Infliximab But Not Methotrexate Induces Extra-High Levels of VLDL-Triglyceride in Patients with Rheumatoid Arthritis

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ABSTRACT ***Objective***. Tumor necrosis factor (TNF-α), a pivotal inflammatory cytokine, is known to induce proatherogenic changes in the lipid profile and may increase the cardiovascular risk of patients with rheumatoid arthritis (RA). We examined the effects of anti-TNF-α antibody (infliximab, IFX) compared with methotrexate (MTX) on lipid profiles in patients with RA.

Methods. We selected retrospectively all patients with refractory RA (n = 32) who achieved a successful outcome (DAS-28 score < 2.6) in 6 months with IFX treatment, and control groups of age- and sex-matched patients with active RA treated with MTX and healthy participants. We traced fasting serum levels of total cholesterol (TCHO) and triglyceride (TG) for 6 months and used an online dual enzymatic method for simultaneous quantification of cholesterol (CHO) and TG by high performance liquid chromatography (HPLC).

Results. Mean C-reactive protein levels (baseline 4.5) fell to below 1 in 6 months. MTX treatment elevated and normalized TCHO and TG levels. IFX treatment, however, preferentially induced extra-high TG levels. HPLC analyses identified similar CHO profiles between patients treated with IFX or MTX, but IFX selectively induced a huge VLDL-TG peak. Statins successfully controlled these extra-high TG levels.

Conclusion. In patients successfully treated with IFX or MTX, CHO levels were elevated and normalized, but IFX treatment preferentially induced extra-high levels of VLDL-TG. Thus, there is differential regulation of the lipid profile between IFX and MTX, necessitating careful attention to TG levels with IFX treatment. (First Release Sept 1 2007; J Rheumatol 2007;34:1997–2004)

Key Indexing Terms:
TUMOR NECROSIS FACTOR-α VLDL TRIGLYCERIDE
RHEUMATOID ARTHRITIS C-REACTIVE PROTEIN

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology predominantly involving multiple joints. During the inflammatory response, multiple alterations of intermediary lipid metabolism occur.

It has been reported that cardiovascular disease (CVD) and mortality are increased in patients with RA compared to the general population[1-3]. Moreover, patients with RA have an increased prevalence of subclinical atherosclerosis, exhibiting increased carotid intima-media thickness as well as decreased arterial compliance[4].

The pattern of lipid metabolism during inflammation is proatherogenic, and is believed to contribute to atherosclerosis, especially in chronic inflammatory diseases such as RA[5].

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Although results vary, these reports suggest that an altered lipoprotein pattern in patients with RA could contribute to the increased risk of CVD in RA[6,7]. In patients with RA, treatment with antifolates was shown to raise homocysteine levels, which was also characterized as an independent risk factor for developing CVD[8].

Tumor necrosis factor-α (TNF-α), one of the major inflammatory cytokines, plays a critical role in RA pathogenesis and reportedly contributes to this altered lipid metabolism[9,10]. TNF-α has been found to increase levels of serum lipids[11]. In recent years, TNF-α has been the target of biological therapy. Infliximab (IFX) is a chimeric anti-TNF-α monoclonal antibody that specifically binds to both soluble and membrane-bound TNF-α and forms stable non-dissociating immune complexes[12].

IFX is used today for the treatment of RA and other rheumatic diseases and is effective against active RA refractory to methotrexate (MTX)[13,14]. However, reports describing the influence of anti-TNF-α on lipid profile are confusing. One group found that lipid profiles became more atherogenic[15], but other groups found an improvement in the lipid profile[16,17]. Moreover, information on the effects of treatment with IFX on triglyceride (TG) is limited.

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We investigated lipid profiles, specifically TG profiles, in patients with RA who were successfully treated with IFX or MTX. In addition, we sought to clarify the differences between the IFX and MTX treatment in their effects on lipid profiles[18,19].

MATERIALS AND METHODS

Patients. We studied Japanese patients with RA who met 1987 American College of Rheumatology revised criteria for RA[20] and were treated at Bell Land General Hospital. Active or refractory RA was defined as a Disease Activity Index 28 Joint Score (DAS-28) of at least 3.2. For patients with active RA, 5 mg of prednisolone was introduced daily, and most patients received MTX (6 mg/m^2 weekly). Patients with RA refractory to treatment using disease modifying antirheumatic drugs (DMARD) that included MTX received IFX in addition to MTX (6 mg/m^2 weekly) and prednisolone (5 mg daily). Patients received IFX at Weeks 0, 2, and 6, and every 8 weeks thereafter.

