Effect of Repeated Infliximab Therapy on Serum Matrix Metalloproteinases and Tissue Inhibitors of Metalloproteinases in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Matrix metalloproteinases (MMP) are involved in the articular tissue destruction processes in the pathogenesis of rheumatoid arthritis (RA). We investigated the effects of multiple infusions of infliximab, a chimeric anti-tumor necrosis factor-α (anti-TNF-α) antibody, on concentrations of serum MMP and tissue inhibitors of metalloproteinases (TIMP) in patients with active RA.

Methods. Patients with RA were scheduled to receive 9 infusions of infliximab (3 mg/kg) at Weeks 0, 2, 6, and every 8 weeks thereafter. The therapy was combined with methotrexate (MTX) (7.5–20 mg/week). Serum concentrations of interstitial collagenase (MMP-1), stromelysin-1 (MMP-3), gelatinase B (MMP-9), TIMP-1, and TIMP-2 were measured by ELISA prior to infusion at Weeks 0, 2, 6, 14, 38, and 62.

Results. The initial infusion of infliximab downregulated serum levels of MMP-1 ($p < 0.001$), MMP-3 ($p < 0.001$), MMP-9 ($p < 0.001$), TIMP-1 ($p < 0.01$), and TIMP-2 ($p < 0.05$). The second drug administration caused even more remarkable reduction of measured MMP ($p < 0.001$ in all cases) but not of TIMP levels. These changes were accompanied by decreased ratios of measured MMP to TIMP. Further infliximab therapy also significantly suppressed serum MMP levels, but was less effective. Before the first infliximab infusion serum concentrations of MMP and TIMP correlated with markers of RA activity such as the Disease Activity Score and C-reactive protein levels. After further drug administrations such associations, although less significant, were also noted.

Conclusion. Anti-TNF-α antibody therapy combined with MTX resulted in rapid clinical improvement and reduced serum MMP concentrations in patients with RA. Further infusions of infliximab maintained the decrease of MMP, although to a lesser extent than the first and second doses. (J Rheumatol 2004;31:238–42)

Key Indexing Terms:
MATRIX METALLOPROTEINASES TISSUE INHIBITORS OF METALLOPROTEINASES
RHEUMATOID ARTHRITIS INFLIXIMAB

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by an invasive and tissue destructive infiltrate of lymphocytes, macrophages, and synoviocytes formed in the joints[1,2]. The etiopathogenesis of the disease and the role of specific cells infiltrating the synovium are not fully understood. Macrophages and synovial fibroblasts are believed to be involved in tissue destruction by several mechanisms, including the production of cytokines and matrix metalloproteinases (MMP)[3-6]. Their production by macrophages and fibroblasts seems to be regulated by lymphocytes[6-8]. MMP are the enzymes responsible for the proteolytic degradation of extracellular matrix components. Their production is stimulated by such cytokines as interleukin 1ß (IL-1ß) and tumor necrosis factor-α (TNF-α)[1,6,9]. The action of MMP is controlled by tissue inhibitor of metalloproteinases (TIMP), which neutralizes MMP. TIMP production is enhanced by cytokines including transforming growth factor-ß (TGF-ß), IL-6, IL-11, and probably also by TNF-α[1,6,10,11]. Thus MMP and TIMP, and especially the imbalance of the enzyme to inhibitor ratios, are thought to play an important role in the remodeling of articular tissues[12-15].

Single administration of the chimeric anti-TNF-α monoclonal antibody infliximab was shown to decrease activity in RA[16-19], and specifically to reduce serum concentrations of MMP-1, MMP-3, and TIMP-1[13]. We investigated the effect of repeated infusions of infliximab on serum MMP and TIMP levels, and ratios of MMP to TIMP, in patients with active RA.

