Biomarkers and prognostic stratification in psoriatic arthritis

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SUMMARY

In rheumatic diseases, biomarkers may serve as surrogate endpoints for diagnosis, prognosis, disease activity, therapeutic response and disease outcome. In recent years a great effort has been made to identify useful tools to establish early diagnosis, prognosis and therapeutic response especially in rheumatoid arthritis (RA). In psoriatic arthritis (PsA) serological biomarkers have been frequently borrowed from RA, but this approach have sometimes lead to inappropriate choices of biomarkers and incorrect conclusions. Furthermore, the heterogeneous spectrum of articular manifestation of PsA and the variable course of the disease can make diagnosis and prognosis difficult. Recently, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) identified two key areas for biomarkers development in psoriasis and PsA: the diagnosis of the articular disease in patients with psoriasis and the evaluation of joint damage in PsA. In this review we revised the currently available and the new potential markers for PsA, such as serum, genetic, cellular and histological biomarkers, clinical and imaging data, with particular attention on the prognostic aspect in order to identify progressive disease suitable for a more aggressive treatment.

Key words: *psoriatic arthritis, biomarkers, joint damage*

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INTRODUCTION

The term biomarker comes from "biological markers", that the US National Institutes of Health (NIH) Biomarkers and Surrogate Endpoint Working Group defines "as objective parameters that can be measured and evaluated as an indicator of biological processes, pathogenic processes or pharmacological responses to therapeutic intervention" (1).

In the pathogenic processes, biomarkers may serve as surrogate endpoints for diagnosis, prognosis, disease activity, therapeutic response and outcome of the disease. In the last ten years, with the new and now consolidated concepts of "early diagnosis" (2-5) and "treat to target" (6, 7) a huge effort has been made to identify useful tools to establish early diagnosis, prognosis and therapeutic response in rheumatoid arthritis (RA) (8, 9).

For this, a great endeavour has been made for the identification of serological, clinical and instrumental parameters, helpful for identify patients at risk of developing persistent and aggressive disease, requiring early and aggressive therapeutic intervention. Among these parameters, acute phase reactants(10), rheumatoid factor (RF) and its isotypes, anti-citrullinated peptide antibodies (ACPA) (11-18) , simple clinical index as the number of swollen joints and composite index as the disease activity score (DAS) (19), the presence of ultrasonographic power doppler despite clinical remission of the disease, the bone oedema on MR imaging and the erosions in MR and plain radiographs (20-26), have been identify in RA as biomarkers of disease activity or prognostic factors and currently used in the evaluation of RA patients.

Unfortunately, in Psoriatic Arthritis (PsA), traditional methods in evaluation of disease assessment and research for biological markers, have not kept pace with the accelerated development of the concept of early diagnosis and prognostic stratification, the appearance of the new

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therapeutic options and also with the new PsA classification and the re-evaluation of their different clinical subsets (27) (from the Moll and Wright to the CASPAR classification) (28-30).

So, in PsA, serological biomarkers, such as the domains assessing clinical outcome (for example swollen and tender joints, visual analogical scale (VAS) for patient and physician global assessment, VAS for pain, Health Assessment Questionnaire (HAQ)), have been frequently borrowed from RA because of the similarities between the diseases and the good response to the same therapeutic approach with biological drugs (31, 32). Nevertheless, this "copy-past" approach from RA to PsA have sometimes lead to inappropriate choices of biomarkers and subsequently to incorrect conclusions.

Compared with RA, PsA is a more complex disease from both clinical and pathogenetic point of view and the use of RA biomarkers may be reductive and make diagnosis and prognosis difficult.

Recently, the increased data demonstrating the different pathogenesis and disease process in PsA (33) and RA (34), rises new attention among PsA researchers in the identification and validation of specific biomarkers. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) identified two key areas for biomarker development in psoriasis and PsA:

1. articular disease diagnosis in patients with psoriasis;
2. joint damage in PsA (35).

With particular attention on the second key area, in the 2008 GRAPPA meeting held in Leeds (UK), a special working group for the development of soluble and synovial tissue biomarkers in PsA, under the umbrella of the Outcome Measures in Rheumatology (OMERACT), began to develop validation tools reflecting the variety of different process and phisiopathological mechanisms in PsA (37).

The aim of this review is to summarize the actually available biomarkers for PsA with a particular attention on those that may help clinicians in the prognostic stratification of PsA patients.