Of the 43 patients with refractory RA we treated with IFX, 32 patients achieved a successful outcome. We retrospectively selected all patients with refractory RA (n = 32) who achieved a successful outcome (DAS-28 score less than 2.6) in 6 months with IFX treatment. In addition, 32 age- and sex-matched patients with active RA treated with MTX (6 mg/m^2 weekly) and prednisolone (5 mg daily) who had a successful outcome were selected, as well as healthy controls who were also enrolled in the study. All participants were living independently and taking no medications known to affect lipid metabolism (such as lipid-lowering agents, ß-blockers, oral contraceptives, estrogen, progestin, or thyroxine). Patients with signs of liver or kidney disorder, nephrotic syndrome, alcoholism, and thyroid abnormalities were excluded. No patient was selected who had diabetes mellitus, syphilis, acute infection, malignant neoplasm, sign of ischemic heart disease, iatrogenic Cushing's disease, or obesity. Pregnant women were excluded, as were patients with a history of blood transfusion. No patient was overweight or on a vegetarian diet. At the beginning of the study, we instructed the patients not to change lifestyle during the study, especially diet. This study was conducted with the approval of the Human Experimentation Committee of our institute and with the informed consent of the patients.

Measurement of lipid profiles and C-reactive protein (CRP). Lipid profiles were examined at baseline and then monthly. Blood samples were collected in the early morning after a 12-h overnight fast. Blood was allowed to clot for 45 min at room temperature, and serum was obtained immediately by centrifugation at 3000 rpm for 10 min. TCHO and TG were measured using Boehringer diagnostic kits employing an enzymatic colorimetric method. CRP was measured using routine methods.

Quantification of CHO and TG by high performance liquid chromatography (HPLC). Serum samples were obtained from the patients and serum lipoproteins analyzed by HPLC, as described[21,22]. In brief, 5 µl of whole-serum sample was injected into 2 connected columns (300 × 7.8 mm) of TSKgel Lipopropak-XL (Tosoh, Tokyo, Japan) and eluted with TSKeluent Lp-1 (Tosoh). The effluent from the columns was continuously monitored at 550 nm after an online enzymatic reaction with a commercial kit, Determiner L TC (Kyowa Medex, Tokyo, Japan). The CHO and TG concentrations in major lipoproteins and their subclasses were calculated using a computer program designed to process complex chromatograms with modified Gaussian curve-fitting for resolving overlapping peaks.

We determined the number, position, and width of each Gaussian component peak for subclass analysis to carry out a sufficient curve-fitting analysis of various samples under constant conditions in which the peak width and position of each Gaussian curve did not change.

Treatment with HMG-CoA reductase inhibitor. In some patients, the HMG-CoA reductase inhibitor atorvastatin (Pfizer, 10 mg/day) was given orally after 6 months of IFX therapy to counter unfavorable elevation of the levels of TCHO and TG, especially VLDL-TG.

Statistical analysis. Results are expressed as means ± SD. Lipid values in RA patients and controls were compared using the unpaired Student's t test. Within-group changes were analyzed with analysis of variance test. A $p < 0.05$ was considered to indicate significance.

RESULTS

Patient characteristics. Following treatment in 43 patients with refractory RA with IFX, 32 patients had a successful outcome. In the 11 patients with unsuccessful outcomes, 3 had stopped IFX 6 months before, and DAS-28 score at 6 months was > 2.6 in 8 patients. Moreover, CRP levels in these patients did not decrease significantly in 6 months and the levels of TCHO and TG did not change significantly (Table 1) when the data of unsuccessful outcomes were compared with those of successful patients.

Of the 32 patients with refractory RA who had achieved successful outcome with IFX, 27 were women. As a control, 32 age- and sex-matched patients with active RA who had achieved successful outcomes with MTX and 32 healthy controls were selected and enrolled.

The mean age of patients was 57 years, and their disease duration was 9.5 (IFX) and 6.1 (MTX) years, respectively (Table 2). At baseline, the mean DAS-28 score and the mean CRP levels did not differ between the 2 groups. All patients had already received 5 mg of prednisolone at baseline.