MATERIALS AND METHODS

Patients and samples. Fourteen patients who fulfilled the American College of Rheumatology 1987 revised criteria for RA[20] were enrolled into an open, non-placebo-controlled study. No patient had a history of tuberculosis or symptoms of infectious diseases in the previous 3 months. Chest radi-

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Submitted February 21, 2003; revision accepted July 11, 2003.

ographs performed before first infliximab infusion were normal in all patients. One patient stopped the infliximab treatment because of tuberculosis, which was diagnosed after the third infliximab infusion. One patient developed zoster 4 weeks after the sixth drug infusion, and another experienced anaphylactic reaction during the third infliximab infusion. All 3 patients with adverse events discontinued infliximab therapy, and received appropriate treatment. The remaining 11 patients completed 9 infusions of infliximab with no adverse events.

All patients recruited for the study had active RA, as defined by ≥ 6 tender joints, ≥ 6 swollen joints, and 2 of the following: morning stiffness > 45 min, C-reactive protein (CRP) > 20 mg/l, and erythrocyte sedimentation rate (ESR) > 28 mm/h. Clinical and demographic characterization of patients is shown in Table 1. All participants were receiving methotrexate (MTX) (median 12.5 mg/week, range 7.5–20 mg/week) in a stable dose for at least 2 months and nonsteroidal antiinflammatory drugs (NSAID) in a stable dose for at least 4 weeks before enrollment into the study. Five patients were receiving corticosteroids (median 5 mg/day prednisone, range 5–10 mg/day) in a stable dose for at least 4 weeks before beginning the trial. Such treatment regimen with MTX, NSAID, and prednisone was continued through the whole study.

Patients were scheduled to receive 9 infusions of infliximab (3 mg/kg) at Weeks 0, 2, and 6, and every 8 weeks thereafter with the same dose. Blood samples obtained prior to infusion at Weeks 0, 2, 6, 14, 38, and 62 (8 weeks after the last drug infusion) were clotted for 30 min and then centrifuged 10 min at 1000 g. Serum aliquots were stored at –80°C. The study protocol was approved by the local ethics committee and patients' written consent was obtained.

Clinical and laboratory assessment. Evaluations included the duration of morning stiffness (minutes), Ritchie index[21], number of tender joints (of 68 joints assessed), number of swollen joints (of 66 assessed), ESR, Disease Activity Score (DAS)[22], CRP measured by radial immunodiffusion (Nanorid, The Binding Site Ltd., Birmingham, UK), white blood cell (WBC) and platelet counts, and rheumatoid factor (RF). Radiological analysis of joint destruction was performed according to the Steinbrocker criteria[23].

Enzyme linked immunosorbent assays (ELISA). Measurements of serum concentrations of interstitial collagenase (MMP-1), stromelysin-1 (MMP-3), gelatinase B (MMP-9), TIMP-1, and TIMP-2 were carried out with commercial ELISA kits (Biotrak, Amersham Pharmacia Biotech, Little Chalfont, Buckinghamshire, England) according to the manufacturer's instructions as described[8].

Statistical analysis. The normally-distributed data were compared by paired Student's t test. Wilcoxon signed-rank test was used to evaluate the differences between non-normally distributed data. Correlations between variables were assessed by Spearman rank order test. P values < 0.05 were considered statistically significant.

RESULTS

Serum concentrations of MMP and TIMP. After initial infliximab infusion, the concentration of interstitial collagenase (MMP-1) in serum of patients with RA decreased rapidly ($p < 0.001$) (Figure 1). The lowest serum level of MMP-1 was observed after the second infliximab administration. Further drug infusions maintained MMP-1 suppression, although to a lesser extent than the first 2 doses of infliximab. Similarly to the MMP-1, serum concentration of stromelysin-1 (MMP-3) was downregulated following infliximab infusion ($p < 0.001$) (Figure 2). MMP-3 was especially diminished after the second infliximab infusion. The next doses of infliximab prolonged MMP-3 decrease in RA patient serum. The initial infliximab infusion also caused significant reduction in the concentration of gelatinase B (MMP-9) in the RA patient serum ($p < 0.001$) (Figure 3). The MMP-9 level dropped especially after the second infliximab administration. Further drug infusions maintained MMP-9 suppression, although to a lesser extent than the first 2 doses of infliximab.

