Original Research

Serological markers in psoriatic arthritis: promising tools

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Abstract

The aim of this study was to identify specific biomarkers that could be used to screen for psoriatic arthritis (PsA), as well as to assess disease activity and treatment outcome in affected patients. Forty-three outpatients considered eligible for anti-TNF-α treatment (etanercept 50 mg/week) were enrolled. Serum samples of vascular endothelial growth factor (VEGF), metalloproteinase-3 (MMP3), pentraxin 3 (PTX3), and high-sensitive C-reactive protein (hs-CRP) were collected at baseline (t0) and after 6 (t6), 12 (t12), and 24 months (t24) of treatment. Baseline values were compared with those of a group of healthy controls matched for age and sex. Disease activity scores and functional tests (DAS28, BASDAI, PASI, BASFI, HAQ, VAS pain, and VAS patient global disease activity) after treatment were found to be significantly different from baseline values. At baseline, MMP3, hs-CRP and VEGF values in the PsA-patients were found to be significantly higher with respect to levels in the controls. There were no differences in the PTX3 values. MMP3 was significantly lower at t6 ($P < 0.0001$), t12 ($P < 0.0001$) and t24 ($P < 0.0001$). hs-CRP and VEGF were significantly lower, respectively, at t12 ($P < 0.01$; $P < 0.05$) and t24 ($P < 0.05$; $P < 0.01$). PTX3 was significantly higher at t24 ($P < 0.05$). A correlation was found between MMP3 and hs-CRP ($r = 0.45$, $P = 0.0005$).

MMP3, hs-CRP, and VEGF appear to be useful for the early detection of PsA and to monitor disease progression. The rise in PTX3 did not appear to be linked to the inflammatory state of the disease but might be an expression of the atherosclerotic process frequently observed in PsA.

Keywords: Psoriatic arthritis, biological markers, inflammation, tumor necrosis factor-alpha, vascular endothelial growth factor, metalloproteinase-3

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Introduction

Psoriatic arthritis (PsA) is an inflammatory joint disease with marked clinical heterogeneity that affects 0.3–1% of the population.[1–3] Unlike rheumatoid arthritis, PsA lacks specific biomarkers.[4] Serological markers to detect an early preclinical stage of the disease diagnosis and to monitor disease activity and treatment response would be extremely useful. Biomarkers could also provide insights into the pathogenesis of the disease.[5] According to the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), studies on biomarkers should be given priority in their members' research agenda.[6]

PsA can be considered a systemic expression of psoriasis. As the majority of patients initially show skin psoriasis, it is important to identify clinical features and biomarkers that pinpoint disease onset and are sensitive to disease evolution and treatment outcomes, to prevent adverse outcomes such as early mortality, progression of joint damage, and disability.

A marked association has been found between PsA and the human leukocyte antigen (HLA) system. Depending upon the disease's clinical features, HLA-B*27, HLA-B*38, and HLA-B*39 are frequently found in PsA. Biomarkers of inflammation and cartilage damage have also been studied to assess disease activity. hs-CRP, osteoprotegerin, matrix metalloprotein–3 (MMP-3), and the ratio of C-propeptide of Type II collagen to collagen fragment neoepitopes Col2-3/4(long mono) have likewise been investigated in an attempt to determine whether these could be considered reliable markers, but the results have been ambiguous.[7]

This study aimed to evaluate MMP-3, VEGF, PTX3, and hs-CRP as potential markers of PsA activity: hs-CRP, because of its link to inflammation[8]; vascular endothelial growth factor (VEGF), because of its link to angiogenesis[9]; and MMP3, because of its link to extracellular matrix remodeling.[10] Until now only studied in psoriasis patients, pentraxin-3 (PTX3), a protein belonging to long pentraxin family,[11] was also included in this study.[12] Serum levels of

these four potential biomarkers were thus assessed before (baseline) and after anti-TNFα treatment to evaluate their usefulness in diagnosing PsA. These parameters were also evaluated in connection to the patients' disease activity progression and response to anti-TNF-α treatment.

