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Vascular endothelial growth factor (VEGF), cartilage oligomeric protein (COMP) and matrix metalloproteinase 3 (MMP-3) as serum biomarkers in psoriatic arthritis

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ABSTRACT*: **Introduction.** Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disorder characterized by axial and peripheral joint involvement as well as extra-articular manifestations such as skin and nail disease, enthesitis, dactylitis, uveitis, etc. Given the broad clinical spectrum, the assessment of the natural course, activity, therapeutic response and prognosis of PsA is difficult. The discovery and implementation of biomarkers would allow personalization of the management of PsA patients.*
***Materials and methods.** The serum levels of vascular endothelial growth factor (VEGF), cartilage oligomeric matrix protein (COMP) and matrix metalloproteinase 3 (MMP3) and C-reactive protein were measured in 106 patients with psoriatic arthritis – naive and treated with methotrexate and/or biologics (adalimumab, etanercept, infliximab, ustekinumab). Multiple clinical measures, indices and questionnaires used in PsA were also assessed.*
***Results.** Patients with achieved minimal disease activity, CPDAI and PASDAS remission had significantly lower serum VEGF concentrations (619.55 pg / ml vs 430.50 pg / ml, p = 0.009; 489.682 vs. 768.991 pg / ml, p = 0.005; and 459, 72 vs 726, 94 pg / ml, p = 0, 004 respectively). Serum levels of VEGF (rs = 0.327; p = 0.015), COMP (rs = 0.328; p = 0.001) and MMP-3 (rs = 0,213; p = 0,028) positively correlated with CRP. There was also a positive association of VEGF levels with PASI (rs = 0.279; p = 0.004), BSA (rs = 0.225, p = 0.02), PASDAS (rs = 0.269; p = 0.005), CPDAI (rs = 0.213; p = 0.014), HAQ-DI (rs = 0.331; p = 0.001), DLQI (rs = 0.232 p = 0.017) and PsAQoL (rs = 0.256; p = 0.008). Serum COMP levels were positively linked with the swollen joints number (rs = 0.204; p = 0.035), PASI (rs = 0.205; p = 0.034) and BSA (rs = 0.247; p = 0.010). MMP-3 correlated with the number of swollen joints (rs = 0.255; p = 0.008). **Conclusion.** COMP, MMP-3 and especially VEGF could be used as potential biomarkers in psoriatic arthritis.*

KEYWORDS – *biomarkers, COMP, MMP-3, psoriatic arthritis, VEGF*

I. INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disorder characterized by axial and peripheral joint involvement as well as extra-articular manifestations such as skin and nail disease, enthesitis, dactylitis, uveitis, etc. Given the broad clinical spectrum, the assessment of the natural course, activity, therapeutic response and prognosis of PsA is difficult. The discovery and implementation of biomarkers would allow personalized management of patients with the disease.

The biomarker is a feature that is measured and evaluated as an indicator of normal biological process, pathological process or pharmacological response to a therapeutic intervention. Biomarkers can be used to identify disease risk factors and immunopathogenesis. Preferably, biomarkers should be present in easily obtainable samples, such as urine or serum.

Angiogenesis plays a central role in the development of psoriatic disease. Vascular abnormalities occur both in the psoriatic plaques and in the synovial membrane. Vascular endothelial growth factor (VEGF) is considered to be the most specific angiogenic cytokine for endothelial cells, playing an important role in their structure and function. Overexpression of VEGF is detected in both the plaques and serum of patients with psoriasis vulgaris, with its values varying according to the disease activity[1-4].In patients with psoriatic arthritis, there is a close relationship between VEGF levels in synovial fluid and synovial vascular morphology, with increased VEGF levels in these patients. Studies of serum VEGF levels are scarce but indicate elevated cytokine levels.[5,6]

Cartilage oligomeric matrix protein (COMP) is also known as thromboplastin 5. It is involved in the formation of collagen type I and II fibrils, which are associated with aggrecan - a major component of the cartilage matrix. COMP is considered a marker of cartilage destruction. Except in cartilage, the protein is identified in ligaments, menisci, tendons, osteoblasts, vascular smooth muscle [7]. It is important to note that dermal fibroblasts also express COMP [8].

Matrix metalloproteinase 3 (MMP3), also known as stromelysin-1, is an enzyme that plays an important role in bone and cartilage destruction. It breaks down various components of the extracellular matrix and can activate other metalloproteinases. In studies primarily in patients with rheumatoid arthritis, MMP-3 is identified as a synovial inflammatory marker that correlates well with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and interleukin (IL)-6 levels [9].