Dyslipidemia in patients with active and refractory RA at baseline. In the patients with active and refractory RA, the fasting serum levels of TCHO and TG were compared (Table 2). The mean levels of total cholesterol (TCHO) and TG in both groups of RA patients were lower than those in healthy controls but were within normal limits and did not differ significantly between the 2 groups. These results suggest that the patients with active and refractory RA showed similar dyslipidemia[23,24] at baseline.

Efficacy of IFX and MTX treatments. When patients with

Table 1. Characteristics of the patients with and without successful outcomes by IFX. Forty-three patients with refractory RA were treated with IFX and 32 patients obtained successful outcome in 6 months. Of 11 patients with unsuccessful outcomes, 3 stopped IFX before 6 months. The data of the 3 patients were obtained at the end of the study and were included as data at 6 months.

	Outcome Therapy	At Baseline	At 6 mo	p
CRP, mg/dl	Successful (n = 32)	4.5 ± 2.4	0.3 ± 0.2	< 0.001
	Unsuccessful (n = 11)	4.9 ± 2.1	3.3 ± 1.5	0.067
			p < 0.001*	
DAS-28	Successful	4.6 ± 0.9	2.2 ± 0.3	< 0.001
	Unsuccessful	4.9 ± 0.7	4.7 ± 0.7	0.120
			p < 0.001*	
TCHO, mg/dl	Successful	167 ± 28	214 ± 39	< 0.001
	Unsuccessful	167 ± 38	178 ± 33	0.478
			p = 0.006*	
TG, mg/dl	Successful	92 ± 35	207 ± 71	< 0.001
	Unsuccessful	95 ± 39	105 ± 38	0.589
			p < 0.001*	

* p value (successful vs unsuccessful outcome).

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Table 2. Baseline demographic and clinical characteristics of the study subjects.

	Active RA Treated with MTX, n = 32	Refractory RA Treated with IFX, n = 32	Controls, n = 32
Male/female	5/27	5/27	5/27
Age, yrs	57 ± 13	57 ± 13	57 ± 13
Disease duration, yrs	6.1 ± 4.7	9.5 ± 7.2	—
Body mass index, kg/m^2	20.8 ± 1.8	21.8 ± 2.1	21.2 ± 1.9
IgM rheumatoid factor, +/–	22/10	23/9	2/30
CRP mg/dl			
At baseline	4.9 ± 2.2	4.5 ± 2.4	< 0.3
At 6 mo	0.4 ± 0.2	0.3 ± 0.2	
DAS-28			
At baseline	4.8 ± 1.0	4.6 ± 0.9	—
At 6 mo	2.3 ± 0.3	2.2 ± 0.3	
Prednisolone use, 5 mg/day	100%	100%	—
MTX use, 6 mg/m^2	0%	89%	—
Other DMARD*	21%	100%	—
NSAID use	95%	89%	—
TCHO, mg/dl†	163 ± 24	167 ± 28	199 ± 22
TG, mg/dl†	85 ± 33	92 ± 35	122 ± 18

DAS-28: Disease Activity for 28 Joint Indices Score; DMARD: disease modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drug. * Before starting of MTX and IFX therapy, the patients had received D-penicillamine, gold sodium thiomalate, minocycline, or sulfasalazine. † Blood samples were collected in the early morning after 12-h overnight fast.

refractory disease were treated with IFX, levels of CRP decreased rapidly, i.e., in a month or 2; in contrast, CRP levels in RA patients with active disease treated with MTX decreased gradually (Figure 1A). After 6 months of treatment, the mean levels of CRP had fallen to below 1 in both groups of patients. Clinical improvement occurred in parallel with the decrease in CRP levels and DAS-28 scores.

