

# Soluble Biomarkers Associated with Response to Treatment with Tumor Necrosis Factor Inhibitors in Psoriatic Arthritis

Vinod Chandran, Hua Shen, Remy A. Pollock, Fawnda J. Pellett, Adele Carty, Richard J. Cook, and Dafna D. Gladman

**ABSTRACT. Objective.** To identify soluble biomarkers associated with response to therapy with tumor necrosis factor inhibitors (TNFi) in patients with psoriatic arthritis (PsA).

**Methods.** The study was conducted at a PsA clinic where patients are assessed every 6 months, and serum samples are collected and stored once a year at the time of clinical assessment. Forty patients with active PsA who gave serum samples prior to treatment with TNFi and after at least 3 months of therapy were identified. Patients were classified as TNFi responders if tender joint count was  $< 3$ , swollen joint count was 0, and Psoriasis Area and Severity Index score was  $< 4$  at the time the second sample was collected. The following biomarkers were tested by ELISA: TNF superfamily 14, matrix metalloproteinase-3 (MMP-3), receptor activator of nuclear factor kappa-B ligand, osteoprotegerin, cartilage oligomeric matrix protein (COMP), CPII, C2C and C1-2C, CS-846, and highly sensitive C-reactive protein. Paired t tests and logistic regression was used for statistical analyses.

**Results.** After a mean treatment duration of 11 months with TNFi (etanercept 28 patients, adalimumab 6, golimumab 4, infliximab 2), 29 patients were classified as TNFi responders. Baseline level of MMP-3 was independently associated with responder status (OR 1.067 for each 1-unit increase,  $p = 0.045$ ). A reduction in MMP-3 levels with therapy increased the odds of achieving response (OR 1.213 for each 1-unit change,  $p = 0.030$ ), whereas a reduction in COMP decreased the odds (OR 0.587, for each 100-unit increase,  $p = 0.039$ ). None of the other biomarkers was associated with response.

**Conclusion.** Baseline as well as reduction in serum MMP-3 and increase in serum COMP are independently associated with response to TNFi therapy in patients with PsA. (First Release May 1 2013; J Rheumatol 2013;40:866–71; doi:10.3899/jrheum.121162)

## Key Indexing Terms:

PSORIASIS  
TREATMENT

PSORIATIC ARTHRITIS

BIOMARKERS  
TUMOR NECROSIS FACTOR INHIBITORS

Psoriatic arthritis (PsA) is defined as an inflammatory musculoskeletal disease associated with psoriasis, usually seronegative for rheumatoid factor, and it is classified according to the CASPAR (Classification for Psoriatic ARthritis) criteria<sup>1,2</sup>. Tumor necrosis factor inhibitors (TNFi) are efficacious in the treatment of PsA and have

revolutionized the management of PsA<sup>3</sup>. However, not all patients with PsA treated with a TNFi achieve a good response. In the pivotal clinical trials with TNFi in PsA, only around 60% of cases achieved an American College of Rheumatology 20 response<sup>4</sup>. Observational data from our clinic have shown that 78% of 95 patients with PsA treated

From the Department of Medicine, Division of Rheumatology, University of Toronto; Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital, Toronto; and the Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, Ontario, Canada.

Supported in part by a grant from The Arthritis Society, the Canadian Institutes of Health Research (CIHR) Institute of Musculoskeletal Health and Arthritis, and the Krembil Foundation. Dr. Chandran was supported by a CIHR Clinical Research Initiative Fellowship and by the Krembil Foundation. He has received research funds from Abbott Canada, and has also received honoraria from Abbott Canada, Amgen/Pfizer Canada, Janssen Canada, Merck Canada, and Bristol-Myers Squibb Canada. Dr. Cook is a Canada Research Chair in Statistical Methods for Health Research and is supported by the CIHR. Dr. Gladman has received research grants from Abbott Canada, Amgen Canada, and Janssen, and has served as consultant to Abbott, Amgen, BMS, Centocor, Janssen, Pfizer, and UCB.