II. MATHERIALS AND METHODS

The present cross-sectional study included 106 patients with psoriatic arthritis, fulfilling The ClASsification for Psoriatic ARthritis (CASPAR) criteria: 17 naive, 11-treated with methotrexate monotherapy, 19-treated with adalimumab, 25 with etanercept, 16 with infliximab, 18 with ustekinumab. Patients met the following inclusion criteria: duration of treatment for at least 6 months, lack of concomitant intake of corticosteroids or NSAIDs within 24 hours, absence of other inflammatory arthropathies or clinically relevant osteoarthritis, absence of clinically relevant other concomitant diseases such as, but not limited to: poorly controlled diabetes or cardiovascular disease, malignancy, infection etc.

The serum levels of vascular epithelial growth factor, matrix metalloproteinase 3 and human cartilage oligomeric protein were measured in serum samples by enzyme-linked immunosorbent assay (ELISA). C-reactive protein was measured by turbidimetric analysis.

Clinical assessment of patients was made using several measures and indices: number of painful (tender) and swollen joints from a total of 68/66 by American College of Rheumatology (ACR), Leed's enthesitis index (LEI), Leeds dactylitis index (LDI), Modified Nail Psoriasis Severity Index (mNAPSI), Psoriasis Area Severity Index (PASI), percentage of involved body surface area (BSA).

All patients completed the following questionnaires: Short Form 36 (SF-36) questionnaire version 2.0, Health Assessment Questionnaire - HAQ-DI, Dermatology Quality of Life Index (DLQI), Psoriatic Arthritis Quality of Life. The patient's pain (PtPain) and global assessment of the disease (PtGA) of the were also measured by 100 mm visual analogue scale (VAS).

The disease activity was determined by: Disease Activity Score in 28 joints (DAS 28-CRP), Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI) and Psoriatic Arthritis Disease Activity Score (PASDAS). The number of patients achieving minimal disease activity (MDA) was also calculated.

Statistical analysis was done with SPSS software version 20. Descriptive statistics, parametric and non-parametric tests, multiple linear regression were used. The level of significance was set to 0.05.

III. RESULTS

There were no statistically significant differences in the serum concentrations of VEGF ($H(2) = 6.325$, $p = 0.388$), COMP ($H(2) = 6.536$, $p = 0.366$) and MMP3 ($H(2) = 3.916$, $p = 0.688$) between naive patients and those treated with methotrexate monotherapy and biological agents (anti-TNF and ustekinumab). Patients treated with adalimumab (mean difference 27.08 mg /L, $p < 0.01$) , etanercept (mean difference 26.18 mg / L, $p < 0.01$) and infliximab (mean difference 24.21 mg /L, $p < 0.01$) had significantly lower CRP levels compared to naive patients ($F = 6.099$, $p < 0.001$) (fig. 1).

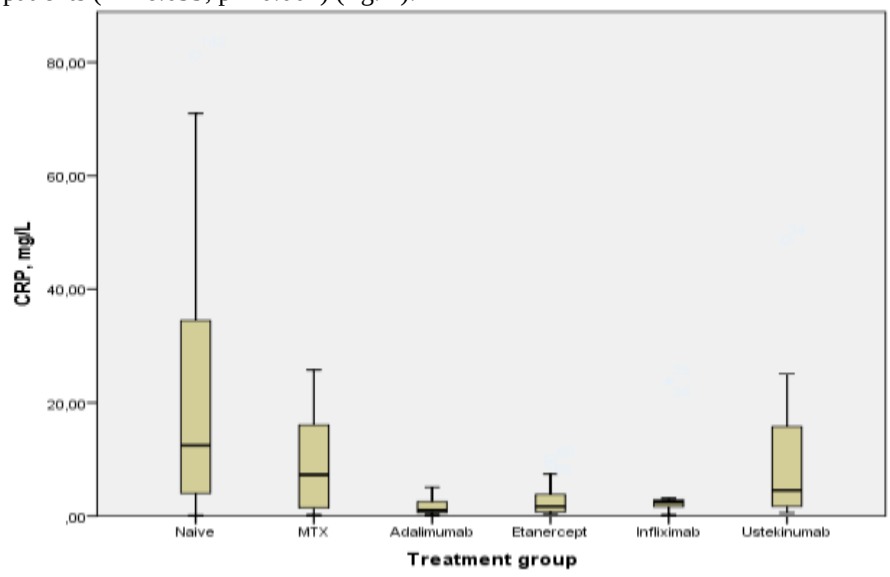

Figure 1: C-reactive protein (mg / L) levels in individual patient groups.

Patients with achieved MDA had significantly lower serum VEGF concentrations (430.50 pg / ml vs 619.55 pg / ml, p = 0.009), the same was valid for the patients attaining CPDAI (489.68 vs. 768.99 pg / ml, p = 0.005) and PASDAS remission (459. 72 vs 726, 94 pg / ml, p = 0.004) (fig. 2, 3 and 4).