Serum levels of TIMP-1 and TIMP-2 were also decreased after the initial infliximab infusion, from median 481.0 to 418.0 ng/ml ($p < 0.01$) and from a median 84.0 to 73.5 ng/ml ($p < 0.05$), respectively. However, repeated drug administrations were followed by a tendency to increases of the measured serum TIMP concentrations toward baseline values (data not shown).

Downregulation of serum MMP and TIMP levels was accompanied by decreased ratios of the measured MMP to TIMP-1, and this was especially marked after the second infliximab infusion (Figure 4). However, only in the MMP-3/TIMP-1 ratio was a significant decrease maintained through the whole study. Ratios of measured MMP to

Table 1. Clinical and demographic details of patients with RA. Data are means ± SD.

	RA Patients
Sex, F/M	12/2
Mean age, yrs	45.4 ± 13.4
Mean disease duration, yrs	10.7 ± 6.5
RF positive patients, n	12
Radiological stage II*, n	1
Radiological stage III*, n	9
Radiological stage IV*, n	4

* Steinbrocker criteria.

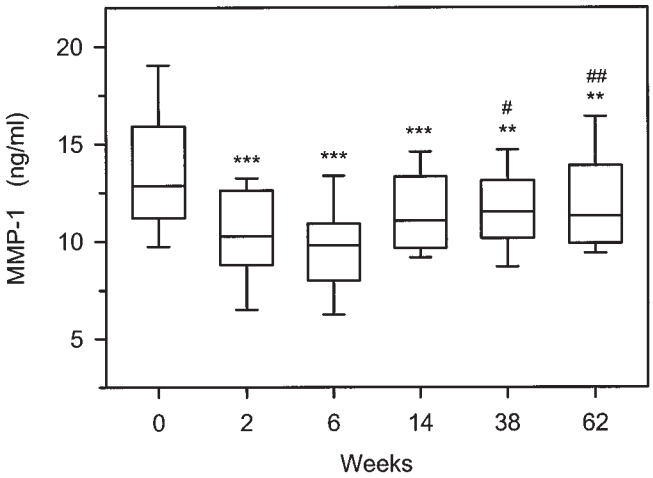

Figure 1. Serum concentrations of interstitial collagenase (MMP-1) in RA patients, by ELISA. Patients were treated with infliximab (3 mg/kg) on Weeks 0, 2, 6, 14, 22, 30, 38, 46, and 54. Blood samples were obtained prior to infusion at Weeks 0, 2, 6, 14, 38, and 62. Box plots represent median (line), 25th and 75th percentiles (box), and 10th and 90th percentiles (whiskers). Significance of differences between preinfusion MMP-1 values at Week 0 and the following weeks: *p <0.05, **p < 0.01, ***p < 0.001. Significance of differences between preinfusion MMP-1 values on Week 2 and the following weeks: #p <0.05, ##p < 0.01, ###p < 0.001.

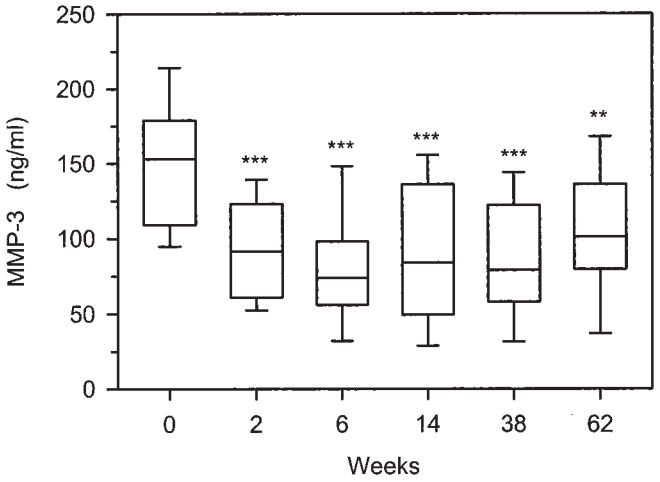

Figure 2. Serum concentrations of stromelysin-1 (MMP-3), determined and presented as described in legend to Figure 1.