V. Chandran, MBBS, MD, DM, Assistant Professor of Medicine, Department of Medicine, Division of Rheumatology, University of Toronto; Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital; H. Shen, MMath, Department of Statistics and Actuarial Science, University of Waterloo; R.A. Pollock, MSc, Research Technologist; F.J. Pellett, BSc, Research Technologist; A. Carty, BA, Research Assistant, Toronto Western Research Institute, Toronto Western Hospital, University Health Network, University of Toronto; R.J. Cook, PhD, Professor, Department of Statistics and Actuarial Science, University of Waterloo; D.D. Gladman, MD, FRCPC, Professor of Medicine, University of Toronto, Senior Scientist, Toronto Western Research Institute, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital.

Address correspondence to Dr. D.D. Gladman, Toronto Western Hospital, 399 Bathurst Street, 1E-410B, Toronto, Ontario M5T 2S8, Canada. E-mail: dafna.gladman@utoronto.ca

Accepted for publication February 14, 2013.

with TNFi achieved 40% reduction in baseline active joint count<sup>5</sup>. Higher swollen joint count at baseline and no prior use of TNFi were shown to predict response<sup>5</sup>.

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention<sup>6</sup>. Biomarkers may help in predicting and monitoring clinical response to TNFi therapy in PsA. Identification of soluble biomarkers that predict response to therapy with TNFi in PsA can potentially assist PsA case management and is a perceived need among clinicians managing patients with PsA.

We hypothesized that soluble biomarkers of inflammation and cartilage and bone destruction and repair, some of which differentiate PsA patients from those with psoriasis without PsA, may potentially be biomarkers of response to treatment with TNFi<sup>7</sup>. We aimed to identify candidate biomarkers associated with response to therapy with TNFi in patients with active PsA using biological samples and clinical information collected from a large observational cohort.

MATERIALS AND METHODS

The study was conducted at the University of Toronto PsA clinic. Patients are followed at 6-month intervals. Most patients fulfill the CASPAR criteria for classification of PsA<sup>8</sup>. Patients are evaluated according to a standard protocol<sup>9</sup>. At each protocol visit, symptoms, physical examination (including complete musculoskeletal examination and assessment of psoriasis severity), current use of medications, and laboratory findings are recorded in a computerized database. Blood samples are drawn at the time of clinical assessment, processed immediately, and serum aliquots are stored at -80°C in a biobank until biomarker analyses.

*Patient selection.* From the database and linked biobank, 40 patients treated with TNFi were identified who had had serum samples drawn prior to treatment with TNFi and a subsequent sample drawn at least 3 months after treatment; and their serum samples and clinical information were retrieved. Patients were classified as TNFi responders if at time of second sample collection the actively inflamed (tender or swollen) joint count (AJC) was < 3, swollen joint count (SJC) was = 0 (i.e., tender joint count < 3, SJC = 0), and Psoriasis Area and Severity Index (PASI) score was < 4. Those not achieving this state were classified as nonresponders.

*Soluble biomarkers.* Candidate biomarkers were identified through literature review. Since PsA is an inflammatory disease that leads to joint destruction, we specifically chose markers of inflammation and cartilage and bone destruction and repair that have previously been shown to be important in inflammatory rheumatic diseases.

The serum level of the acute-phase reactant C-reactive protein (CRP) is elevated in patients with psoriasis with or without PsA<sup>10</sup>. Matrix metalloproteinase-3 (MMP-3; stromelysin-1) is an enzyme that plays a part in the destruction of cartilage in rheumatic diseases characterized by synovitis, such as rheumatoid arthritis (RA), polymyalgia rheumatica, PsA, and acute crystal arthritis<sup>11</sup>. Serum MMP-3 is also elevated in active ankylosing spondylitis (AS), decreases with treatment, and predicts structural damage progression<sup>12,13,14</sup>. Receptor activator of nuclear factor kappa-B ligand (RANKL) and TNFSF14 (TNF superfamily 14) are molecules of the TNF receptor family. RANKL plays a pathogenic role in inflammatory diseases associated with bone loss<sup>15</sup>. TNFSF14 plays a pathogenic role in diseases such as RA, AS, and inflammatory bowel disease<sup>16,17,18</sup>. Osteoprotegerin (OPG) is a cytokine that inhibits osteoclast differentiation and promotes bone formation. Synovial tissue from PsA has been shown to express high