Methods

Forty-three PsA outpatients attending the Rheumatology Clinic of the University of Padova (Italy) Medical Center, fulfilling the CASPAR classification criteria,[13] and considered eligible for TNFα-inhibitor therapy were enrolled in the study between January 2010 and October 2012.

The study protocol was approved by the Local Research Ethics Committee and all study candidates gave written, informed consent.

In accordance with ASAS/EULAR recommendations, these patients were being considered for TNFα-inhibitor therapy (etanercept 50 mg/week) after the failure of NSAIDs or one DMARD. Some of the patients were also prescribed low doses of DMARDs and/or steroids.

Healthy volunteer blood donors matched for age and sex were used as a control group at baseline.

Clinical examinations

The patients were assessed clinically at each appointment: at baseline before beginning TNF-α therapy (t0), and after 6 (t6), 12 (t12), and 24 (t24) months of treatment. The patients' peripheral arthritis was evaluated using the Disease Activity Score 28 based on C-reactive protein (DAS28-CRP) as the study began before the PsARC index was validated.[14,15] The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was used to evaluate the patients with predominantly axial involvement. The Maastricht Ankylosing Spondylitis Entheses Score (MASES) was utilized for the patients with entheseal disease, and the Psoriasis Area and Severity Index (PASI) score was used for those with skin psoriasis involvement. Patients were monitored for pain using the Visual Analogue Scale for pain (VASp) and for global assessment using the Visual Analogue Scale for global assessment (VASg), the Bath Ankylosing Spondylitis Functional Index (BASFI), and the Health Assessment Questionnaire (HAQ).

Biomarkers

Blood samples, collected at t0, t6, t12, and t24, were centrifuged at $3000 \times g$ for 10 min and stored at 20°C until they were analyzed. VEGF (IBL International), MMP3 (Raybiotech), and PTX3 (Alexis) serum levels were determined using a commercial enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions. Serum hs-CRP was determined using a sensitive immunonephelometric method (DADE Behring, Milan, Italy) on a BN II Analyzer.

Statistical analysis

Statistical analyses were carried out using SPSS 12.0.1 for Windows. Clinical data and biomarkers levels were collected, registered, and compared using a repeated measures ANOVA test followed by *post hoc* Dunnett's test. The Spearman rank correlation coefficient was used to assess associations. Patients' values were compared with those of healthy subjects using the paired t test. A cut-off value of $P < 0.05$ was considered statistically significant.

Results

Forty-three PsA patients (34 males, 9 females) were enrolled in the study (Table 1). The patients could be classified as having: peripheral involvement (PI), axial involvement (AI), enthesitis involvement, and/or psoriasis. Out of the total, 53.9% showed PI, 41.4% showed AI, 95.3% showed both PI and AI, 4.7% (two patients) had exclusive axial involvement, 44.1% had enthesitis involvement, and 79% had psoriasis (Table 1). In the peripheral arthritis group, 69.7% showed poliarticular involvement.

All the patients received etanercept (50 mg/week). Some of the patients were also prescribed other drugs: 25.5% DMARDs, 6.9% DMARDs + steroids (4 mg methylprednisolone), and 2.3% (one patient) 4 mg methylprednisolone. In the DMARDs patient group, 92.8% were treated with methotrexate at an average dose of 7.5 mg/week.

Twenty-four months after etanercept therapy was begun, the DAS28-CRP, BASDAI, BASFI, PASI, HAQ, VASd, and VASg were all significantly decreased. All of these parameters, with the exception of the BASFI whose reduction was significant after 12 months, were already significantly lower 6 months after treatment was begun (Table 2).

Biomarkers

At baseline, the serum levels of the biomarkers studied (MMP3, hs-CPR, and VEGF) were significantly higher in the patient with respect to the control group, but there were no differences in the PTX3 values (Figure 1).

