Effects of Etanercept on Serum Biochemical Markers of Cartilage Metabolism in Patients with Spondyloarthropathy

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ABSTRACT. ***Objective.*** Anti-tumor necrosis factor (TNF) therapies provide symptomatic benefit in patients with spondyloarthropathy (SpA). Their effect on structural lesions has not yet been assessed. Biochemical markers of cartilage turnover revealing type II collagen degradation and synthesis are associated with joint damage in rheumatoid arthritis; their role in SpA is unknown. We describe the effects of etanercept on biochemical markers of type II collagen synthesis and degradation in patients with SpA followed for 2 years.

Methods. A total of 29 patients with SpA aged 22–68 years were included in a prospective 2-year study. Each patient received etanercept (25 mg twice a week) because of active disease despite optimal treatment. Cartilage degradation was investigated by measuring serum levels of the type II collagen fragments Helix-II and C2C, whereas the C-terminal propeptide of type II collagen (PIICP) was used as a marker of type II collagen synthesis. These markers were measured at baseline and after 1, 3, 6, 12, and 24 months of treatment.

Results. Over 2 years, there was a significant decrease of serum C2C ($p = 0.0035$ by repeated Friedman's test) and serum Helix-II ($p = 0.004$). Compared to baseline, the decrease of serum C2C was significant at Month 12 (–12.1%; $p = 0.004$), whereas the decrease of serum Helix-II was observed as early as 1 month (–18.1%; $p = 0.015$) after start of therapy, reaching a maximum decrease of –33.4% ($p = 0.0079$) at Month 12. Conversely, PIICP increased significantly by 17% ($p = 0.006$) at 24 months.

Conclusion. These data suggest that etanercept may have beneficial effects on cartilage metabolism in patients with SpA. (First Release Jan 15 2008; J Rheumatol 2008;35:310–14)

Key Indexing Terms:
ETANERCEPT
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Spondyloarthropathy (SpA) is a progressive disease in which an acute and chronic inflammation can lead to extensive new bone formation[1]. SpA is characterized by enthesitis, defined as inflammation at sites of ligamentous and tendinous insertions onto bone[2]. Peripheral joint synovitis can also be a prominent feature. Short-term studies have shown that anti-tumor necrosis factor-α (TNF-α) treatment provides symptomatic benefit in patients with SpA[3-5], but the potential benefit of this treatment for structural lesions has not yet been assessed.

The aim of such treatment is not to treat established structural changes, diagnosed on radiographs, but rather to prevent further structural damage. Biological markers of inflammation such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are used to evaluate disease activity; while they have been shown to predict structural damage in patients with rheumatoid arthritis (RA), they are increased in only a minority of patients with SpA[6]. Radiological scores such as the Bath Ankylosing Spondylitis Radiology Index and the modified Stoke Ankylosing Spondylitis (AS) Spinal Score have been developed to assess structural damage, but a 1 to 2 year followup is required before changes in these scores can be documented[7-9]. Magnetic resonance imaging (MRI) provides information on the alterations of the different joint tissues but its use is limited by cost and accessibility. Moreover the predictive value of MRI signals in SpA remains to be determined.

Biochemical markers have been proposed as indices that could provide information on joint structural changes. Degradation of type II collagen, the most abundant protein of cartilage matrix, is considered to be the hallmark of cartilage degradation in arthritis[10-12]. Recently, circulating and urinary

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markers reflecting the synthesis and degradation of type II collagen have been developed[13]. Some of these biochemical markers have been shown to have predictive validity for structural damage in both RA and osteoarthritis (OA)[14-19]. Conversely, although SpA is an inflammatory disease involving cartilaginous structure in the spine and peripheral joints, only 2 small studies have reported changes of type II collagen markers and the short-term (< 16 weeks) effects of anti-TNF-α therapies on these markers[20,21].

Our aim was to describe the longterm effects of etanercept on new biochemical markers of type II collagen synthesis and degradation in patients with SpA followed prospectively for 2 years.