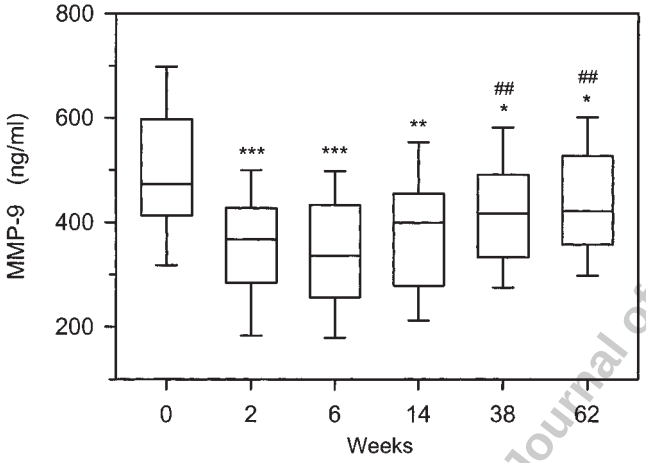

Figure 3. Serum concentrations of gelatinase B (MMP-9), determined and presented as described in legend to Figure 1.

TIMP-2 were also decreased following infliximab therapy (data not shown).

Correlations between serum levels of MMP or TIMP and clinical data. Prior to the first infliximab infusion the serum concentration of MMP-1 correlated with markers of RA activity such as the DAS ($r = 0.653$, $p < 0.05$) and CRP levels ($r = 0.631$, $p < 0.05$). The serum level of MMP-3 was associated with DAS ($r = 0.745$, $p < 0.01$), CRP ($r = 0.780$, $p < 0.001$), and duration of morning stiffness ($r = 0.752$, $p < 0.01$). The serum concentration of MMP-9 correlated with the DAS ($r = 0.921$, $p < 0.001$), CRP ($r = 0.578$, $p < 0.05$), and duration of morning stiffness ($r = 0.607$, $p < 0.05$). The serum level of TIMP-1 was associated with DAS ($r = 0.793$, $p < 0.001$) and CRP ($r = 0.565$, $p < 0.05$). The serum concentration of TIMP-2 correlated with DAS ($r = 0.771$, $p < 0.001$), CRP ($r = 0.547$, $p < 0.05$), and duration of morning stiffness ($r = 0.578$, $p < 0.05$). Such associations were also noted after further drug administrations, but were less