Effects of IFX and MTX treatments on the levels of TCHO. In

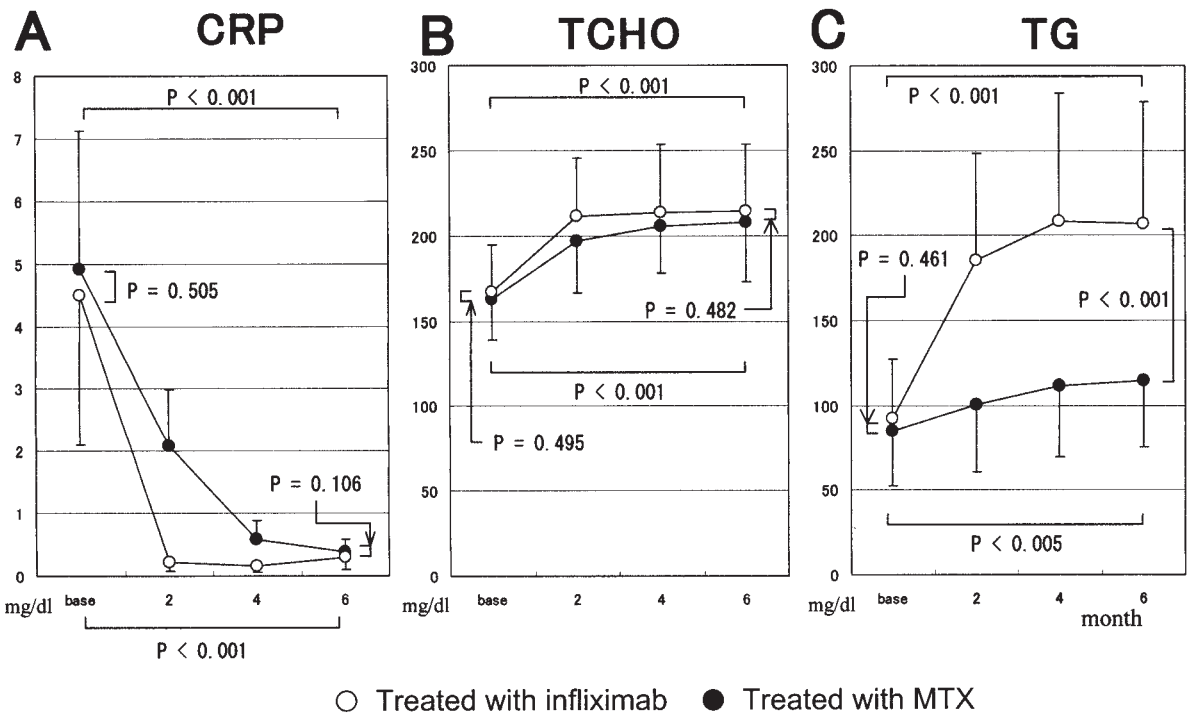

Figure 1. Changes from baseline in serum levels of C-reactive protein (CRP), total cholesterol (TCHO), and triglycerides (TG) in patients with RA treated with infliximab (IFX) and methotrexate (MTX). Levels of CRP (A), TCHO (B), and TG (C) were traced for 6 months in 32 RA patients treated with IFX and in 32 age-matched RA control patients treated with MTX. The mean levels (SD) of CRP, TCHO, and TG are shown. Each parameter was compared with its baseline value. Values are the mean for each group at each point.

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patients with active or refractory RA who achieved a successful outcome with either IFX or MTX treatment, the levels of TCHO and TG were traced. At 6 months, TCHO levels were elevated and normalized in both groups of patients (Figure 1B), and the levels of TCHO did not differ significantly between the 2 groups. The response of the TCHO levels exhibited a strong inverse correlation with the response of CRP in patients treated with IFX and MTX. These results suggest that the upregulation of TCHO is not the result of treatment but is actually the result of an improvement in disease activity or dyslipidemia.

Induction of high levels of TG preferentially in patients treated with IFX. When patients were successfully treated with IFX and MTX, TG levels were also significantly elevated (Figure 1C). At 6 months after a successful outcome, assessment of TG showed levels were upregulated and normalized in patients treated with MTX. In contrast, TG levels were above normal limits in patients treated with IFX. Elevation of TG levels in IFX-treated patients (117%) was significantly greater than that in MTX-treated patients (34%).

Quantification of CHO and TG levels by HPLC whole-serum samples from patients and healthy controls were analyzed for CHO and TG using a dual-detection HPLC system with 2 connected TSK columns. The elution patterns of age-matched patients were compared before and at 6 months after treatment (see Figure 2 for a typical sample). The results gave 3 separate peaks in the CHO and TG profiles. In the age-matched healthy controls (Figure 2A and 2B), the first peak eluted at fractions 4–6 and contained VLDL; the second peak, at fractions 8–11, contained LDL; and the third peak, eluted at fractions 15–19, contained high density lipoprotein (HDL). In an MTX-treated patient (Figure 2C, 2D), the peaks of LDL and HDL were elevated only slightly in the CHO and TG profile. When the samples of an age-matched patient treated with IFX were examined, the CHO profiles were similar to those of the patient treated with MTX (Figure 2E). In contrast, a huge peak of VLDL-TG was induced at about fractions 3–6 on the TG profile in the IFX-treated patient (Figure 2F). This VLDL-TG peak was very small in the age-matched healthy control group and patients treated with MTX. The profiles of the LDL- and HDL-TG peaks did not differ significantly among IFX- and MTX-treated patients and healthy controls.