SERUM BIOMARKERS

Erythrocyte sedimentation rate (ESR) and C- reactive protein (CRP)

Recently, Chandran and co-workers show that highly sensitive CRP (hs-CRP) levels are higher in PsA patients compared with those observed in patients with psoriasis alone and that it may be a biomarker of PsA because indicates additional inflammation (36). Nevertheless, hs-CRP is not available for routine analysis and classical acute phase reactant, such as ESR and CRP, are generally used. However, ESR and CRP are reported as normal in up to 50% of patients with PsA despite clinically active disease; their contribute for diagnosis is very limited while they may have a role in the assessment of disease activity (37, 38). More than 20 years ago, Gladmann and co-workers found that acute phase reactants correlate with a higher number of involved joints and represent a negative prognostic predictor, especially in the peripheral subset of PsA with respect to the axial and enthesitic form (38). In a recent study, CRP has been evaluated as a marker for response to therapeutic intervention with tumor necrosis factor-alpha (TNFalfa) antagonists in patients with PsA. Moreover, higher levels of CRP were found to be a good predictor of response and along with other clinical features (lower HAQ-DI score, polyarthritis) increased the chance of achieving clinical improvements with anti-TNFalfa drugs (39).

Cytokines

Significantly higher serum levels of IL-6, IL-10, soluble receptor of IL-2 (sIL-2R) and IL-1 receptor antagonists (IL-1ra) were found in patients with PsA in comparison with healthy volunteers (40). In previous studies, a correlation between IL-6 levels and the number of painful and swollen joints was demonstrated (41); moreover, serum IL-6 appears to be a better marker of inflammation than the classical acute phase reactants (ESR and CRP) and correlates with the number of affected joints (42) in patients with psoriasis and inflammatory joint disease. More recently, Elkayam O et

al. did not found any correlation between IL6 levels and severity of joint involvement. This discrepancy may be due to differences in the patients' population (polyarticular vs oligoarticular involvement) suggesting that this association may exists only in polyarticular arthritis (42). However, studies of markers of inflammation both in healthy subjects and in patients with RA have shown a statistically significant circadian variation in levels of IL-6, suggesting that it would be a less robust marker than those without diurnal variation (43).
In the same study by Elkayam and coworkers, no association was found between levels of IL-10 and sIL-2R and clinical parameters, whereas levels of IL-1ra seem to correlate with the number of tender and swollen joints in patients with peripheral form. No significant association was found between IL-1ra serum levels and clinical lumbar involvement, suggesting that IL-1ra, as well as IL-6, may be useful in the future as serum biomarkers of disease activity in Psa, especially in the peripheral form (42).

Autoantibodies

Rheumatoid factor (RF) is the longest-standing autoantibody test to distinguish RA from other forms of arthritis and included in the recentlu published 2010 classification criteria for RA (4), replacing the 1987 American College of Rheumatology (ACR) criteria (44). It has been documented as a useful marker for the diagnosis and the prognosis of RA, with a sensitivity of 68-81% and a specificity of 60-85%, until the identification of anti cyclic cytrullinated peptides antibodies (ACPA), showing a higher specificity (90-98%) and comparable sensitivity (45). Although RF facilitated the classification of polyarthritis, the differential diagnosis between RA and PsA is a complex clinical work and the utility of autoantibodies is frequently considered marginal. For example, it is well known that in adult people of Northern Italy, RF may be related to HCV infection, which occurs in 5 to 10% of the general population, not associated with arthritis (46). This may lead to an increased rate of RF posotivity in otherwise seronegative arthritis (47).
Despite in the Moll and Wright classification criteria for PsA (30) RF is an exclusion criteria and in the new CASPAR classification a negative RF is considered as a minor criteria for the diagnosis (31), RF was found in a variable percentage of PsA, ranging between 2% and 16,5% in patients with psoriasis and inflammatory arthritis (48-51). In all of the studies no significant correlation was found between RF positivity and erosive disease or number of swollen and/or involved joints.
More than RF, ACPA are considered highly specific markers of RA, with a predictive value for subsequent structural damage (52, 53), persistence of synovitis (54, 55), the need for intensive treatment (56), decline of function in the course of disease (57) and premature death (58). In unidifferentiated Polyarthritis (UPA), several studies describe high predictive value of ACPA positivity at baseline with respect to the development of overt RA at 1-year follow-up (54, 55, 59, 60). Moreover, the presence of ACPA has been linked to development of RA even in healthy populations (61).
Despite their high specificity for RA, ACPA have also reported in other conditions such systemic lupus erythematosus (SLE) (62, 63) , Sjögren syndrome (64), systemic sclerosis (65) and others connective tissue disease (66) and in the majority of cases ACPA were associated with erosive joint involvement (64, 65, 67, 68) suggesting that the risk of deforming and erosive arthritis is closely related to ACPA positivity. Moreover, ACPA have been observed also in psoriatic arthritis, with a proportion ranging from 5 to 16% (51, 53, 67, 68). In PsA, as in RA, ACPA seems to be useful in detecting those patients with a higher number of involved and swollen joints (51, 59) and with an increased risk of erosion, requiring early DMARD treatment with conventional drugs or biological agents (53).
It is possible that RA with RF or ACPA positivity may occur in patients with psoriasis, even if the reported association between ACPA and erosive arthritis in more

then one disease, different from RA, require a more complex explanation. Interesting, in the study by our group, enthesitis, dactylitis and axial or DIP involvement was similar in the ACPA positive patients compared to the ACPA negative group, meaning that ACPA are not restricted to those patients with a clear-cut clinical picture of RA, as they may be present in patients with features usually regarded as typical of PsA and seronegative spondyloarthropathies.