levels of RANKL and very low quantities of OPG, providing a possible mechanism for bone erosions in PsA<sup>19</sup>. The ratio of RANKL to OPG reflects osteoclast activation and was shown to predict joint destruction in early RA<sup>20</sup>. Cartilage destruction and remodeling are features of inflammatory arthritis. The products of cartilage synthesis and destruction are released into the serum during this process. These markers can be measured in the sera and may serve as biomarkers of arthritis. The articular cartilage is composed of a type II collagen-based fibrillar network complexed with aggrecan, a proteoglycan<sup>21</sup>. Excessive and progressive cleavage of type II collagen by collagenases generates the type II collagen neopeptides Col2-3/4C<sub>long mono</sub> (C2C) and Col2-3/4C<sub>short</sub> (C1-2C)<sup>22</sup>. As type II collagen is degraded, chondrocytes upregulate their synthesis of procollagen. The rate of synthesis of type II collagen is directly proportional to the content of C-propeptide of type II collagen (CPII) in cartilage. The CPII:C2C ratio reflects the balance between type II collagen synthesis and degradation. The balance is more informative than either biomarker alone<sup>22</sup>. Cartilage oligomeric matrix protein (COMP), a tissue-specific noncollagenous matrix protein, is a marker of cartilage turnover detectable in synovial fluid and blood, and may also be a marker of psoriasis activity<sup>7,23</sup>. Aggrecan 846 epitope (CS-846) is a marker of synthesis of chondroitin sulfate. Levels of CS-846 have been shown to be elevated in osteoarthritis cartilage and synovial fluid and to be correlated with progression of joint damage in RA<sup>24,25,26</sup>.

Based on the above evidence from previous studies, the following biomarkers were selected and assayed in our research laboratory using commercial ELISA kits according to manufacturers' instructions: highly sensitive CRP (hsCRP), TNFSF14, MMP-3 (all R&D Systems), RANKL (Biovendor), OPG (RayBiotech), and cartilage biomarkers C2C and CPII, CS-846 (all IBEX Pharmaceuticals) and COMP (Biovendor).

*Statistical analysis.* Paired t tests were used to determine the statistical significance of the change in biomarker levels in the 2 samples identified in each of the 40 subjects. The association between baseline and change in biomarker levels with TNFi responder status was determined using univariate and multivariate logistic regression. Further, separate linear regression analyses were performed to determine the association between change in biomarkers levels and change in joint counts and PASI score. A p value < 0.05 was considered to indicate statistical significance.

All study subjects' written consent was obtained according to the Declaration of Helsinki. The study was approved by the University Health Network's Research Ethics Board.

RESULTS

The demographic and disease characteristics of the 40 selected patients at the time of the first serum sample are given in Table 1. The 40 patients had previously failed treatment with disease-modifying agents (methotrexate, n = 36, sulfasalazine 15, leflunomide 9, intramuscular gold 8,

Table 1. Demographic and disease characteristics of the 40 study subjects.

Characteristic	At First Sample	At Second Sample	p
Males/females	29/11	—	—
Age, yrs*	44.3 (10.9)	—	—
Age at diagnosis of psoriasis, yrs*	27.3 (12.5)	—	—
Age at diagnosis of PsA, yrs*	31.9 (11.8)	—	—
No. patients with erosions (%)	34 (85)	—	—
Actively inflamed joint count†*	12.2 (9.9)	1.6 (3.1)	< 0.0001
Swollen joint count*	5.5 (4.8)	0.5 (1.3)	< 0.0001
PASI score*	6.4 (9.9)	1.8 (2)	< 0.0028

\* Mean (standard deviation). † Number of tender or swollen joints. PsA: psoriatic arthritis; PASI: Psoriasis Area and Severity Index.

azathioprine 7, cyclosporine 2, antimalarials 9, oral steroids 4). The patients were treated with the following TNFi: etanercept 28, adalimumab 6, golimumab 4, and infliximab 2. Twenty-seven subjects were treated with the following disease-modifying antirheumatic drugs (DMARD) in combination with TNFi: methotrexate 9, leflunomide 5, sulfasalazine 2, azathioprine 1, intramuscular gold 1, methotrexate and sulfasalazine 4, methotrexate and leflunomide 2, methotrexate and cyclosporine 1, methotrexate and hydroxychloroquine 1, and leflunomide and sulfasalazine 1. As shown in Table 1, overall there was a significant reduction in AJC, SJC, and PASI scores at the second timepoint. Based on our definition of response, 29 patients were classified as responders and the remaining 11 as non-responders at the time of the second sample, which was obtained after a mean duration of 11 (range 4–40) months after the first sample.