MATERIALS AND METHODS

Twenty-nine patients with a diagnosis of SpA (17 men, 12 women) according to the European Spondylarthropathy Study Group (ESSG) criteria, aged 22–68 years, were included in a 2-year prospective open study. All patients had adult-onset SpA at the mean age of 27.2 (± 9.6) years. Twenty-five patients (85%) had the antigen HLA-B27. Among these patients, 24 had axial involvement and 5 had both axial and peripheral involvement. Three patients had psoriatic arthritis and 2 inflammatory bowel disease. Each patient received etanercept (25 mg twice a week) because of persistent active disease despite optimal treatment according to the Assessment in AS (ASAS) criteria for 2 years[22]. Four (13.7%) were treated with methotrexate during the study, at a mean weekly dose of 10 mg. Twenty-seven (93%) patients used nonsteroidal antiinflammatory drugs at the beginning of the study, and none received corticosteroids during the followup.

The clinical activity and severity of the disease were evaluated by visual analog scale (VAS) for global pain, Bath AS Disease Activity Index (BASDAI), and Bath AS Functional Index (BASFI). At baseline, the mean (SD) scores were 67.5 (± 26.2) for VAS pain, 56.1 (± 21.5) for BASDAI, and 43.8 (± 28.3) for BASFI. At baseline, mean ESR was 24.6 (± 19.6) mm/h and CRP was 28.6 (± 48.6) mg/l. Global pain by VAS, BASDAI, BASFI, ESR, and CRP were assessed at 1 and 2 years. Cartilage degradation was investigated by measuring the serum levels of 2 type II collagen fragments. The C2C, which detects a neoepitope at the carboxy terminus of the long amino fragment generated by collagenase cleavage[23], was measured by a competitive ELISA (Ibex Technologies, Montreal, Quebec, Canada). Intraassay variations were < 10% and interassay variation < 18%. Helix-II, which detects a neoepitope generated by cleavages of the triple helical region of type II collagen, was measured using a competitive polyclonal-based ELISA[23-25]. Intraassay variations were < 10% and interassay variation < 15%. Cartilage synthesis was assayed by measuring the concentration of the C-terminal propeptide of type II collagen (PIICP) using a competitive ELISA (CP II Elisa; Ibex Technologies). Intraassay coefficient of variability (CV) was < 9% and interassay CV < 18%. These biochemical markers were measured at baseline and after 1, 3, 6, 12, and 24 months of treatment in a single-assay batch with all samples from the same patient in a single run to reduce analytical variability.

Statistical analysis. Changes with time in serum concentrations of biochemical markers of cartilage metabolism were analyzed using the nonparametric paired Friedman's test with Dunn's post-hoc multiple comparisons. Relationships between biochemical markers of type II collagen metabolism and clinical and biological indices of disease activity were analyzed by Spearman rank correlation analyses.

RESULTS

At baseline, mean levels (± SD) of C2C, PIICP, and Helix-II were 29.9 (± 7.2) ng/ml, 683 (± 219) ng/ml, and 29.1 (± 15.8) ng/ml, respectively. At baseline there was no significant correlation between serum C2C, Helix-II, or PIICP and the disease activity indices ESR, CRP, BASDAI, and BASFI. At baseline there was a significant association between serum Helix-II and serum PIICP ($r = 0.39$, $p = 0.039$), but no associations were found between C2C and either PIICP or Helix-II.

After 2 years of therapy, we observed a significant improvement of the clinical measures: global pain VAS (–56%; $p < 0.0001$), BASDAI (–50.4%; $p < 0.0001$), and BASFI (–51.3%; $p < 0.0001$) and the biological inflammation markers ESR (–65.1%; $p < 0.0001$) and CRP (–30%; $p < 0.0001$). Changes in biochemical markers of cartilage metabolism are shown in Figures 1 and 2.

Over 24 months, there was a significant decrease of serum C2C (p for repeated measurements = 0.0035) and serum Helix-II ($p = 0.004$). However, the decrease of these markers was mainly observed during the first year of treatment, then the markers increased toward baseline at 24 months. Compared to baseline, the decrease of serum C2C was significant only at Month 12 (median –12.1%; $p = 0.004$). The decrease of serum Helix-II was significant as early as 1 month after start of therapy (median –18.1%; $p = 0.015$), reaching a maximum median decrease of –33.4% ($p = 0.0079$) at Month 12 (Figure 1). Serum PIICP was significantly higher at Month 24 compared to baseline (Figure 1). The ratio of PIICP/Helix-II increased significantly 1 month after start of etanercept (median increase +36.2%; $p < 0.05$) and remained significantly higher compared to baseline at all times and up to 24 months (Figure 2). The ratio of PIICP/C2C was also slightly but significantly higher at Month 24 compared to baseline (median increase +10.2%; $p < 0.01$). The percentage changes after 24 months of C2C correlated with the corresponding changes of Helix-II ($r = 0.57$, $p = 0.0062$) and PIICP ($r = 0.57$, $p = 0.0060$). Changes of Helix-II at 24 months also correlated with changes in PIICP ($r = 0.45$, $p = 0.030$).