Further experiments were carried out to examine whether the appearance of the VLDL-TG applied to other patients treated with IFX. The typical samples of dual-HPLC analysis of 3 IFX- and age-matched MTX-treated patients are shown (Figure 3). The huge VLDL-TG peaks were eluted at fractions 4–6 in all patients treated with IFX, with variations in the peak

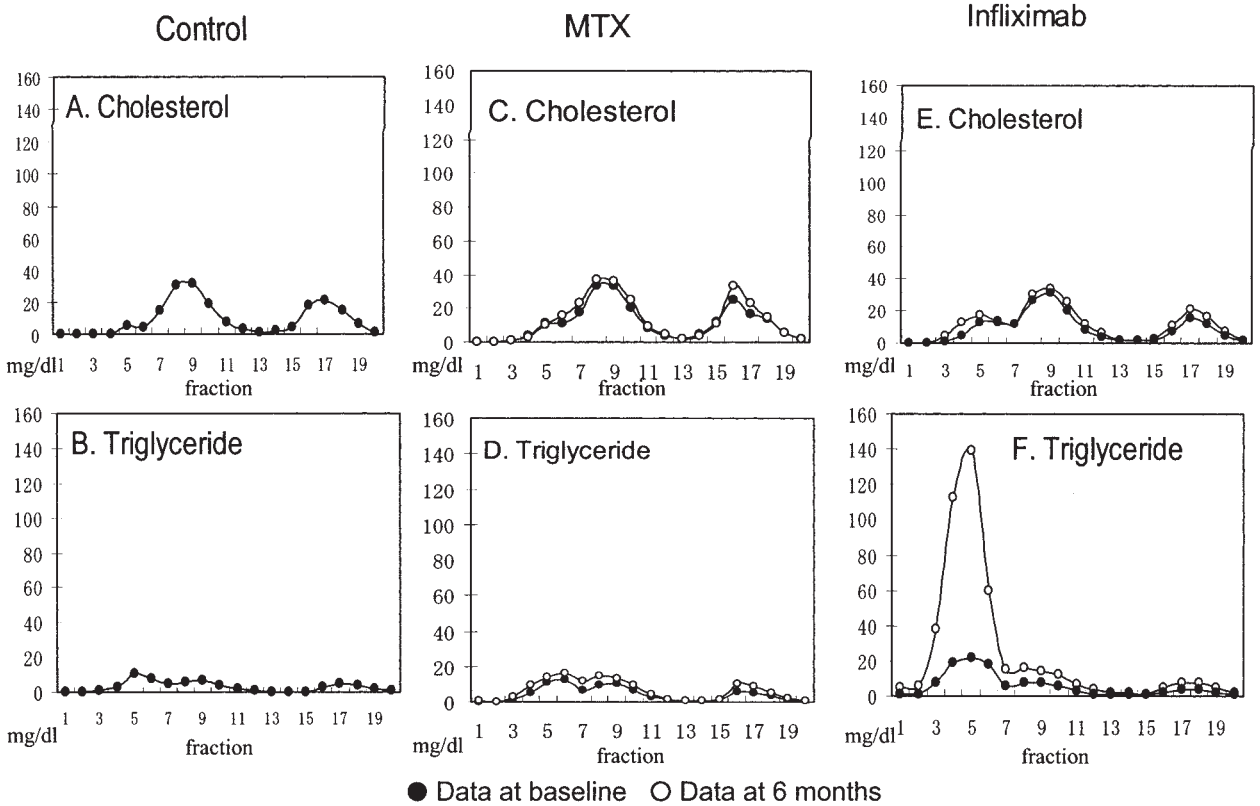

Figure 2. Comparison of the CHO and TG profiles in patients treated with MTX versus IFX-treated patients, using high performance liquid chromatography (HPLC) analysis at baseline and at 6 months. Serum samples from age- and sex-matched representative RA patients (65-year-old women) treated with IFX (E, F) and MTX (C, D) at baseline and after 6 months were subjected to gel-filtration HPLC, and the TG and CHO content of each fraction was examined. As a control, a sample of age- and sex-matched healthy control subjects (A, B) was also analyzed.