The change in serum levels of the 10 biomarkers tested between sample 1 and sample 2 are shown in Table 2. There was a statistically significant decrease in the levels of hsCRP and MMP-3, whereas the level of C2C was significantly increased. No change in the ratio of RANKL to OPG or CII to C2C could be demonstrated. There was a significant correlation between reduction in MMP-3 and hsCRP (Pearson correlation coefficient 0.43,  $p = 0.005$ ). The kits used for testing provided mean values in “normal” samples for MMP-3 and hsCRP. The range of normal values was not provided. The mean “normal” MMP-3 level provided was 18.1 ng/ml. Of the 40 patients tested, 12 had MMP-3 values below this level in their pretreatment sample. After treatment, 6 of these 12 “normal” subjects actually showed

further reduction in MMP-3 levels. For hsCRP, the mean normal value provided was 1.769 mg/l. In the 40 subjects tested, only 6 had a “normal” hsCRP level at baseline.

The association between baseline and change in biomarker levels with responder status at the time of sample 2 was subsequently investigated. Table 3 shows the results from investigation of the association between baseline biomarker levels and responder status. In univariate analyses only MMP-3 levels were associated, although there was a trend with hsCRP. All 10 biomarkers as well as the ratios RANKL:OPG and CII:C2C were then entered into a multivariate logistic regression model and a reduced model derived by backward elimination. In this reduced model, only MMP-3 (OR = 1.07 for each 1-unit increase,  $p = 0.045$ ) was associated with response to TNFi. The mean MMP-3 levels of responders and nonresponders were 36.3 ( $\pm 23.8$ ) ng/ml and 19.8 ( $\pm 6.6$ ) ng/ml, respectively.

The association between change in biomarker levels between the 2 samples and responder status at sample 2 was also investigated. Table 4 shows these results. In univariate analyses, change in none of the biomarkers was statistically significant, although MMP-3 and TNFSF14 showed a trend. Change in all 10 biomarkers was then entered into a multivariate logistic regression model and a reduced model derived by backward elimination. In this reduced model, changes in MMP-3 as well as COMP were independently associated with responder status; reduction in MMP-3 (OR 1.213 for each 1-unit decrease,  $p = 0.023$ ) as well as increase in COMP levels (OR 1.704 for 100-unit increase,  $p = 0.039$ ) independently increased the odds of achieving responder status.

Using linear regression, exploratory analyses of the association between change in biomarker levels of the sample at the first and at the second assessment and the change in joint counts were conducted. There was no association between the change in biomarker levels and change in active joint counts in both univariate and multivariate analyses. However, reduction in TNFSF14 was associated with a reduction in swollen joint count in both univariate ( $p = 0.014$ ) and full multivariate analysis that included all biomarkers ( $p = 0.038$ ). There was also no association between the change in biomarker levels and change in PASI score in either univariate or multivariate analyses.

In all the regression analyses, the effect of the duration between the 2 samples as well as concomitant treatment with DMARD were investigated. These covariates had no effect on the model either individually or jointly.

## DISCUSSION

With the advent of very effective but expensive targeted therapeutics, identifying biomarkers for good response to treatment has become a research priority so that the most appropriate drug is used for the appropriate patient to avoid unnecessary cost and risk of adverse effects. However, few

Table 2. Change in biomarker levels between sample 1 (pre-TNFi treatment) and sample 2 (on TNFi treatment).

Biomarker	Pre-TNFi Treatment	On TNFi Treatment	p
hsCRP, mg/l	6.8 (3.8)	2.0 (2.1)	< 0.001
MMP-3, ng/ml	31.8 (21.8)	19 (9.3)	0.001
RANKL, pg/l	301.2 (153.3)	376.4 (199.3)	0.062
OPG, pg/ml	626.2 (145.5)	625.7 (183.2)	0.988
RANKL:OPG	0.52 (0.32)	0.70 (0.52)	0.063
TNFSF14, pg/ml	217.2 (172.0)	219 (127.6)	0.958
C2C, ng/ml	167.8 (44.6)	190.2 (54.3)	0.048
C1-2C, $\mu$ g/ml	0.2 (0.1)	0.3 (0.1)	0.469
CPII, ng/ml	407.8 (345.7)	394.2 (297.9)	0.851
CPII:C2C	2.35 (1.62)	2.04 (1.04)	0.317
CS-846, ng/ml	101 (36.1)	98.4 (42.7)	0.766
COMP, ng/ml	1044.7 (471.2)	1060.4 (438.9)	0.878

