Biomarkers in psoriatic arthritis: a systematic literature review

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Keywords: psoriasis, spondyloarthritis, genes, personalized medicine, therapeutics**.**

Abstract.

Psoriatic arthritis (PsA) is characterized by chronic inflammation of peripheral joints and axial skeleton, associated with a strong genetic background. Clinics include enthesitis or dactylitis and extra-articular involvement as uveitis or inflammatory bowel disease, while treatment options range from NSAIDs to biologics, targeting TNFalpha or Th17. No serum autoantibody is associated with PsA, while other biomarkers have been proposed for early diagnosis or to predict treatment response. To better discuss this area of growing interest we performed a systematic review of the literature on biomarkers in PsA. Our research retrieved 408 papers, and 38 were included in the analysis. Based on the available literature, we draw some recommendations for the use of biomarkers in the management of patients with PsA.

Keywords: psoriasis, spondyloarthritis, genetics, autoantibodies, personalized medicine, biologics**.**

Introduction.

Psoriatic arthritis (PsA) is a systemic chronic inflammatory disease that involves the synovial tissue and the entheses, in association with active psoriasis or a personal or family history of the skin affection. PsA belongs to the broader group of spondyloarthritis (SpA), which also include ankylosing spondylitis (AS), reactive arthritis, enteropathic arthritis, and undifferentiated spondyloarthritis [1]. All SpA share a strong genetic predisposition, as represented by the association of AS with the HLA-B*27 allele, but, differently from other rheumatic diseases, there is no female preponderance or serum specific autoantibodies [2]. Within the spectrum of seronegative diseases, PsA is frequently associated with comorbidities (especially cardiovascular and metabolic disease) and screening of such complications is not well established [3]. The response to treatment in PsA is currently mostly evaluated with clinimetric indexes derived from other diseases, such as the disease activity score (DAS28) in rheumatoid arthritis (RA) or the Bath AS disease activity index (BASDAI), but new composite scores have been developed and validated for PsA, such as composite psoriatic disease activity index (CPDAI) and others [4-8]. The research agenda is currently moving forward to the identification of biomarkers that could help clinicians to identify subsets of patients requiring a more targeted therapy or strict monitoring and ideally to diagnose PsA at an earlier or preclinical stage in patients with skin manifestations [9] but this remains a long-term goal for which data are limited.

The term biomarker, or biological marker, refers to measurable indicator of a medical state, and was defined in 1998 by the National Institutes of Health Biomarkers Definition Working Group as a 'characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention' [10]. A classic example of biomarker is a laboratory test that can be used to classify a disease, such as rheumatoid factor and anti-citrullinated protein antibody (ACPA) in RA [11]. In the case of ACPA, this represents a diagnostic and prognostic factor, and also a treatment response biomarker as ACPA-positive RA is more aggressive [12]. In rheumatic diseases, biomarkers are mainly genetic,

soluble, cellular, synovial or imaging features [13] and in the case of PsA, where the diagnosis is exquisitely clinical and inflammatory markers frequently normal, these may be pivotal to differentiate other conditions, such as fibromyalgia. The identification of biomarkers of PsA is thus of enormous importance, as nearly 50% of patients will develop erosions in the first 2 years of disease, and 20% of patients with polyarticular involvement may suffer from a severe form of the disease, with radiologic evolution over time [14]. Moreover, the detection of patients with poor prognostic factors will help choose which patients need more aggressive treatment with biologic agents, which are not free of side effects [15] and are burdened by high costs. Aim of this systematic literature review is to elucidate the state of biomarkers discovery in PsA, and in particular regarding specific biomarkers for diagnosis, disease activity, therapy response and comorbidities. We propose our point of view about this key issue in rheumatology clinical practice and foresee the future research agenda.

Methods for the systematic literature review.

Our systematic literature review was conducted to identify biomarkers for the diagnosis, prognosis, therapy, or comorbidities of PsA. Systematic review procedures adopted conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. Structured literature researches were conducted as of September 2015 in the following databases: The Cochrane Library, PubMed/MEDLINE and EMBASE. Search terms included the medical subject headings (MeSH) o Emtree terms for "psoriatic arthritis" and "serum/genetic and synovial biomarkers". Titles and abstract were screened to determine if they met the inclusion criteria and if potentially of interest, two independent reviewers selected relevant abstracts. Articles of particular interest not being included in the first research were also included independently.