There was no significant association between 12-month changes of ESR, CRP, BASDAI, or BASFI and changes of serum C2C and Helix-II (Table 1). PIICP was slightly but significantly correlated with the 12-month BASDAI changes ($r = 0.46$, $p = 0.044$), and there was a trend for a correlation with the 12-month changes of ESR, CRP, and BASFI.

DISCUSSION

This open, prospective, 2-year study showed that etanercept therapy in patients with SpA is associated with a significant decrease in serum concentrations of C2C and Helix-II, which are specific markers of type II collagen degradation, and a significant increase in PIICP that reflects cartilage synthesis. The decreases of serum Helix-II were significant as early as 1 month after start of therapy and were maintained up to 12 months, whereas the drop of C2C was significant only at 12 months and the increase of PIICP at 24 months. These results suggest that etanercept may exert transient beneficial effects on cartilage metabolism in patients with SpA. As most of our patients had axial involvement without peripheral arthritis, the

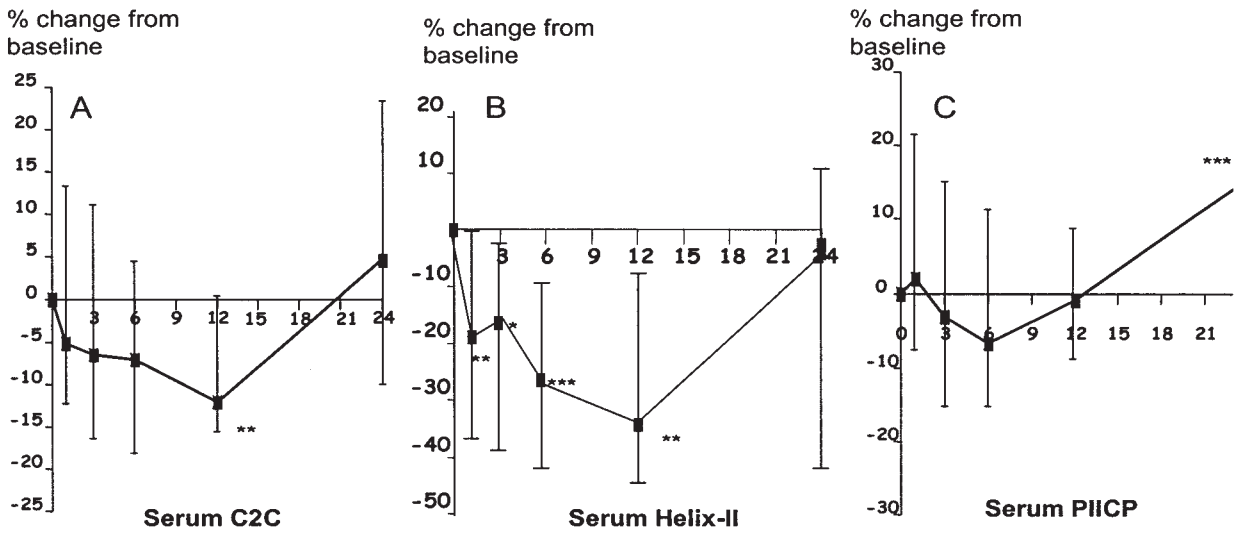

Figure 1. Changes of serum C2C (A), Helix-II (B), and PIICP (C) during etanercept treatment of patients with SpA. Data show median percentage change from baseline and the corresponding 25th and 75th percentiles. *p < 0.05, **p < 0.01, ***p < 0.001 vs baseline.