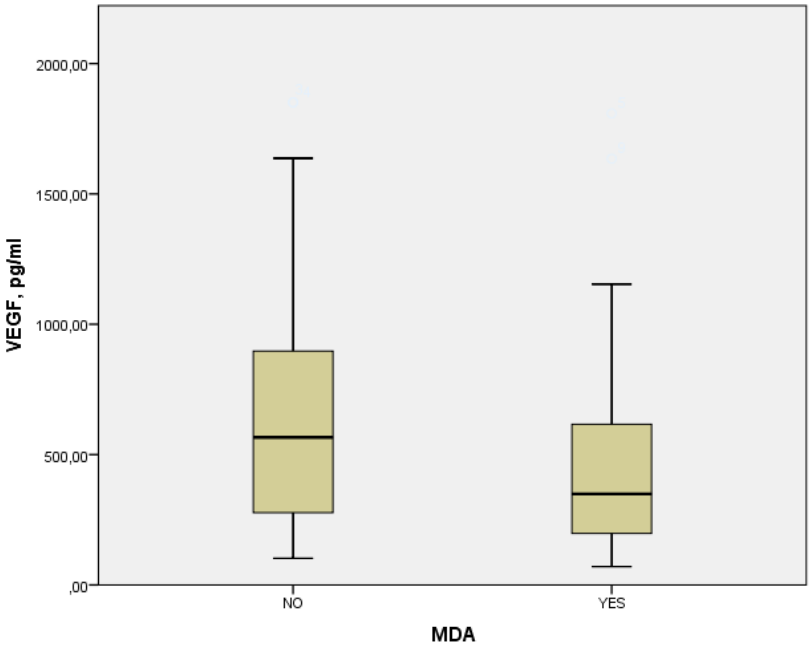

Figure 2: Comparison of serum VEGF levels between patients by MDA status.

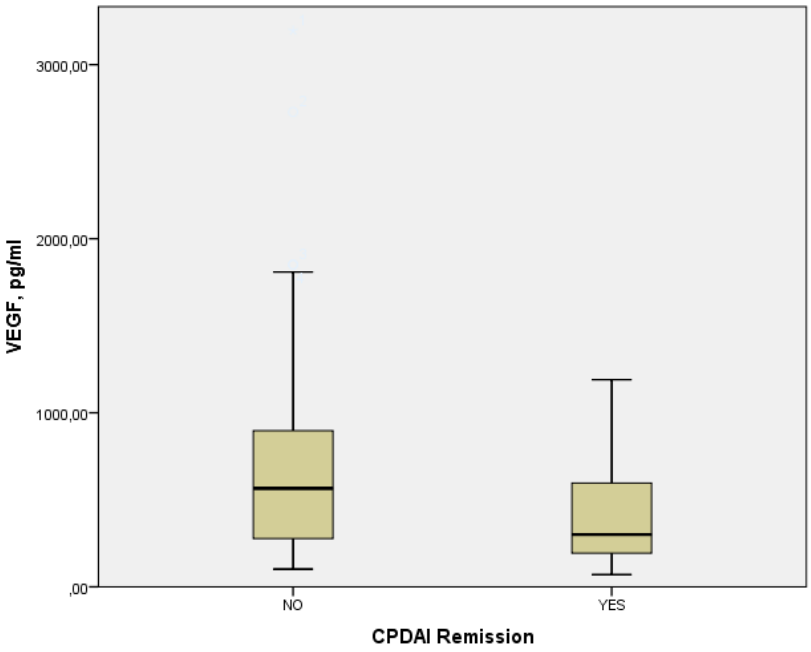

Figure 3: Comparison of serum VEGF levels between by CPDAI remission status (CPDAI ≤ 2).