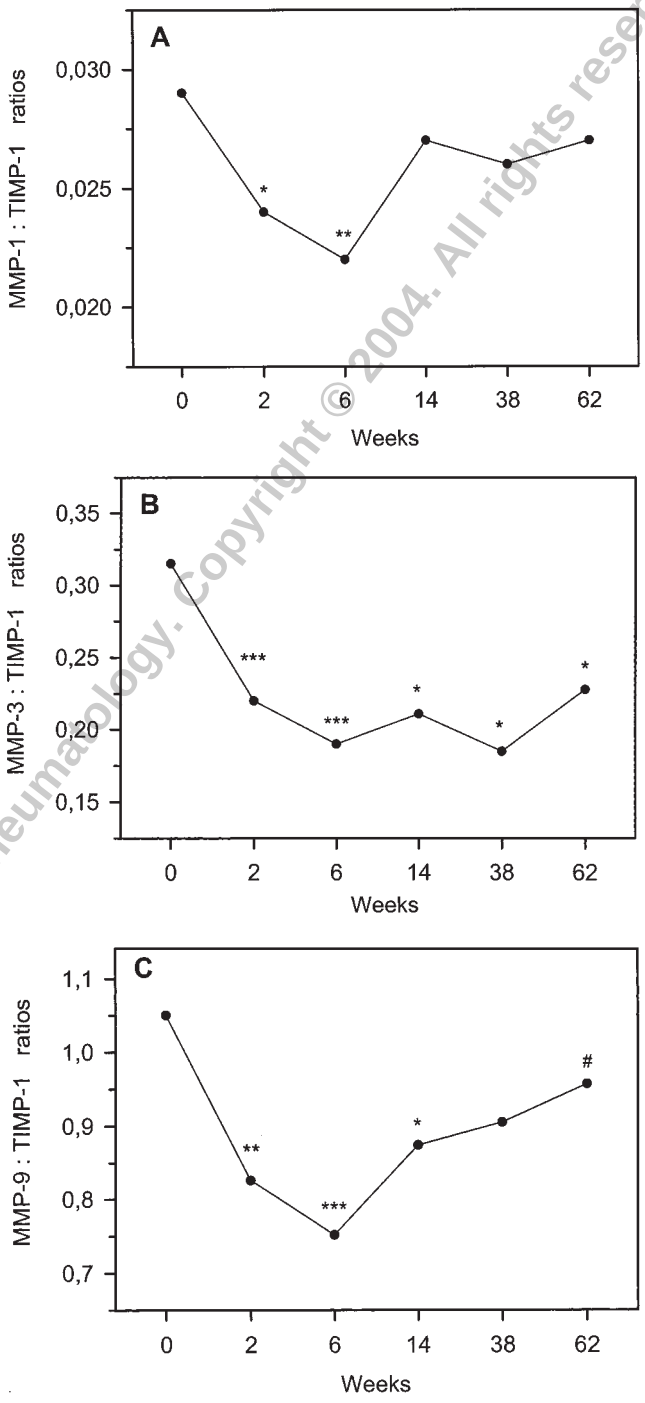

Figure 4. Serum concentration ratios of MMP to TIMP-1. MMP-1:TIMP-1 ratios (A). MMP-3:TIMP-1 ratios (B). MMP-9:TIMP-1 ratios (C). Data presented as described in the legend to Figure 1.

significant. We observed no correlations between patient age, disease duration, and rheumatoid factor with any serum MMP or TIMP concentrations.

Clinical response. The DAS significantly decreased after the first infusion of infliximab as evaluated on Week 2, prior to the next infliximab infusion ($p < 0.001$). The second drug

administration caused even more remarkable reduction of the DAS, and its values remained stable through the whole study (Figure 5). Disease activity measures such as CRP, the Ritchie index, and duration of morning stiffness also decreased significantly after the first infusion of infliximab as assessed on Week 2 (in all cases $p < 0.001$). The second drug administration caused even more remarkable reduction of the Ritchie index and duration of morning stiffness, which remained stable until the end of the study (data not shown).

DISCUSSION

Matrix metalloproteinases and tissue inhibitors of metalloproteinases, and particularly the imbalance of the enzyme to inhibitor ratios, are believed to play an important role in the remodeling of articular tissues in the pathogenesis of RA[4,12,14,15]. Interstitial collagenase (MMP-1) is involved in the degradation of articular cartilage and synovium[1,6,11]. Stromelysin-1 (MMP-3) degrades the components of extracellular matrix and various types of collagens[1,6,11,24]. Increased amounts of MMP-1[8,25,26], MMP-3[8,24-29], and gelatinase B (MMP-9)[8,12,30] have been found in the serum of patients with RA. MMP-1 and MMP-3 levels are increased even in early RA, and correlate with the number of erosions and disease progression[4,29,31,32]. Thus the assessment of serum MMP-1 and MMP-3 may be an important tool in early disease diagnosis and can be used as a marker of RA progression. MMP production was shown to be upregulated by cytokines such as IL-1ß and TNF-α[1,6,9]. Single administration of the chimeric anti-TNF-α monoclonal antibody, infliximab, was reported to decrease RA activity[16-19] and was observed to reduce serum levels of MMP-1 and MMP-3[13]. We investigated the effects of repeated infusions of infliximab on serum MMP-1, MMP-3, MMP-9, TIMP-1, and TIMP-2 levels and ratios of measured MMP to TIMP in patients with active RA.