During and after anti-TNFα treatment, there was a significant reduction in MMP3 ($P < 0.0001$), hs-CRP ($P = 0.01$), VEGF ($P = 0.0037$), while PTX3 was significantly higher ($P = 0.001$). Serum MMP3 levels were significantly lower after 6 months of therapy (t6) and remained low after 12 (t12) and 24 months (t24) ($P < 0.001$). hs-CRP was significantly lower after 12 months (t12) ($P < 0.01$), and remained low at t24 ($P < 0.05$). Serum VEGF levels were significantly lower after 12 months (t12) ($P < 0.05$) and remained low after 24 months (t24) ($P < 0.01$). Serum PTX3 levels were significantly higher with respect to baseline values after 24 months ($P < 0.05$). The hs-CRP was significantly lower

Table 1 Patients' clinical classification and treatment utilized

Patient, N	43	PI + AI, %	41.4
Prevalence M, %	79	AI, %	4.7
Mean age, yrs	49.9 ± 8.5	Comorbidities, %	58.1
MDA, yrs	11 ± 7.6	Etanercept, % (N)	100 (43)
MDP, yrs	12 ± 10.2	DMARDs, % (N)	25.1 (11)
Psoriasis, %	79	DMARDs + S, % (N)	6.9 (3)
PI, %	53.9	S, % (N)	2.3 (1)

M: male; MDA: mean duration arthritis; MDP: mean duration psoriasis; PI: peripheral involvement; AI: axial involvement; S: steroids.

after 6 months ($P < 0.001$) and remained significantly low at t12- and t24-visit (Figure 2).

There were correlations at baseline between the DAS28 and VASp (r = 0.49, $P = 0.0002$) and VASg (r = 0.51, $P = 0.0001$); between the PASI and the HAQ (r = 0.41, $P = 0.003$) and the BASFI (r = 0.48, $P = 0.04$). The BASDAI was correlated with the HAQ (r = 0.62, $P = 0.005$), the BASFI (r = 0.67, $P = 0.002$), the VASd (r = 0.71, $P = 0.0009$), the VASg (r = 0.66, $P = 0.002$), and the ESR (r = 0.54, $P = 0.01$). BASFI correlated with HAQ (r = 0.61, $P = 0.006$), VASd (r = 0.67, $P = 0.002$), and VASg (r = 0.68, $P = 0.049$). The most interesting correlations were between the BASFI and VEGF (r = 0.85, $P = 0.006$) (Figure 3) and between MMP3 and the hs-CRP (r = 0.45, $P = 0.0005$) (Figure 4).

Discussion

Although clinical features can identify PsA patients who are likely to develop a severe form of the disease, biomarkers capable of identifying the disease at its earliest stages and of predicting response to treatment have become a research priority,[16] in view of preventing further joint damage progression and improving patients' quality of life. Soluble biomarkers can potentially be useful in screening psoriasis patients for underlying PsA so that a rheumatolgical referral can be made, diagnosis can be facilitated, and disease activity and treatment can be monitored.

Given their connection to vessel properties, neovascularization, and inflammatory response, four specific biomarkers (MMP3, VEGF, hs-CRP, and PTX3) were studied in PsA patients being treated for a 24-month period with anti-TNFα receptors. No side effects, and in particular no infections, were observed.[17] The patients' levels were compared with those of matched healthy subjects at baseline and between time point values during/after the treatment period.