Circulating mediators of cartilage and bone remodelling

Cartilage destruction and remodeling are features of inflammatory arthritis. The products of cartilage synthesis and destruction are released into the serum during this process and may also serve as biomarkers (38). Whereas RA primarily results in bone and cartilage resorption, PsA combines destructive elements with anabolic bone responses and cartilage apposition (70).

Osteoprotegerin (OPG) is a cytokine and a potential marker of periostitis and new bone formation which is a characteristic feature of PsA that differentiated it from other inflammatory arthritis. Recent studies have shown that an increased level of OPG may be used as a marker of PsA in patients with psoriasis and may indicate the presence of new bone formation (38).

Another informative marker of cartilage remodeling is the ratio between C-propeptide of type II collagen (CPII) and collagen fragment neoepitopes (C2C), that reflects the balance between type II collagen synthesis and degradation. This parameter is an independent biomarker for PsA and may indicate new bone formation. Also, matrix metalloproteinase-3 (MMP-3), an enzyme with a role in the destruction of cartilage and bone in rheumatic diseases characterized by synovitis, has been shown to be associated with PsA (38). However, these biomarkers may be useful to identify patients with psoriasis at increased risk of having PsA, helping in early diagnosis, but no association was found with disease activity and prognosis of PsA.

Instead, the extent of bone loss at the peripheral joints is associated with elevated circulating macrophage-colony stimulating factor (M-CSF) and receptor activator of nuclear factor kappa-B ligand (RANKL) concentrations in serum samples from PsA patients. Serum levels of M-CSF in particular are elevated in patients with erosive arthritis and strongly correlate with severity of peripheral erosive disease. Therefore, markers such as M-CSF and RANKL may have a role to identify patients in whom progressive or accelerated joint damage will develop (71).

Furthermore, cartilage oligomeric matrix protein (COMP), a glycoprotein expressed in cartilage, tendons, meniscus and synovial membrane, can be used as a parameter for the extent of cartilage destruction because its release pattern in serum may reflect cartilage turnover. Serum levels of COMP have been demonstrated to be an indicator for disease activity in patients with PsA, because those with active disease showed significantly elevated COMP serum levels compared to the patients with low disease activity. Indeed, this parameter correlates significantly with acute-phase reactants (CRP) and the number of swollen joints (72).

Clinical biomarkers

PsA is classified as a spondyloarthropathy because of the presence of axial involvement in up to 40% of patients with a characteristic asymmetrical distribution (73, 74). Nevertheless, prognostic factors have not been extensively studied for the axial form of PsA and it is not clear from the literature if axial involvement imply a worse prognosis of PsA patients (75, 76). Moreover, it is frequently difficult to establish with certainty the presence of inflammatory back pain (IBP) in patients with PsA (77) who generally have less pain than patients with ankylosing spondylitis (AS) (78).

The only demonstrated clinical predictor of aggressive PsA is the involvement of the peripheral joints. Cohort studies have suggested a link between inflammation and joint damage, showing that swollen joints are a predictor of future increase in the clinically damaged joint count (79, 80)

and of radiologic progression (53, 81). Particularly, in the study of Gladmann DD et al., polyarticular onset of the disease, with more than five involved joints and a high medication level at presentation to the clinic, predicted the progression of the disease, with an increased joint damage (40). In another study, the polyarticular disease at onset predicted not only the development of clinical deformities but also an erosive disease (82). More recently, Simon P et al concluded that also an increasing number of swollen joints, during a 12-month period of follow-up, heralds progression of radiological damage in PsA patients (83).

IMAGING

Imaging studies have demonstrated the direct link between inflammation and joint damage in RA, using a combination of ultrasound (US), conventional radiography and MRI (72, 84, 85). In PsA, such data are currently unavailable and the link between inflammation of enthesis and/or synovium with joint damage, is still under investigation. Nevertheless, similar to RA (86), in observational cohort studies in PsA radiological damage was found to be predictive of increased mortality (87).

Recently, US and MRI have been validated as sensitive techniques in the early diagnosis of synovitis (88) and enthesitis (89) in PsA, but no clear data are available on their prognostic value.