Inclusion criteria. Clinical trials, both interventional and observational, including patients with PsA and data on biomarkers based on the proposed definition [10] were included.

Exclusion criteria. Articles not concerning PsA, and reviews or editorials, in languages different from English, if they included children or animals were excluded. The selection process was performed by two authors, based on titles, abstracts and subsequently full text papers. **Figure 1** represents the flowchart of the selection process of this systematic literature review.

Data extraction. The year of publication, geographical area, study design and number of patients were recorded. Demographic data, such as sex, age, disease duration were also recorded. The outcome was defined by the identification of a biomarker for diagnosis, disease activity, therapy response and comorbidities. Articles were divided into four categories whether the investigation regarded: diagnosis, disease activity, therapy response, or comorbidities. Quality assessment of the included studies was performed using the Newcastle Ottawa Scale [17].

Results of the systematic literature review.

The full text analysis included 41 articles, ranging from 1991 to 2015. Most of the studies investigated biomarkers in term of diagnosis (**Table 1**), while fewer were dedicated to disease activity (**Table 2**) and response to therapy (**Table 3**) or comorbidities (**Table 4**).

Diagnostic Biomarkers

Biomarkers used for diagnosis are particularly helpful in PsA, as no autoantibody has been so far associated with the disease, and the diagnosis is frequently made in chronic polyarthritis that have a familiarity for psoriasis but then have different clinical and prognostic features. The results of our systematic literature review are reported in **Table 1** and 16 studies investigating the biomarkers in diagnosis were included, however the studies were investigating patients with an existing PsA diagnosis, thus limiting their efficacy.

Genomic factors represent important candidates to differentiate patients with psoriasis more susceptible to PsA than other but only 4 studies investigated this issue. HLA-B and C molecules are of interest, and one study reported that HLA-B*27 (p=0.002), B*38 (p=0.04), B*39 (p=0.03), and C*12 (p=0.005) are potential genetic markers of PsA in patients affected by psoriasis and family members of probands [18]. Another study included analyzed HLA alleles in 678 PsA patients and 688 healthy controls in a case-control design, and demonstrated in a large population than PsA was most frequently associated with HLA-C*12/B*38, HLA-B*27 and HLA-C*06/B*57 [19]. Moreover, a third study included showed that in psoriatic disease there are two HLA alleles that are predominant: HLA-C*06 in psoriasis and HLA-B*27 in PsA, possibly demonstrating that it represents a genetic heterogeneous disease [20]. The interleukin-13 (IL13) gene polymorphisms have also been associated with psoriatic disease, and moreover one included study showed that the major alleles of rs1800925*C, rs20541*G and rs848*C are significantly more represented in PsA compared to healthy controls and patients with psoriasis [21]. Killer-cell immunoglobulin-like receptor gene polymorphisms have also been associated with PsA, and in particular the alleles

KIR2DS1 and KIR2DS2. A recent study demonstrated that KIR2DS2 is significantly associated with PsA (OR 1.34, 95% CI 1.04-1.73, p= 0.024), thus suggesting that the association is likely to be specific to arthritis [22]. Of interest, an included study showed a protective role of the T allele of VEGF in + 936 for PsA [23].

Serum biomarkers for PsA are being researched both as autoantibodies but also as collagen fragments and cytokines that may correlate with disease activity and predict therapeutic response. Among cytokines, serum IL2 and IL10 levels are higher in PsA and may discriminate patients from healthy subjects and psoriasis [24, 25]. Other studies investigated different autoantibodies (anti-agalactosyl IgG, antibodies targeting mutated citrullinated vimentin (anti-MCVs) and ACPA), showing that these autoantibodies may be positive in PsA, but also in other inflammatory arthritis (i.e. RA) and identify different subsets of patients with a more severe disease (i.e. polyarticular and erosive arthritis) [26-28]. Other soluble markers, both inflammatory, metabolic and of bone metabolism, have been associated with PsA and may help differentiate psoriatic patients that may develop PsA or discriminate PsA from other forms of arthritis, but the results are disparate and may be difficult to translate into clinical practice [25, 29-33].

Synovial biomarkers derive from the synovial fluid or tissue and are primarily being investigated as therapy response biomarkers, but are helpful also for diagnostic purposes, in this view protein oxidative markers have been studies both on sera and synovial fluid of patients with inflammatory arthritis, namely sulphydryl (SH) and carbonyl (CO) groups. Results show that SH groups sera levels are higher in PsA than RA and lower than osteoarthritis (OA), while being lower in PsA and RA synovial fluids compared to osteoarthritis [34].