CRP serum levels were analyzed using ultrasensitive methods capable of detecting negligible values and identifying even subtle changes. Most traditional CRP measurements can detect a minimum value of 0.6 mg/L, while the new methodology can distinguish concentrations as low as 0.00035 mg/L.[18] In our study, the percentage of patients with high hs-CRP levels was 23.2% when the patients' baseline serum levels of the four biomarkers were compared to those of healthy matched volunteers.[10] PTX3 values were found to be similar in the two groups. Little information is available in the literature about PTX3, although one study described higher levels in psoriatic patients with respect to controls.[12]

MMP3, the major methalloproteinase involved in cartilage degradation,[19] was significantly lower after six months. This finding is in agreement with previous studies reporting lower serum levels after anti-TNFα therapy[10,20] as well as after treatment with DMARDs (methotrexate).[21] According to recent findings,[22] a prompt decrease in MMP3 seems to reflect a good response to anti-TNFα therapy.

Consistent with findings by Chimenti et al.[23] concerning their study of patients suffering with PsA who were treated with anti-TNFα for 22 months, hs-CRP levels were

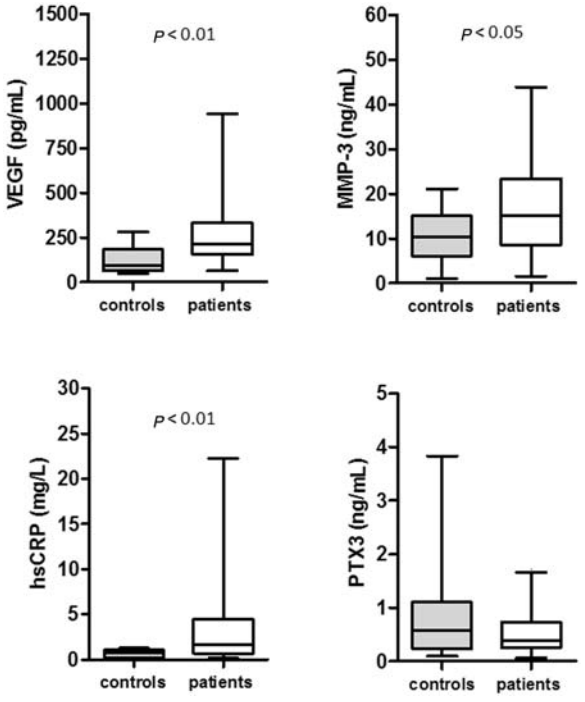

Figure 1 Comparison of the biomarkers MMP3, hs-CRP, VEGF and PTX3 serum levels in patients and controls at baseline. MMP3: matrix metalloprotein–3; hs-CRP: high-sensitive C-reactive protein; PTX3: pentraxin 3; VEGF: vascular endothelial growth factor

Table 2 Mean functional and disease activity scores at baseline and at study time points

	t0	t6	t12	t24	*P* (ANOVA)
DAS28	4.25 (0.58)	2.43 (0.83)[a]	2.08 (0.69)[a]	2.01 (0.66)[a]	<0.0001
BASDAI	65.01 (22.26)	40.58 (27.04)[a]	38.15 (26.17)[a]	36.90 (24.14)[a]	<0.0001
BASFI	49.93 (33.85)	37.19 (29.03)	30.47 (24.67)[b]	27.27 (22.95)[b]	<0.005
PASI	5,45 (8.49)	1.47 (1.36)[a]	0.94 (1.07)	0.80 (0.97)	<0.0001
HAQ	0.95 (0.47)	0.50 (0.41)[a]	0.43 (0.40)[a]	0.37 (0.39)[a]	<0.0001
VASp	86.06 (12.31)	40.34 (20.33)[a]	28 (19.5)[a]	21.88 (18.24)[a]	<0.0001
VASg	82.41 (21.90)	49.59 (25.33)[a]	29.03 (20.96)[a]	23.25 (19.27)[a]	<0.0001

Data are expressed as mean (standard deviation).
[a]$P < 0.0001$ vs t0, *post hoc* Dunnett's multiple comparison test.
[b]$P < 0.001$ vs t0, *post hoc* Dunnett's multiple comparison test.