TNFi: tumor necrosis factor inhibitor; COMP: cartilage oligomeric matrix protein; hsCRP: highly sensitive C-reactive protein; RANKL: receptor activator of nuclear factor  $\kappa$ -B ligand; OPG: osteoprotegerin; RANKL:OPG: ratio of RANKL to OPG; TNFSF14: TNF super family member 14; MMP-3: matrix metalloproteinase-3; CS-846: aggrecan chondroitin sulfate 846 epitope; C1-2C: Col2-3/4C<sub>short</sub>; CPII: C-propeptide of type II collagen; C2C: Col2-3/4C<sub>long mono</sub>; CPII:C2C: ratio of CPII to C2C.

Table 3. Association between baseline biomarker values and TNFi treatment response in patients with psoriatic arthritis.

Biomarker	Univariate Model			Multivariate Model					
	OR	95% CI	p	OR	Full Model 95% CI	p	OR	Reduced Model 95% CI	p
MMP-3	1.067	1.002, 1.138	0.045	1.170	1.001, 1.367	0.048	1.067	1.002, 1.138	0.045
COMP	0.969	0.836, 1.123	0.678	0.678	0.453, 1.017	0.060			
hsCRP	1.233	0.995, 1.528	0.056	1.295	0.863, 1.945	0.212			
RANKL	1.000	0.995, 1.005	0.984	1.008	0.997, 1.020	0.155			
OPG	1.002	0.997, 1.007	0.506	1.004	0.993, 1.016	0.476			
RANKL:OPG	0.699	0.082, 5.996	0.744						
TNFSF14	1.005	0.999, 1.012	0.131	1.002	0.99, 1.015	0.699			
CS-846	0.995	0.977, 1.013	0.584	0.978	0.949, 1.007	0.134			
C1-2C	0.017	0.000, 6.026	0.174						
CPII	1.002	0.998, 1.006	0.394	1.011	0.999, 1.022	0.065			
C2C	1.001	0.985, 1.017	0.891	0.967	0.921, 1.016	0.187			
CPII:C2C	1.516	0.609, 3.775	0.372						

Odds ratios (OR) reflect the effect of having a 1-unit higher value of each biomarker, except for COMP (100-unit higher value); for abbreviations see Table 2.

Table 4. Association between reduction in biomarker values between the 2 samples and TNFi treatment response in patients with psoriatic arthritis.

Biomarker	Univariate Model			Multivariate Model					
	OR	95% CI	p	OR	Full Model 95% CI	p	OR	Reduced Model 95% CI	p
MMP-3	1.107	0.987, 1.242	0.081	1.211	0.942, 1.557	0.135	1.213	1.019, 1.445	0.030
COMP	0.805	0.598, 1.083	0.151	0.490	0.247, 0.974	0.042	0.587	0.354, 0.973	0.039
hsCRP	1.113	0.900, 1.376	0.325	1.049	0.686, 1.604	0.827			
RANKL	1.004	0.998, 1.010	0.209	1.006	0.998, 1.014	0.132			
OPG	0.998	0.993, 1.003	0.476	0.997	0.989, 1.004	0.393			
TNFSF14	1.004	0.999, 1.008	0.096	1.005	0.997, 1.014	0.236			
CS-846	1.004	0.982, 1.026	0.739	0.980	0.944, 1.016	0.267			
C1-2C	0.017	0.000, 4.672	0.155	0.000	0.000, 3.980	0.072			
CPII	0.999	0.995, 1.003	0.584	1.000	0.989, 1.010	0.972			
C2C	0.998	0.986, 1.010	0.781	1.045	0.999, 1.094	0.057			

OR reflects the effect of having a 1-unit higher decrease of each biomarker, except for COMP, for which the OR reflects the effect of a 100-unit decrease; for abbreviations see Table 2.

studies have investigated biomarkers for response to TNFi in PsA. Acute-phase reactants such as hsCRP have been shown to decrease with treatment in patients with psoriasis and PsA<sup>10</sup>. High baseline CRP values were also shown to be independently associated with a good therapeutic response to infliximab in PsA<sup>27</sup>. However, acute-phase reactants are elevated in only around 50% of patients with PsA despite clinically active disease<sup>28</sup>. Therefore, other biomarkers of disease activity and response to therapy are being actively investigated<sup>29</sup>. We investigated a panel of soluble biomarkers for association with treatment response. We chose to investigate these biomarkers because they are potential markers of inflammation and joint destruction and repair.