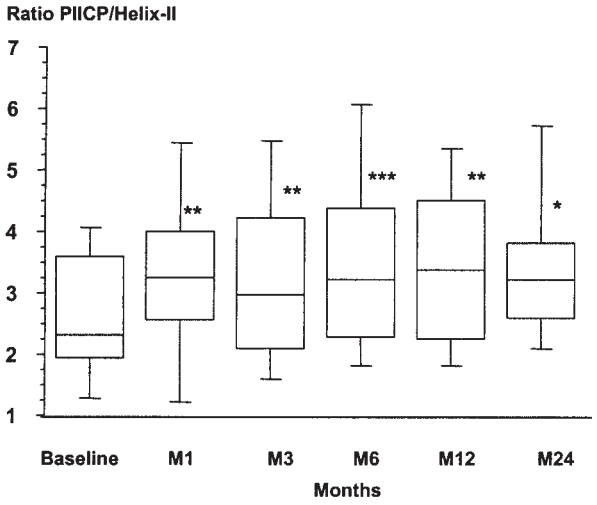

Figure 2. Changes of absolute values of the ratio between serum PIICP and serum Helix-II during etanercept treatment in patients with SpA. Boxes indicate 25th, 50th (median), and 75th percentiles; bars indicate 10th and 90th percentiles. *p < 0.05, **p < 0.01, ***p < 0.001 vs baseline.

biochemical changes we observed may reflect intervertebral disc and facet joint cartilage metabolism.

Several biochemical markers of articular cartilage turnover and degradation have been shown to have predictive validity for structural damage in both RA and OA[14-19,26,27]. Among these, recent data indicate that the markers of type II collagen degradation including C2C[26], Helix-II[24], and CTX-II[14] are strongly associated with radiological progression of RA independently of disease activity and biological indices of inflammation. In addition, in the Combinatietherapie bij Reumatoïde Artritis (COBRA) study, a randomized controlled trial comparing the efficacy of pulse prednisolone and methotrexate plus sulfasalazine with sulfasalazine alone, urinary CTX-II decreased within 3 months after start of treatment, and patients whose CTX-II levels normalized under therapy had a higher probability of nonprogression over 5 years than patients whose CTX-II levels were increased at baseline and 3 months[14,15]. More recently, a significant association between early changes of serum C2C and radiological progression in patients with RA treated with various biological therapies was also reported[28]. These results suggested that the early changes of biochemical markers of type II collagen metabolism such as urinary CTX-II and serum C2C may predict the longterm effects of treatment on radiological progression in early RA.

Few studies have investigated biochemical markers of cartilage turnover in SpA. An increase in matrix metalloproteinases (MMP), especially in MMP-3, has been reported in SpA patients with peripheral arthritis[29-31]. In a recent longitudinal study in 97 patients with SpA, Maksymowych, *et al* showed that baseline MMP-3 was significantly associated with 2-year radiographic progression, especially in patients with preexisting radiographic damage[32]. In another study of 23 patients with SpA, serum levels of C-propeptide of type II collagen and the aggrecan 846 epitope were reported to be higher than in healthy controls, whereas no significant difference was observed for C2C[20]. In 18 patients recruited from a placebo controlled trial of etanercept (9 placebo and 9 on active treatment) there was a significant 15.4% decrease of serum C2C and a significant increase in the 846 epitope ($p = 0.01$) after 16 weeks of treatment with etanercept[21]. Conversely, in an observational cohort of 14 patients receiving infliximab, there were no significant changes of C2C after 14 weeks of treatment[21], suggesting that the effects on markers may vary according to the type of anti-TNF therapy and/or according to patient population, patients included in the infliximab analyses being in a more active status.

Table 1. Relationships between biomarkers of type II collagen metabolism (C2C, Helix II, and PIICP) and clinical and biological markers of disease activity (Spearman rank correlation analysis).

	C2C		Helix-II		PIICP	
	Baseline	12-mo Change	Baseline	12-mo Change	Baseline	12-mo Change
ESR						
Baseline	r = –011, p = 0.56	—	r = –0.01, p = 0.97	—	r = 0.025, p = 0.89	—
12-mo change	—	r = 0.09, p = 0.07	—	r = 0.11, p = 0.60	—	r = 0.43, p = 0.06
CRP						
Baseline	r = 0.21, p = 0.27	—	r = 0.06, p = 0.32	—	r = 0.02, p = 0.95	—
12-mo change	—	r = –0.23, p = 0.32	—	r = 0.04, p = 0.87	—	r = 0.44, 0.054
BASDAI						
Baseline	r = 0.20, p = 0.12	—	r = 0.06, p = 0.78	—	r = 0.20, p = 0.30	—
12-mo change	—	r = –0.27, p = 0.25	—	r = 0.31, p = 0.17	—	r = 0.46, 0.044
BASFI						
Baseline	r = 0.30, p = 0.30	—	r = 0.08, p = 0.67	—	r = 0.20, p = 0.32	—
12-mo change	—	r = –0.39, p = 0.09	—	r = 0.21, p = 0.36	—	r = 0.41, 0.075