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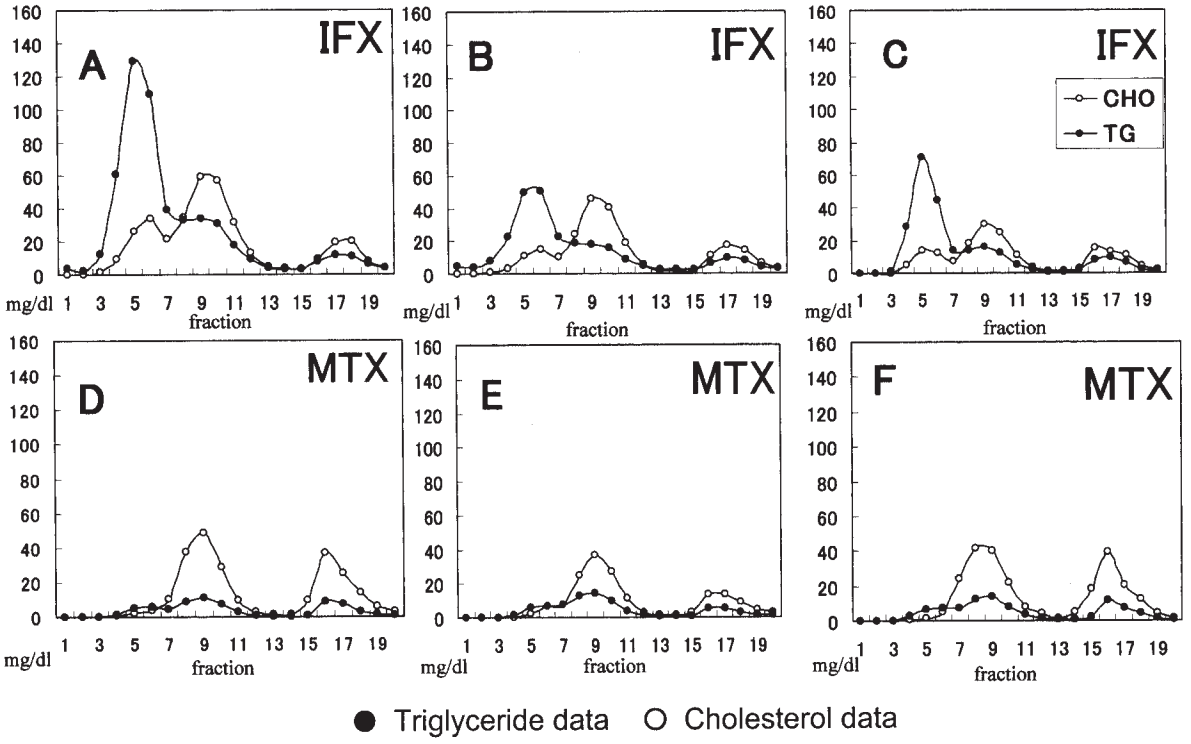

Figure 3. Representative lipid profiles from HPLC analysis of patients with RA treated with IFX and with MTX. After treatment with IFX (A, B, C) or MTX (D, E, F) for 6 months, serum samples were subjected to gel-filtration HPLC, and the TG and CHO content of each fraction was examined.

height. However, no significant VLDL-TG peak was eluted in the age-matched, MTX-treated patients. In IFX-treated patients, the smaller VLDL-CHO peaks were also confirmed. The heights of the HDL- and LDL-CHO peaks did not differ among patients. These results suggest that successful treatment with MTX and IFX upregulates the CHO profile similarly, while IFX treatment induces the VLDL peak, especially VLDL-TG, preferentially.

Recovery of the levels of TG and TCHO by statin therapy. To counter the unfavorable elevation of the levels of TCHO and TG, especially VLDL-TG, in IFX-treated patients, the HMG-CoA reductase inhibitor atorvastatin was given orally at 6 months. In response, levels of both TG and TCHO were downregulated and normalized in 4 months (Figure 4). Moreover, the VLDL-TG peak was also downregulated, based on HPLC analysis. The HPLC analysis was carried out at 6 months and at 10 months in 2 representative patients treated with IFX.