Although the interest in this field is growing, US and MRI studies of PsA are fewer than those in RA and further studies are needed to clarify the relevance of the typical aspects of extracapsular enhancement and enthesitis of PsA. At now, these characteristics seems to be more relevant to underline the "enthesis-related origin" of PsA proposed in contrast to the primarily synovial inflammation of RA (90, 91), than useful to identify prognostic aspect of the disease.

Moreover, bone erosions in PsA are probably less frequent and progressive than in RA and bone oedema is unlikely to predict the appearance of erosions in patients with PsA (92). So, while many GRAPPA members expressed considerable support for the advantages provided by MRI as an outcome measure in PsA, since no scoring technique has yet been validated, the inclusion of MRI as a primary outcome imaging tool may be premature. Thus, plain radiographs of hands and feet were considered an essential primary radiologic outcome measure for progression of erosions, with MRI sub-study strongly recommended, where feasible.

An early use of MRI has recently described also for diagnostic and prognostic stratification of patients with axial involvement in which the clinical symptoms of low-back pain and the typical radiographic aspects may be observed only when the disease is still consolidated (79).

OTHERS BIOMARKERS: NEW PROSPECTIVE FROM THE GENETIC TO CELLULAR AND HISTOLOGICAL BIOMARKERS

Genetic factors are very important not only for psoriasis susceptibility (93, 94), but also in the expression of PsA, and their role is evident when considering the strong heritability of PsA (95). Nevertheless, genetic association studies of PsA are limited by its changing articular pattern over time and because of each pattern of PsA may not be genetically distinct, considering the frequent overlapping between clinical subgroups. So, although the strong evidence for the genetic basis of PsA (96) only a few genes have been identified thus far as independent susceptibility genes for PsA.

At the moment genetic factors appear to be related with the clinical phenotype of PsA (axial involvement, polyarticular involvement) rather than with diagnosis or prognosis (97-99).

The HLA-DR4 antigen has been reported to be increased in PsA with a clinical picture resembling RA and particularly in patients who developed radiological erosions (100, 101), but recently, Queiro-Silva at al. do not support the notion of the HLA-

DR4 antigen as a marker of disease severity (102).
A positive correlation with disease activity was found for peripheral blood mononuclear cell (PBMC) gene expression of bone morphogenetic protein-4 (BMP-4), emphasizing the importance of alterations in bone metabolism in active PsA and identifying BMP-4 as a disease severityAnother marker that may be relevant in the near future is represented by the increased number of circulating osteoclast precursors (OCPs) in blood samples from PsA patients that may indicate the presence of a severe erosive disease (104, 105).
Finally, some typical aspects of synovial biology of PsA, such as synovial infiltrate, expression of pro-inflammatory cytokines and adhesion molecules and dysregulated angiogenesis with increased vascularity, have been recently investigated as possible prognostic marker (106-110). Nevertheless, although much has been learned about the pathogenesis of PsA, much remains to be defined regarding the link between synovial biology and different disease outcomes. The rapid advance in ultrasound technology, through minimal invasive biopsy, has enabled the collection of synovial tissue from arthritis patients (111) with a realistic prospect to correlate different PSA phenotypes, ultrasound images and cellular and molecular mechanisms of abnormal bone remodeling of PsA, useful to improve prognostic algorithms.

CONCLUSIONS

In recent years, there has been a growing appreciation of the potential severity of PsA. Whereas PsA was previously considered to be a relatively mild form of arthritis, it is now clear that it can be progressive, destructive and deforming (82, 112-114). In fact, about 20% of the patients develop a very destructive disabling form of arthritis and a recent study of early onset PsA showed that within two years of onset, 47% of patients demonstrated at least one bone erosion (115). Disability and quality of life are adversely affected in patients with PsA to an equivalent degree as in RA (122); so, remission is considered to be the ultimate goal of therapy in PsA like in RA (9, 33). Nevertheless, between the rheumatic diseases, experts recognized that remission in PsA may be difficult to achieve and maintain and it has been concluded that "near remission" or "low disease activity" could be an appropriate goal, today acceptable for PsA (116, 117).
So, it seems crucial from a practical point of view, to identify prognostic factors in PsA tha enable clinicians to differentiate from the beginning the more aggressive form of disease and to treat it accordingly. At the moment, it is quite clear that polyarticular onset, with more than 5 joints involved, high ESR at presentation, ACPA positivity and the presence of erosion at plan radiographs, identify an erosive and progressive arthritis, in which aggressive and early therapy may improve the prognosis (3, 5, 7-9).
The recent update on biomarkers in PSA from the GRAPPA 2010 annual meeting, summarize the current knowledge biomarkers but in the same time underline that one important critical area is the identification of biomarkers of joint damage in PsA, including both erosive change and new bone formation. More studies on this important topic are warranted in the next future.

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