In a pilot observational study in a selected group of patients with active PsA treated with TNFi who failed conventional therapy, we show that hsCRP, MMP-3, and C2C levels change with TNFi therapy. Baseline levels of

MMP-3 were associated with response to TNFi therapy. Moreover, reduction in serum MMP-3 levels and increase in COMP levels were independently associated with response to TNFi therapy.

Soluble biomarkers (CPII, procollagen type I N-terminal propeptide, melanoma inhibitory activity, MMP-3, C2C, COMP, osteocalcin, N-terminal telopeptide of type I collagen, and pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen) were investigated in 24 patients with PsA who were randomized to receive either adalimumab 40 mg subcutaneously every other week or placebo for 4 weeks and subsequently adalimumab in an open-label extension phase<sup>30</sup>. After 4 weeks, there was a significant decrease in serum MMP-3 levels and increase in serum melanoma inhibitory activity among the adalimumab-treated patients, while no change was observed in the placebo group. After 12 weeks, there was a marked reduction in serum MMP-3 in both groups. No change in



other biomarkers was noted. Thus MMP-3 showed promise as a biomarker for response to adalimumab treatment in PsA<sup>30</sup>. A study in an observational cohort of 49 patients with spondyloarthritis (17 with PsA) treated with TNFi showed that plasma interleukin 6, vascular endothelial growth factor, human cartilage glycoprotein-39, and MMP-3 decreased upon treatment with TNFi over a 3-year period<sup>31</sup>. However, MMP-3 was shown to decrease in both responders and nonresponders<sup>31</sup>. MMP-3 was also shown to be a biomarker that can differentiate psoriasis from PsA<sup>7</sup>. We show that serum MMP-3 decreases following treatment with TNFi. High baseline levels as well as a decrease in MMP-3 levels are associated with achieving good response. The correlation between reduction in MMP-3 and hsCRP was only moderate. Thus, MMP-3 may be further evaluated as a biomarker for screening and response to therapy in PsA, independent of CRP.

In a small study of 9 subjects with active PsA, 6-week treatment with infliximab led to a significant decrease in COMP levels<sup>32</sup>. COMP was also shown to be a biomarker for psoriatic disease, but did not differentiate between PsA and psoriasis without PsA, and may be a marker for psoriasis activity<sup>7</sup>. Here, although in univariate analysis there was no change in serum COMP levels pre- and post-TNFi therapy, when changes in other biomarkers were controlled for, an increase in COMP levels was associated with good response to treatment with TNFi. Thus, COMP is a candidate biomarker for treatment response and disease activity in PsA.

Our study, however, has a few shortcomings. Only 40 subjects were studied. A convenience sample was obtained based on the availability of samples pre- and on treatment with TNFi. The samples were obtained at irregular intervals reflecting the large variation in the time that samples were collected after commencement of therapy. Most patients showed at least some response at the time of second sample collection. Moreover, it is quite possible that some patients may have initially responded to treatment and then were secondary nonresponders at the time of second sample collection. To address this issue in the analysis, the effect of the duration between the 2 samples was investigated in the regression analysis. No effect on the model was demonstrated. Twenty-eight (70%) of the patients included in the study were treated with etanercept, because etanercept was the first TNFi approved for management of PsA in Canada, and we investigated the response to the first TNFi used. Differences, if any, between etanercept and the anti-TNF antibodies were not investigated, owing to the small sample size. Because in clinical practice physicians aim to achieve a state of minimal disease activity and not merely a reduction in joint counts or skin scores, we arbitrarily defined achievement of a state of good response where there is minimal activity in the joints and only mild skin activity. Information on achieving a state of minimal disease activity

as defined by Coates, *et al* or a Disease Activity Score was not available for all patients<sup>33</sup>. Composite disease activity scores such as those available in RA have not been fully validated in PsA, although they are being developed<sup>34</sup>. Moreover, the effect size and the level of significance demonstrated are rather modest and may not be sufficient as a clinically useful predictor for response. However, the study provides further evidence in an observational setting on the potential role of MMP-3 as a biomarker for treatment response in PsA. The decrease in MMP-3 levels probably reflects the actions of TNFi on synovial fibroblastoid cells. The increase in COMP levels is more intriguing. Since serum COMP is a marker of cartilage turnover, increased COMP levels may indicate cartilage growth and healing of joint damage. Treatment with TNFi has been shown to lead to dramatic improvement in radiographic damage in PsA<sup>35</sup>.