DISCUSSION

Three primary findings confirmed in our study are as follows: (1) successful treatment of disease activity with both IFX and MTX upregulated and normalized TCHO levels; (2) successful treatment with MTX normalized TG levels but IFX induced high TG levels, especially VLDL-TG; and (3) atorvastatin therapy downregulated the levels of VLDL-TG in these patients.

We show for the first time that successful treatment with IFX but not MTX induced extra-high levels of VLDL-TG in patients with RA. Published reports regarding patients with refractory RA treated with IFX yielded variable results for lipid profiles[15,25-27], but most articles reported that TCHO and TG levels were elevated and normalized[16,18,19,27]. These results are in accordance with our present findings for patients treated with MTX. However, with IFX treatment we observed that TG levels, especially VLDL-TG, became extremely high, in contrast to reports by others[18,19,27,28] showing elevation of TG levels within normal limits, although information on the effects of treatment with IFX on TG is limited[18,19].

The discrepant results may arise from the fact that these studies were conducted without consideration of the efficacy of IFX therapy. We enrolled all patients who achieved a successful outcome over 6 months because, as reported, not all patients achieve successful control with IFX or MTX[29]. In our study, 32 patients out of 43 obtained a successful outcome. In patients who could not obtain a successful outcome with IFX or MTX, TCHO and TG levels were as low as those of patients with refractory disease at baseline (Table 2). Moreover, we analyzed lipid profiles employing a unique method[21,22] that enabled the quantification of TCHO and TG simultaneously by HPLC, and these analyses yielded high levels of VLDL-TG with IFX therapy in patients with RA.

Our study was done in a Japanese population and we selected only good responders. Therefore, we must consider

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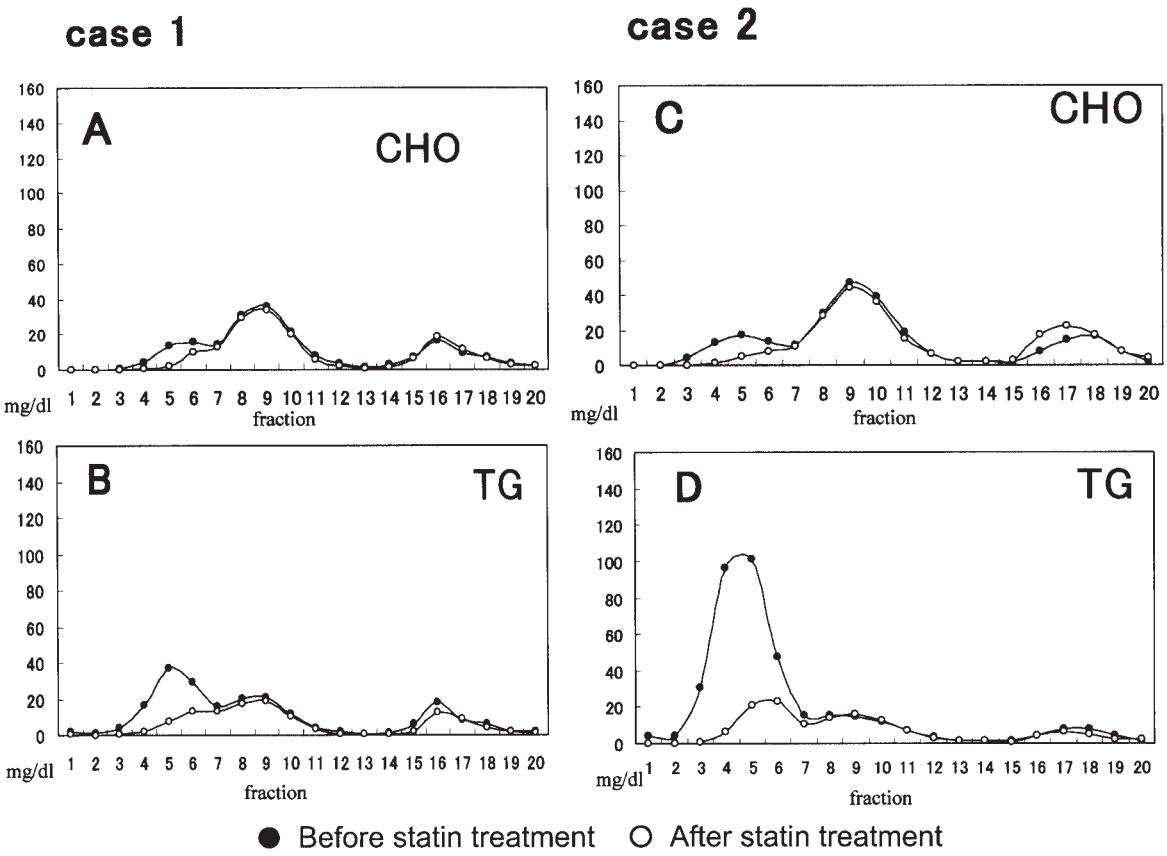

