patients (infliximab and MTX groups) and control individuals (control group)

Serum samples were collected from RA patients in the infliximab, MTX, and control groups and stored at −80°C until IL-17 and IL-23 were assayed.

Measurement of serum levels of IL-17 and IL-23

Serum levels of IL-17 and IL-23 were measured using an ELISA (IL-17 kit; Biosource, Nivelles, Belgium, IL-23 kit; Biovender, Heidelberg, Germany). All samples were measured in duplicate. To demonstrate that this assay was not affected by RF interaction, IL-17 and IL-23 levels of the serum from five RA patients without infliximab treatment with RF (+) were measured after absorption procedure of RF by human IgG-bound (1 mg/ml, 24 h incubation) protein G beads, following our methods described previously [15]. Absorption of RF was made as follows: 100 μl of human IgG (1 mg/ml) was mixed with 100 μl of protein G beads for 8 h at room temperature. The beads were washed twice with phosphate-buffered saline (PBS). The serum samples were incubated with the immunoglobulin-coupled beads (1:1 vols.) for 2 h to eliminate RF. The IL-17 and IL-23 levels of the samples, which were incubated with or without immunoglobulin-coupled beads, were assayed. There was no significant difference in the cytokine levels between the nontreated serum and the serum incubated with the immunoglobulin-coupled beads (data not shown).

Statistical analysis

All data were indicated as the mean ± standard deviation. The comparison between pre- and posttreatment data was performed using the Wilcoxon signed rank test. The serum levels of IL-17 and IL-23 in RA patients was compared with those of the control group by using the Mann–Whitney *U* test. Single regression analysis was performed between the levels of serum IL-23 and other clinical and laboratory parameters at baseline before the initial treatment with infliximab or MTX in RA patients. In addition, the correlation analysis between the differences of serum IL-23 levels (ΔIL-23) and those of other clinical and laboratory parameters at baseline and 30 weeks from initial treatment of infliximab in RA patients was performed. The differences of the serum levels of IL-23, IL-17, CRP, and CA-RF, ESR/1h, DAS28, the number of swollen joints and the number of tender joints at baseline and 30 weeks from initial treatment of infliximab in RA patients were also shown by ΔIL-23, ΔIL-17, ΔCRP, ΔCA-RF, ΔESR/1h, ΔDAS28, Δ number of swollen joints, and Δ number of tender joints. The statistical significance in correlation was determined with Pearson's

correlation test. In this study, p values <0.05 were evaluated to be significantly different. All statistical analysis was performed on a Macintosh computer using the Statcel software package.

Results

Clinical and laboratory disease activity of RA patients

In the infliximab group, CRP levels decreased from 3.07 ± 1.82 mg/dl at pretreatment to 1.57 ± 1.93 mg/dl ($p < 0.05$) and 1.67 ± 1.42 mg/dl ($p < 0.05$) at 14 and 30 weeks, respectively, after the initial infusion. ESR levels also decreased, from 58.8 ± 31.0 mm at pretreatment to 41.2 ± 31.1 mm/h ($p < 0.05$) and 37.3 ± 28.6 mm/h ($p < 0.05$) at 14 and 30 weeks, respectively, after the initial infusion. Serum CA-RF levels, DAS28 score and the number of swollen and tender joints also significantly decreased at 14 and 30 weeks compared with those at pretreatment (Table 1). In EULAR response criteria, at 14 weeks after the initial administration of infliximab, good response was acquired in eight patients, moderate response in 12, and no response in six. At 30 weeks, good response was obtained in ten patients, moderate response in 12, and no response in four.

In the MTX group, CRP, ESR, DAS28, the number of swollen joints, and the number of tender joints were significantly decreased at 14 and 30 weeks after the initial administration of MTX, whereas CA-RF levels were significantly decreased only at 30 weeks. In EULAR response criteria, at 14 weeks after the initial administration of MTX, good response was acquired in three patients, moderate response in 13, and no response in four. At 30 weeks, good response was obtained in three patients, moderate response in 12, and no response five.

Serum levels of IL-17 and IL-23 at pre- and posttreatment in the infliximab group, the MTX group, and the control group

Baseline levels of serum IL-23 and IL-17 in the infliximab and MTX groups were higher than those in the control group (Table 1). In the infliximab group, IL-17 levels did not show a significant change at 14 or 30 weeks after the initial infusion compared with those at pretreatment. These data are similar to our previous data [8]. In the MTX group, IL-17 levels did not show a significant change at 14 or 30 weeks after the initial administration compared with levels at pretreatment. In the infliximab group, serum IL-23 levels were significantly decreased from 112 ± 249 pg/dl at pretreatment to 39 ± 58 mg/dl ($p < 0.05$) and 28 ± 52 mg/dl $p < 0.05$) at 14 and 30 weeks after the initial infusion, respectively. In the MTX group, IL-23 levels did not show a significant change at 14 or 30 weeks after the initial treatment compared with levels at pretreatment.