Our study provides evidence for further investigation of MMP-3 and COMP as soluble biomarkers for response to treatment in patients with PsA.

## REFERENCES

1. Moll JM, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973;3:55-78.
2. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006;54:2665-73.
3. Ash Z, Gaujoux-Viala C, Gossec L, Hensor EM, Fitzgerald O, Winthrop K, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: Current evidence and meta-analysis informing the EULAR recommendations for the management of psoriatic arthritis. *Ann Rheum Dis* 2012;71:319-26.
4. Mease PJ. Psoriatic arthritis: Update on pathophysiology, assessment and management. *Ann Rheum Dis* 2011;70 Suppl 1:i77-84.
5. Eder L, Chandran V, Schentag CT, Shen H, Cook RJ, Gladman DD. Time and predictors of response to tumour necrosis factor-alpha blockers in psoriatic arthritis: an analysis of a longitudinal observational cohort. *Rheumatology* 2010;49:1361-6.
6. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther* 2001;69:89-95.
7. Chandran V, Cook RJ, Edwin J, Shen H, Pellett FJ, Shanmugarajah S, et al. Soluble biomarkers differentiate patients with psoriatic arthritis from those with psoriasis without arthritis. *Rheumatology* 2010;49:1399-405.
8. Chandran V, Schentag CT, Gladman DD. Sensitivity of the classification of psoriatic arthritis criteria in early psoriatic arthritis. *Arthritis Rheum* 2007;57:1560-3.
9. Gladman DD, Shuckett R, Russell ML, Thorne JC, Schachter RK. Psoriatic arthritis — clinical and laboratory analysis of 220 patients. *Q J Med* 1987;62:127-41.
10. Strober B, Teller C, Yamauchi P, Miller JL, Hooper M, Yang YC, et al. Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. *Br J Dermatol* 2008;159:322-30.
11. Ribbens C, Martin y Porras M, Franchimont N, Kaiser MJ, Jaspard JM, Damas P, et al. Increased matrix metalloproteinase-3 serum levels in rheumatic diseases: relationship with synovitis and steroid treatment. *Ann Rheum Dis* 2002;61:161-6.
12. Yang C, Gu J, Rihl M, Baeten D, Huang F, Zhao M, et al. Serum levels of matrix metalloproteinase 3 and macrophage