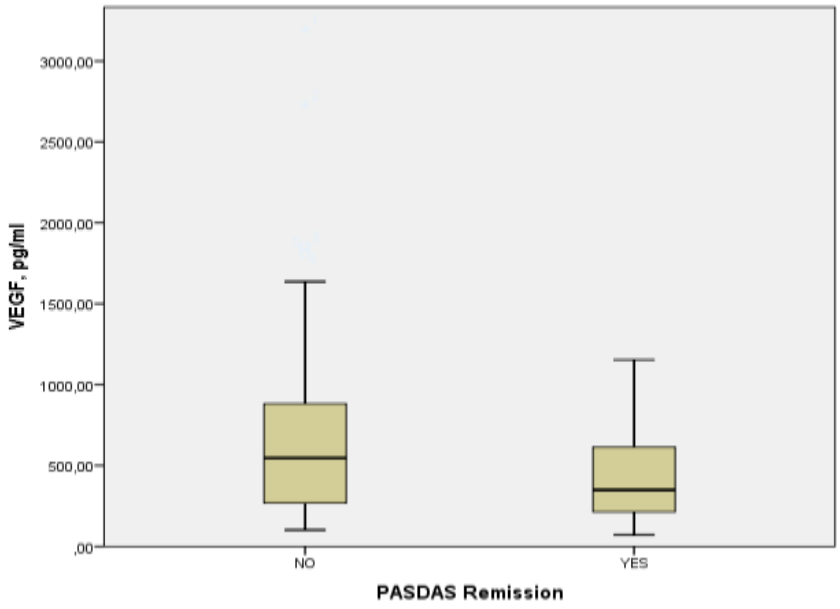

Figure 4: Comparison of serum VEGF levels between achieved and non-achieved PASDAS remission (PASDAS ≤ 2.4)

Mean CRP levels were significantly lower in patients that have achieved DAS 28 remission (2.13 mg/L vs 20.34 mg/L; p = 0.001) and DAPSA remission (2.10 mg/L vs 12.82 mg/L; p = 0.001), but not in those in CPDAI remission (7.40 mg/L vs 13.57 mg/L; p = 0.201), PASDAS remission (6.26 mg/L vs 14.86 mg/L; p = 0.193), and with MDA (6.30 mg/L vs 14.80 mg/L; p = 0.161). There was a positive correlation between the serum levels of VEGF (rs = 0.237; p = 0.015), COMP (rs = 0.328; p = 0.001) and MMP-3 (rs = 0.213; p = 0.028) with those of CRP, as well between VEGF and COMP (rs = 0.318; p = 0.001). In assessing the relationship between the biomarkers tested and various clinical and patient questionnaires, VEGF levels were found to correlate positively with PASI (rs = 0.279; p = 0.004), BSA (rs = 0.225, p = 0.02), PASDAS (rs = 0.269; p = 0.005) and CPDAI (rs = 0.213; p = 0.014). A positive relationship was also found between VEGF and HAQ-DI (rs = 0.331; p = 0.001), DLQI (rs = 0.232 p = 0.017) and PsAQoL (rs = 0.256; p = 0.008). Serum COMP levels were positively associated with the swollen joints number (rs = 0.204; p = 0.035), PASI (rs = 0.205; p = 0.034) and BSA (rs = 0.247; p = 0.010). For MMP-3, only a link with the number of swollen joints was found (rs = 0.255; p = 0.008).

Serum CRP correlated with the number ot swollen (rs = 0.523; p < 0.001) and tender joints (rs = 0.372; p < 0.001), BSA (rs = 0.409; p <0.001), PASI (rs = 0.414; p <0.001) and to a lesser degree with LEI (rs = 0.185; p = 0.028) and LDI (rs = 0.209; p = 0.013). After regression analysis only swollen joints were predictor for an increased CRP (p < 0.05).

IV. DISCUSSION

In our cohort we were unable to detect statistically significant differences in serum levels of VEGF, COMP and MMP3 between naive and treated with biologics patients. This is in contrast with similar studies and may be related to the relatively small sample size for each group. We found a significant relationship between these three biomarkers and the well-known proinflammatory C-reactive protein, indicating that they might reflect the activity of the disease.

VEGF was found to positively correlate with the degree of skin involvement, the PsA-specific CPDAI and PASDAS activity indices, the degree of disability measured by HAQ-DI, the skin quality of life, and the specific PsAQoL questionnaire.

Significantly lower VEGF levels were found in patients who achieved remission based on the PsA-specific indices - CPDAI, PASDAS, and fulfilling the minimal disease activity criteria. In contrast, the most significant differences in CRP serum concentrations were found for patients in remission according to the predominantly "joint" indices DAS 28 and DAPSA.

Fewer correlations with the disease measures and indices were found for COMP and MMP-3. We confirm the previously found by other authors link between COMP and skin involvement measured by PASI and BSA. This and the fact that COMP is positively associated with the joint count number support the hypothesis that COMP could be a marker for both joint and skin involvement. MMP3 is associated with the number of swollen joints, which is logical given the role of this enzyme in the pathogenesis of inflammatory arthropathies.

Of the three new biomarkers examined, VEGF reflects most extensively the disease activity in PsA patients - there is a link with the conventional proinflammatory parameters, clinical measures and patient questionnaires for disability and quality of life. A larger cohort is needed to determine the cut-off levels of this signal protein for distinguishing patients in remission from those with disease activity and to further prove its role in managing patients with PsA.

V. CONCLUSION

There is a correlation between the serum levels of VEGF, COMP and MMP3 with those of C-reactive protein levels and clinical status in psoriatic arthritis patients, with VEGF being the best in this regard. The latter could be used as a potential biomarker in clinical practice.

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