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

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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 metalloprotease-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 PSORIATIC ARTHRITIS BIOMARKERS
TREATMENT 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[1,2]. Tumor necrosis factor inhibitors (TNFi) are efficacious in the treatment of PsA and have revolutionized the management of PsA[3]. 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[4]. Observational data from our clinic have shown that 78% of 95 patients with PsA treated

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

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[6]. 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[7]. 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[8]. Patients are evaluated according to a standard protocol[9]. 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[10]. 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[11]. Serum MMP-3 is also elevated in active ankylosing spondylitis (AS), decreases with treatment, and predicts structural damage progression[12,13,14]. 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[15]. TNFSF14 plays a pathogenic role in diseases such as RA, AS, and inflammatory bowel disease[16,17,18]. 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[19]. The ratio of RANKL to OPG reflects osteoclast activation and was shown to predict joint destruction in early RA[20]. 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[21]. Excessive and progressive cleavage of type II collagen by collagenases generates the type II collagen neoepitopes Col2-3/4C$_{long\ mono}$ (C2C) and Col2-3/4C$_{short}$ (C1-2C)[22]. 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[22]. 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[7,23]. 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[24,25,26].

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 nonresponders 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 CPII 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.

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, μg/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 κ-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$_{short}$; CPII: C-propeptide of type II collagen; C2C: Col2-3/4C$_{long\ mono}$; CPII:C2C: ratio of CPII to C2C.

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 CPII: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 (± 23.8) ng/ml and 19.8 (± 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 3. Association between baseline biomarker values and TNFi treatment response in patients with psoriatic arthritis.

	Univariate Model			Multivariate Model					
				Full Model			Reduced Model		
Biomarker	OR	95% CI	p	OR	95% CI	p	OR	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.

	Univariate Model			Multivariate Model					
				Full Model			Reduced Model		
Biomarker	OR	95% CI	p	OR	95% CI	p	OR	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[10]. High baseline CRP values were also shown to be independently associated with a good therapeutic response to infliximab in PsA[27]. However, acute-phase reactants are elevated in only around 50% of patients with PsA despite clinically active disease[28]. Therefore, other biomarkers of disease activity and response to therapy are being actively investigated[29]. 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 1 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[30]. 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[30]. 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[31]. However, MMP-3 was shown to decrease in both responders and nonresponders[31]. MMP-3 was also shown to be a biomarker that can differentiate psoriasis from PsA[7]. 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[32]. 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[7]. 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[33]. Composite disease activity scores such as those available in RA have not been fully validated in PsA, although they are being developed[34]. 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[35].

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

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