Our study reports for the first time the longterm effects of etanercept on serum Helix-II, C2C, and PIICP on a larger population of patients with SpA. In agreement with Maksymowych, *et al*[21], we found a significant, although modest, and later decrease of serum C2C, reaching a maximum of –12.1% after 12 months. The rapid anticatabolic effects of etanercept were supported by the marked and consistent decrease of serum Helix-II observed as soon as 1 month after start of therapy. Although serum Helix-II and C2C were not significantly associated at baseline, their changes after 24 months of etanercept therapy were correlated. These data suggest that in patients with untreated SpA, these 2 biochemical markers reflect different aspects of cartilage degradation, possibly because they are released from type II collagen by distinct enzymatic pathways. The significant although modest association between changes of serum Helix-II and C2C after treatment suggest, however, that etanercept may influence both these enzymatic mechanisms of type II collagen degradation. For both serum Helix-II and C2C, after an initial decrease during the first 12 months, levels increased during the second year and were not different from pretreatment levels. This suggests that the anti-TNF therapy may decrease cartilage degradation transiently. This result is in accord with recent data indicating that anti-TNF may not inhibit structural deterioration in patients with AS[33,34]. The decrease of type II collagen degradation was associated with a modest but significant increase of serum PIICP, a marker of type II collagen synthesis, and a larger and more consistent elevation of the ratio of PIICP/Helix-II, which is an index of the balance between cartilage synthesis and degradation. Thus, etanercept may stimulate the reparative process of articular cartilage, a finding consistent with the reported increase of epitope 846[21], a marker mostly for the synthesis of aggrecan.

We found no significant association between baseline data or changes of Helix-II or C2C and clinical or biological indices of disease activity such as ESR or CRP. Similar findings were observed by Kim, *et al*[20] in 23 patients with SpA before and after treatment with infliximab. There also was no significant association between C2C and BASDAI or CRP in another population of SpA patients[21], whereas changes in C2C correlated slightly with changes in CRP after 16 weeks of etanercept[21]. We found a slight but significant correlation between 12-month changes of PIICP and 12-month changes of BASDAI, and a trend for a correlation with the 12-month year changes of the other markers of disease activity. Such correlations concerning PIICP have not been previously reported[20]. Together these data suggest that changes of type II collagen metabolism in SpA as assessed by systemic biochemical markers are only modestly associated with disease activity, a situation that is also observed in RA and OA. We thus speculate from our data that biochemical markers of cartilage turnover may not be regarded as indices of disease activity in SpA, but could give information on cartilage damage which is partly independent in patients treated with anti-TNF therapy. This hypothesis will have to be confirmed by larger prospective studies using radiological progression as an endpoint. Further studies would also allow investigation of the clinical significance of changes in the biochemical markers we measured.

Our study has strengths and limitations. Patients were investigated in a single clinical center using standardized procedures. The 2-year duration of the study and the multiple measurements of biochemical markers allowed us to describe the pattern of longterm effects of anti-TNF-α therapy on cartilage metabolism. Such detailed analysis was not possible in previous studies lasting 4 months or less as only one timepoint under therapy was investigated. We observed longitudinal changes of the currently most sensitive biochemical markers of cartilage degradation and synthesis, although we could not measure CTX-II because urine samples were not available. Limitations of our study include the absence of a control group and a structural evaluation of the joints with radiographs.

Our 2-year, open, prospective study showed that etanercept

induced a significant decrease of circulating concentrations of Helix-II and C2C, 2 biological markers of type II collagen degradation, during the first year of therapy, and an increase of PIICP observed at 24 months, suggesting that anti-TNF may have beneficial effects on cartilage metabolism in SpA. However, because of the design limitations and the still exploratory features of the biochemical markers we investigated, the value of measurements of biochemical markers of type II collagen metabolism for assessing structural damage in patients with SpA treated with anti-TNF should be examined further.

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