Correlations between serum IL-23 levels and other clinical and laboratory parameters at baseline before the initial treatment with infliximab or MTX

Serum IL-23 levels showed a significant correlation with DAS28 ($r = 0.263$, $p < 0.05$) and the numbers of swollen joints ($r = 0.283$, $p < 0.05$; Table 2). The serum IL-23 and

Table 1 The change in clinical and laboratory parameters in patients with rheumatoid arthritis (RA) treated with infliximab combined with methotrexate (MTX) and MTX alone

	Infliximab group			MTX group			Control group
	Baseline	14 weeks	30 weeks	Baseline	14 weeks	30 weeks	
Serum IL-23 (pg/ml)	112 ± 249*	39 ± 58**	28 ± 52***	113 ± 240*	97 ± 227	93 ± 200	3 ± 4
Serum IL-17 (pg/ml)	9.8 ± 17.8*	10.6 ± 16.8	7.6 ± 9.8	20.0 ± 36.0*	18.8 ± 34.4	18.0 ± 44.4	2.5 ± 4.2
CRP (mg/dl)	3.07 ± 1.82	1.57 ± 1.93**	1.67 ± 1.42**	4.00 ± 3.10	1.66 ± 1.53**	1.13 ± 1.31**	0.02 ± 0.01
ESR (mm/h)	58.8 ± 31.0	41.2 ± 31.1**	37.3 ± 28.6***	73.7 ± 28.0	48.6 ± 22.6**	40.5 ± 25.0**	7.9 ± 2.7
Serum CA-RF (AU/ml)	362 ± 643	319 ± 630	290 ± 610	529 ± 684	497 ± 713	349 ± 468	N.D.
DAS28	3.95 ± 0.80	2.81 ± 0.73***	2.79 ± 0.57***	4.87 ± 0.61	3.41 ± 0.44**	3.21 ± 0.79**	N.D.
Number of swelling joints	7.33 ± 4.85	5.00 ± 3.21***	4.45 ± 3.75***	7.29 ± 3.55	5.57 ± 3.69**	3.50 ± 1.73**	N.D.
Number of tender joints	3.00 ± 2.14	1.20 ± 1.47***	1.07 ± 1.10***	2.75 ± 2.38	1.14 ± 0.69	1.00 ± 0.58**	N.D.

Data are shown as mean ± standard deviation values. Data at 14 or 30 weeks were compared with those at baseline. Infliximab group consisted of RA patients treated with infliximab combined with MTX and the MTX group of those treated with MTX alone. Serum levels of IL-17 and IL-23 in RA patients at baseline were compared with those of control group using the Mann–Whitney U test

IL interleukin, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *CA-RF* carbohydrate–rheumatoid factor, *DAS28* Disease Activity Scores of 28 joints, *N.D.* not done

* $p < 0.001$ vs. the levels of control group, ** $p < 0.05$ vs. baseline level, *** $p < 0.01$ vs. baseline level

Table 2 Correlations between serum interleukin (IL)-23 levels and other clinical and laboratory parameters at baseline before the initial treatment with infliximab or methotrexate (MTX) in rheumatoid arthritis (RA) patients

	Correlation coefficient	*P* value
Serum IL-17	0.257	0.149
CRP	0.019	0.876
CA-RF	0.007	0.573
ESR/1h	0.001	0.993
DAS28	0.263	0.026*
Number of swollen joints	0.283	0.016*
Number of tender joints	0.183	0.12

Single regression analysis between serum IL-23 levels and other clinical and laboratory parameters was performed. Sample levels and clinical parameters were evaluated at baseline before the initial treatment with infliximab or MTX, and data are shown by correlation coefficient. The statistical significance of correlation was determined with Pearson's correlation test

CRP C-reactive protein, *CA-RF* carbohydrate–rheumatoid factor, *ESR* erythrocyte sedimentation rate, *DAS28* Disease Activity Scores of 28 joints

* $p < 0.05$

Table 3 Correlations between the differences of serum interleukin (IL)-23 levels (ΔIL-23) and those of other clinical and laboratory parameters at baseline and 30 weeks from initial treatment of infliximab in rheumatoid arthritis (RA) patients

	Correlation coefficient	*P* value
ΔIL-17	0.273	0.2
ΔCRP	0.149	0.29
ΔCA-RF	0.201	0.152
ΔESR/1h	0.306	0.035*
ΔDAS28	0.341	0.013*
Δ number of swollen joints	0.083	0.557
Δ number of tender joints	0.377	0.006**