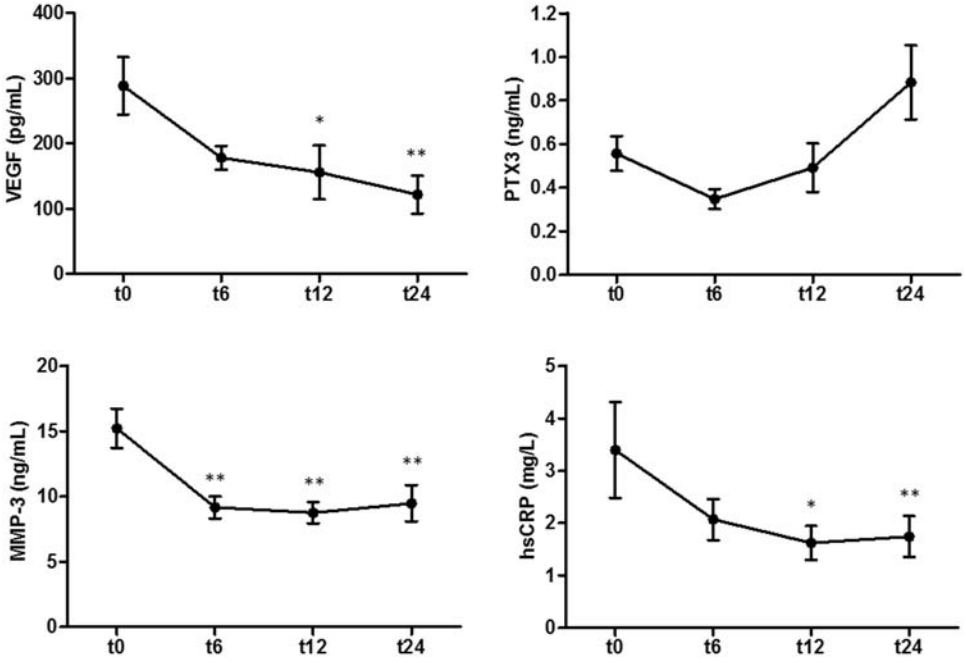

Figure 2 VEGF, PTX3, MMP3 and hs-CRP levels at different time points. *$P < 0.05$ vs t0, **$P < 0.01$ vs t0, *post hoc* Dunnett's multiple comparison test. MMP3: matrix metalloprotein–3; hs-CRP: high-sensitive C-reactive protein; PTX3: pentraxin 3; VEGF: vascular endothelial growth factor

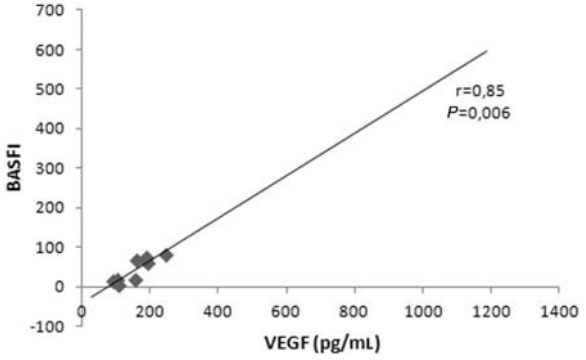

Figure 3 Correlation between BASFI and VEGF serum levels. BASFI: Bath Ankylosing Spondylitis Functional Index; VEGF: vascular endothelial growth factor

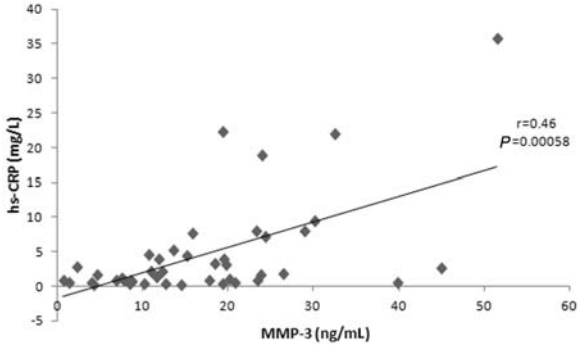

Figure 4 Correlation between hs-CRP and MMP3 serum levels. MMP3: matrix metalloprotein–3; hs-CRP: high-sensitive C-reactive protein

significantly decreased in our patients after 12 months of therapy. Moreover, as already described by Ribbens et al.,[24] a significant correlation was noted between hs-CRP and MMP3 during the treatment period. These findings highlight a link between systemic and local joint inflammation, and confirm that MMP3 can be considered a marker of disease activity and particularly of articular damage.[25]