- colony-stimulating factor 1 correlate with disease activity in ankylosing spondylitis. *Arthritis Rheum* 2004;51:691-9.
13. Chen CH, Lin KC, Yu DT, Yang C, Huang F, Chen HA, et al. Serum matrix metalloproteinases and tissue inhibitors of metalloproteinases in ankylosing spondylitis: MMP-3 is a reproducibly sensitive and specific biomarker of disease activity. *Rheumatology* 2006;45:414-20.
  14. Maksymowych WP, Landewé R, Conner-Spady B, Dougados M, Mielants H, van der Tempel H, et al. Serum matrix metalloproteinase 3 is an independent predictor of structural damage progression in patients with ankylosing spondylitis. *Arthritis Rheum* 2007;56:1846-53.
  15. Leibold A, Penninger JM. RANK/RANKL: regulators of immune responses and bone physiology. *Ann NY Acad Sci* 2008;1143:123-50.
  16. Edwards JR, Sun SG, Locklin R, Shipman CM, Adamopoulos IE, Athanasou NA, et al. LIGHT (TNFSF14), a novel mediator of bone resorption, is elevated in rheumatoid arthritis. *Arthritis Rheum* 2006;54:1451-62.
  17. Haroon N, Tsui FW, O'Shea FD, Chiu B, Tsui HW, Zhang H, et al. From gene expression to serum proteins: biomarker discovery in ankylosing spondylitis. *Ann Rheum Dis* 2010;69:297-300.
  18. Cohavy O, Zhou J, Ware CF, Targan SR. LIGHT is constitutively expressed on T and NK cells in the human gut and can be induced by CD2-mediated signaling. *J Immunol* 2005;174:646-53.
  19. Ritchlin CT, Haas-Smith SA, Li P, Hicks DG, Schwarz EM. Mechanisms of TNF-alpha- and RANKL-mediated osteoclastogenesis and bone resorption in psoriatic arthritis. *J Clin Invest* 2003;111:821-31.
  20. Geusens PP, Landewé RB, Garnero P, Chen D, Dunstan CR, Lems WF, et al. The ratio of circulating osteoprotegerin to RANKL in early rheumatoid arthritis predicts later joint destruction. *Arthritis Rheum* 2006;54:1772-7.
  21. Poole AR. Biochemical/immunochemical biomarkers of osteoarthritis: utility for prediction of incident or progressive osteoarthritis. *Rheum Dis Clin North Am* 2003;29:803-18.
  22. Poole AR. Cartilage in health and disease. In: Koopman WJ, editor. *Arthritis and allied conditions: a textbook of rheumatology*. 14th ed. Philadelphia: Lippincott, Williams & Wilkins; 2001:226-84.
  23. Saxne T, Heinegård D. Cartilage oligomeric matrix protein: a novel marker of cartilage turnover detectable in synovial fluid and blood. *Br J Rheumatol* 1992;31:583-91. Erratum in: *Br J Rheumatol* 1993;32:247.
  24. Rizkalla G, Reiner A, Bogoch E, Poole AR. Studies of the articular cartilage proteoglycan aggrecan in health and osteoarthritis. Evidence for molecular heterogeneity and extensive molecular changes in disease. *J Clin Invest* 1992;90:2268-77.
  25. Lohmander LS, Ionescu M, Jørgensen H, Poole AR. Changes in joint cartilage aggrecan after knee injury and in osteoarthritis. *Arthritis Rheum* 1999;42:534-44.
  26. Månsson B, Carey D, Alini M, Ionescu M, Rosenberg LC, Poole AR, et al. Cartilage and bone metabolism in rheumatoid arthritis. Differences between rapid and slow progression of disease identified by serum markers of cartilage metabolism. *J Clin Invest* 1995;95:1071-7.
  27. Gratacós J, Casado E, Real J, Torre-Alonso JC. Prediction of major clinical response (ACR50) to infliximab in psoriatic arthritis refractory to methotrexate. *Ann Rheum Dis* 2007;66:493-7.
  28. Gladman DD. Natural history of psoriatic arthritis. *Baillieres Clin Rheumatol* 1994;8:379-94.
  29. Chandran V, Gladman DD. Update on biomarkers in psoriatic arthritis. *Curr Rheumatol Rep* 2010;12:288-94.
  30. van Kuijk AW, DeGroot J, Koeman RC, Sakke N, Baeten DL, Gerlag DM, et al. Soluble biomarkers of cartilage and bone metabolism in early proof of concept trials in psoriatic arthritis: effects of adalimumab versus placebo. *PLoS One* 2010;5 pii:e12556.
  31. Pedersen SJ, Hetland ML, Sørensen IJ, Ostergaard M, Nielsen HJ, Johansen JS. Circulating levels of interleukin-6, vascular endothelial growth factor, YKL-40, matrix metalloproteinase-3, and total aggrecan in spondyloarthritis patients during 3 years of treatment with TNF $\alpha$  inhibitors. *Clin Rheumatol* 2010;29:1301-9.
  32. Cauza E, Hanusch-Enserer U, Frischmuth K, Fabian B, Dunky A, Kostner K. Short-term infliximab therapy improves symptoms of psoriatic arthritis and decreases concentrations of cartilage oligomeric matrix protein. *J Clin Pharm Ther* 2006;31:149-52.
  33. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis* 2010;69:48-53.
  34. Coates LC, Mumtaz A, Helliwell PS, Mease PJ, Callis-Duffin K, Krueger GG, et al. Development of a disease severity and responder index for psoriatic arthritis (PsA) — Report of the OMERACT 10 PsA special interest group. *J Rheumatol* 2011;38:1496-501.
  35. Eder L, Chandran V, Gladman DD. Repair of radiographic joint damage following treatment with etanercept in psoriatic arthritis is demonstrable by 3 radiographic methods. *J Rheumatol* 2011;38:1066-70.