The differences of serum IL-23 levels at baseline and 30 weeks from initial treatment of infliximab in RA patients are shown by ΔIL-23. Additionally, differences of the serum levels of IL-17, C-reactive protein (CRP), and carbohydrate–rheumatoid factor (CA-RF), erythrocyte sedimentation rate (ESR)/1 h, Disease Activity Score of 28 joints (DAS28), number of swollen joints, and the number of tender joints at baseline and 30 weeks from initial treatment of infliximab in RA patients are also shown by ΔIL-17, ΔCRP, ΔCA-RF, ΔESR/1 h, ΔDAS28, Δ number of swollen joints, and Δ number of tender joints. Single regression analysis between ΔIL-23 levels and ΔIL-17, ΔCRP, ΔCA-RF, ΔESR/1 h, Δ DAS28, Δ number of swollen joints, and Δ number of tender joints was performed. Data are shown by correlation coefficient. The statistical significance of correlation was determined with Pearson's correlation test

* $p < 0.05$, ** $p < 0.01$

IL-17 levels did not show a significant correlation ($r = 0.257$, $p = 0.149$).

Correlations between the differences of serum IL-23 levels and those of other clinical and laboratory parameters at baseline and 30 weeks from initial treatment with infliximab ΔIL-23 levels showed significant correlation with ΔESR/1 h ($r = 0.306$, $p < 0.05$), ΔDAS28 ($r = 0.341$, $p < 0.05$) and Δ number of tender joints ($r = 0.377$, $p < 0.01$; Table 3).

Discussion

The use of TNF-α inhibitors can affect the production of a variety of cytokines, chemokines, mitogens, and proteases that may exist at a site downstream of a TNF-α cascade in RA patients. To analyze the in vivo mechanism of the clinical efficacy of infliximab, we measured the serum levels of IL-17 and IL-23 in RA patients at pre- and posttreatment of infliximab combined with MTX and of MTX alone. Serum IL-23 levels were significantly decreased by treatment with infliximab combined with MTX but not by that with MTX alone. Interleukin-17 levels remained significantly unchanged in both groups. This indicates the novel function of infliximab and the possibility that the cascade by which TNF-α induces IL-23 production actually occurs in vivo. In three RA patients who had a good response by EULAR response criteria to treatment with MTX, serum IL-23 levels at baseline was not significantly changed at 30 weeks (data not shown). This may suggest the possibility that the reduction of serum IL-23 levels by infliximab treatment depends on not so much on the general suppression of inflammation of RA as TNF-α blocking.

Although the role of IL-23 in the inflammatory process in RA has been incompletely understood, there are several recent reports indicating the association of IL-23 in RA. Interleukin-23 has been detected in RA synovial fibroblasts, monocytes, and monocyte-derived dendritic cells [11]. Interleukin-23 induces the development of collagen-induced arthritis, which has been considered to be an arthritic model of RA [16]. Interleukin-23 stimulates the differentiation of osteoclast precursors by enhancing the differentiation of osteoclast precursors via IL-17 release from CD4(+) T cells, and thus contributes to osteoclastogenesis [17]. In addition, IL-17 has been reported to induce human synoviocytes to produce IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor, and it induces osteoclastogenesis [18] and leads to bone resorption [19, 20]. On the other hand, IL-23 itself has been reported to induce the ex vivo production of IL-1 and TNF-α by macrophages [21].

In our previous study, the soluble TNF-α receptor, etanercept, suppressed disease activity and reduced serum IL-23 levels in RA patients, and DAS28 of the RA patients

was correlated with serum IL-23 levels [22]. In the study presented here, serum IL-23 levels correlated with DAS28 and number of swollen joints. Furthermore, reduction levels of IL-23 after infliximab treatment correlated with those of ESR/1 h, DAS28, and number of tender joints. This may suggest that IL-23 may play some role in the inflammatory processes of RA. In addition, IL-23 levels in RA SF were higher than those in osteoarthritis SF and showed a significant correlation with IL-17 levels [22]. This significant correlation led us to hypothesize that IL-23 induces the production of IL-17. Although the lack of correlation between serum levels of IL-23 and those of IL-17 in this study does not elucidate the existence of this cascade in vivo, the study is an indirect examination in which we used TNF-α blocker to investigate whether IL-17 production depends on IL-23. An experiment in which IL-23 is directly blocked will clarify whether there is a cascade in which IL-23 induces IL-17 production in vivo. Also in this study, serum IL-17 levels in RA patients treated with etanercept were not significantly changed after etanercept treatment [23]. Therefore, it is assumed that IL-17 production in RA patients in vivo may not depend on the direct stimulation by TNF-α but may be induced by another substance. For example, IL-15 has been known to up-regulate IL-17 production [24, 25]. In our study, infliximab reduced the serum levels of IL-23 in RA patients, and this is considered to be an important action of infliximab in RA treatment. Further study of direct blocking of IL-23 in experimental arthritis or in RA patients is important for the development of new treatments for RA. To investigate whether the use of an IL-23 blocker can regulate bone and joint destruction in patients with RA is an interesting theme for future study.

Conflict of interest statement None.

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