Although we did not find any correlation between the clinical disease activity and the biomarkers considered, these could be mainly linked to synovial/cartilage changes at a local and short-term level. It is well known that biomarkers in PsA are frequently unconnected with clinical disease activity as approximately 50% of these patients have normal values despite active symptomatology.

Although it is well established that VEGF is decreased after treatment,[10,26] a significant decrease became apparent only at the 12-month time point in our study. Cañete et al.,[9] instead, observed an early decrease in PsA patients after only three months of infliximab treatment. As already reported in previous studies,[27] we found a correlation between VEGF and BASFI that could at least partially explain the bioumoral and clinical improvement found in treated PsA patients. It is possible that new angiogenesis is the basic pathogenetic mechanism in synovitis, as well as in sacroileitis and enthesitis.[28]

These results, together with previous suggestions,[29] indicate that MMP3, hs-CRP, and VEGF can be considered biomarkers to detect early stages of PsA and to monitor response to treatment in these patients. Other studies are warranted to verify if VEGF can predict more severe forms of the disease. Fink et al.,[30] in fact, reported higher VEGF levels in patients with severe PsA who were compared with other patients with a mild form of the disease as well as

with healthy controls. Elevated VEGF levels have also been found to be associated with erosive changes in RA.[31]

As expected, these results have confirmed the well-known efficacy of etanercept as reflected in statistically significant lower serum MMP3, VEGF, hs-CRP levels and DAS28, BASDAI, PASI, BASFI, HAQ, VASd, and VASg scores. The drug's good safety profile and the relatively low risk of infectious events, and in particular infection relapse,[17] were also corroborated.

Unexpectedly, significantly higher serum PTX3 levels were observed after 24 months of treatment. PTX3 belongs to the pentraxin superfamily and is known to play a fundamental role in atherosclerosis.[32–35] It is well known that the atherosclerotic process is accelerated in several rheumatic diseases, particularly in PsA.[36,37] It is also a well accepted fact that psoriasis patients are more frequently affected with the metabolic syndrome than other subjects.[38] The finding that PTX3 is increased after anti-TNFα blocker treatment is puzzling as a few studies have reported an improvement in some atherosclerotic parameters, such as the carotid artery intima-media thickness and the post-occlusion flow-mediated dilation,[39,40] while others have described contrasting results.[41,42] The latter, in fact, have reported that there is a continuous evolution of vascular damage and an increase in intima-media thickness and a decrease in flow- mediated dilation.[43] As higher PTX3 values did not seem to be an expression of persisting disease activity in our patients, further studies are needed to establish its role in the inflammatory process.

In conclusion, as evidence clearly indicates that early diagnosis of PsA will lead to better long-term outcomes, serological biomarkers could be beneficially employed for the early diagnosis of the disease and to predict more severe forms. At present, there is a high prevalence of underdiagnosed PsA and, in particular of diagnostic delay, both of which favor the progression from joint inflammation to stable damage. Once they have been identified and verified, biomarkers could be used to screen patients to facilitate appropriate referral and treatment. The biomarkers investigated here show promise and warrant further investigation, and new ones are, hopefully, waiting to be discovered.

Author contributions: RR, VM, LP participated in the design and interpretation of the study and in the critical revision of the manuscript; RR, VM wrote the paper; RR, AO, VM assessed the patients; FO, AS, NB performed biochemical investigations; RR, FO, VM, performed data analysis.

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