We confirmed that after infliximab infusion the concentrations of MMP-1 and MMP-3 in RA patient serum decreased rapidly. We also observed reduction of MMP-9 levels. Moreover, we found that measured MMP were especially diminished after the second administrations of infliximab. Interestingly, further drug infusions maintained MMP suppression, although to a lesser extent than the first 2 doses of the drug.

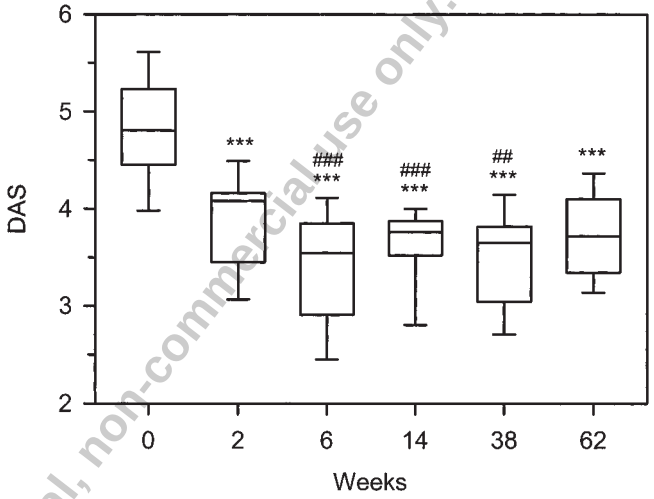

Figure 5. Disease Activity Scores. Data presented as described in the legend to Figure 1.

In our previous study we showed the correlations between MMP-1, MMP-3, and MMP-9 with some markers of disease activity in RA[8], which were similar to those found by others[27,33,34]. Also in the present study, before the first infliximab infusion serum concentrations of MMP and TIMP correlated with markers of RA activity such as the DAS, CRP levels, or duration of morning stiffness. After further drug administrations such associations were less significant.

The activity of MMP is controlled by production of TIMP, their endogenous inhibitors[1,6]. Enhanced amounts of TIMP-1 and TIMP-2 have been reported in RA serum[8,24,25,29]. It was shown by others that single infusions of infliximab decreased serum TIMP-1 concentration in patients with RA[13]. In our study we found that not only TIMP-1 but also TIMP-2 is downregulated following infliximab therapy. However, suppression of the TIMP activity after repeated infliximab infusion was maintained only in the case of TIMP-1. Further drug administrations were followed by the tendency to increases of serum TIMP concentrations toward baseline values. Serum TIMP were found to correlate with markers of disease activity in RA[8,27]. In this study as well, before the beginning of the infliximab therapy serum levels of TIMP-1 and TIMP-2 correlated with DAS, CRP levels, or duration of morning stiffness. However, after further drug administrations such associations were less significant.

Several investigators suggest that the articular destruction in RA is caused by the imbalance between MMP and TIMP[12-15]. Recently we also reported that relative production of TIMP as compared to MMP is decreased in RA, and especially in patients with more severe disease activity[8]. In the present study downregulation of serum MMP and TIMP levels was accompanied by diminished ratios of measured MMP to TIMP, especially after the second infliximab infusion. However, only in the case of the MMP-3/TIMP-1 ratio was a significant decrease maintained through the whole study.

We found that anti-TNF-α antibody therapy combined with MTX, in addition to a rapid clinical improvement, reduced serum MMP-1, MMP-3, MMP-9, TIMP-1, and TIMP-2 concentrations in patients with RA. These changes were accompanied by decreased ratios of the measured MMP to TIMP. Repeated infusions of infliximab maintained the decrease MMP, although they were less effective compared to the first 2 doses of infliximab. Further, we found that serum concentrations of MMP-1, MMP-3, MMP-9, TIMP-1, and TIMP-2 correlated with markers of disease activity such as the DAS and CRP levels prior to the first

infliximab infusion, and to a lesser extent after further drug administrations. These molecules seem to be useful as markers of disease activity in patients undergoing the anti-TNF-α therapy.

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