Figure 4. Effects of statins on lipid profiles of patients treated with IFX. The patients in whom high levels of TG were induced by IFX treatment were given oral statin (atorvastatin). Serum samples were obtained from the representative patients (case 1 and 2) before and after treatment with statin and were subjected to gel-filtration HPLC. The TG (A, C) and CHO (B, D) content of each fraction was examined. TG levels before statin treatment were 213 (case 1) and 382 (case 2), and those after the treatment were 120 (case 1) and 136 (case 2).

the possibility of a particular phenotype allowing them to have such response on TNF blockade.

At baseline, our patients had high disease activity, higher than normal blood levels of acute-phase reactants such as TNF-α and interleukin 6 (IL-6)[30], and important factors in the development of dyslipidemia involving low TCHO and TG levels[23,24]. After patients were successfully treated with IFX or MTX, the levels of CRP normalized, and the levels of TCHO also increased, suggesting that this elevation of TCHO levels merely reflected a decrease in inflammation and recovery from dyslipidemia. However, the induction of high levels of TG, especially VLDL-TG, by IFX treatment cannot be explained as merely the result of successful control of inflammation; successful treatment with MTX did not induce these high TG levels. Taken together, these results suggest differential effects of MTX and IFX treatments on TG levels in patients with RA.

This difference in effect is partly explained by the function of IFX, i.e., the blockade of TNF-α. The critical role of TNF-α in lipid metabolism, especially TG, is unclear because reports describing the influence of TNF-α on the lipid profile are not all in agreement. Among its multiple effects, TNF-α can induce elevation of CHO and TG in murine models[31,32]. In addition, administration of TNF-α in humans can also induce an increase in VLDL-TG[33,34], representing an early manifestation of the acute-phase response. This result is attributable to increased de novo fatty acid synthesis in the liver and esterification to form TG, induction of lipolysis in adipose tissue, and decreased lipoprotein lipase (LPL) activity[35]. In some patients, we compared LPL activity before and after IFX therapy, but at present, the activity did not change significantly.

Based on these assertions, one would expect a decrease in TG concentrations after anti-TNF-α therapy, but this was not the case in our study. The persistent inflammatory condition of elevated serum TNF-α levels in humans reportedly results in low levels of TCHO and TG, especially in RA[23,24], and it has been suggested that in the chronic phase, persistently higher TNF-α levels elicit low TCHO and TG levels, as shown in this study. However, in some circumstances, blockade of TNF-α and the resulting low levels of TNF-α might induce a high level of VLDL-TG. In addition to TNF-α, other cytokines, including IL-1ß and IL-6, can modulate lipid metabolism[36,37]. TNF-α is a major inducer of these cytokines and TNF-α neu-

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tralization may result in their decrease. Therefore, it is possible that the positive effect of TNF-α blockade on the lipid profile is also mediated by inhibition of other cytokines. In support of this idea are findings of high levels of VLDL-TG in IL-6 knockout mice with low levels of TNF-α[38].

Because all patients received 5 mg of prednisolone, the possibility that our findings are due to the effects of prednisolone is ruled out[39]. However, the precise mechanism explaining why VLDL-TG levels were preferentially elevated in patients treated with IFX is not currently clear, and further studies are necessary.

In conclusion, we have shown that IFX therapy induces extra-high levels of TG, which is positively associated with cardiovascular risk. However, statin treatment normalized elevated TG levels. Therefore, we should be careful to assess TG levels, especially VLDL-TG, in treatment with IFX.

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