Disease activity

Markers of disease activity are important when assessing the disease and to compare therapeutic response while severity is generally identified as quality of life; studies included are summarized in **Table 2**. These biomarkers are mainly derived from sera, as frequent monitoring may be necessary.

Differently from RA, high sensitivity C reactive protein (hsCRP) does not represent a valid biomarker for PsA activity as suggested by some studies [35, 36], however others suggest that correlates better than other biomarkers with disease activity [37]. Serum calprotectin has also been investigated based on data in inflammatory bowel disease, and may better correlate with disease severity and erosions leading to radiographic changes [35, 37]. Erythrocyte sedimentation rate (ESR) levels in an old study on few subjects was found to be best correlate with disease activity, possibly performing better that CRP [36]. Cellular biomarkers are also of interest especially with regard to disease progression and erosions, and circulating osteoclast precursors (OCP) represent promising candidates to assess the presence and severity of PsA. Unfortunately, measuring OCP is time consuming and expensive, but the expression of molecules such as CD16 may suggest a transitional state of OCP during osteoclastogenesis and a higher risk of erosions [38]. Metabolic markers, as adiponectin, have also been reported to be associated with PsA severity, and therapy [39]. A recent study investigated the role of programmed death-1 (PD1), a homologue of CD28 and CTLA-4 and belongs to the immunoglobulin superfamily. The results showed that PD1 inversely correlated with DAS28, with a very strong correlation with the joint count, while not being associated with CRP levels and PASI [40].

Response to treatment

Biomarkers for therapeutic response are very important to identify the specific subsets of patients that may benefit from a specific therapy and to justify a stricter follow-up of patients using a therapeutic agent. These biomarkers are usually studied in the serum or synovial fluid, and include cytokines, collagen degradation proteins or metabolic markers. **Table 3** illustrates the studies that investigated therapeutic response biomarkers in PsA; of these, only 4 investigated synovial fluid biomarkers for therapeutic response to anti-TNFalpha agents. One study investigated the effect of intra-articular injections of etanercept on knee arthritis and showed that synovial effusion and synovial fluid cytokines (IL-1beta, IL-1Ra, IL-6, IL-22) are associated with treatment efficacy [41];

however, this approach is currently not utilized in clinical practice. Another study randomized patients with PsA to receive anakinra (directed at IL1beta) or etanercept (soluble TNFalpha receptor) and took arthroscopic synovial biopsies and MR scans of knee arthritis patients. The results of the immunohistochemical analysis show that CD3 and CD68 changes are higher in responders compared to non-responders, and changes in CD3 correlate with DAS28 [42]. The third study investigated synovial biopsies by immunohistochemical analysis to determine cell infiltrates and cytokine and metalloproteinases expression and their results after adalimumab therapy show a reduction in T-cell infiltrates and MMP-13 expression [43]. Cytokine expression has been also investigated in psoriasis skin lesions, and a study showed a decreased expression of IL20 in the skin after alefacept treatment, but not in the synovial tissue [44].

Collagen degradation biomarkers have been reported to decrease after anti-TNFalpha therapy, and may predict better the long-term clinical and radiologic outcomes [45, 46]. Other serum biomarkers (i.e. IL6, VEGF, plasma YKL-40, MMP-3) decrease after anti-TNFalpha therapy in clinical responders [47, 48]. Circulating endothelial cells levels, a marker of vascular injury are also decreased after etanercept therapy [49]. Another study investigated adiponectin, but did not show a decrease in serum levels after anti-TNF treatment [50]. Soluble biomarkers have also been reported to predict the therapeutic response after anti-TNFalpha treatment, MMP-3 levels reduction has been shown to significantly improve the odds of achieving response, conversely a reduction of COMP levels was associated with lower odds of achieving response [51].

Of note, using data derived from the GO-REVEAL trial of the TNFalpha inhibitor golimumab, 92 soluble biomarkers were investigated after treatment, and serum levels of different inflammatory markers were associated with an ACR20 response at week 14, moreover this panel was more predictive of golimumab response compared to CRP alone [52].

Clinical extraarticular features.

Only a few studies investigated biomarkers for the diagnosis and monitoring of comorbidities in PsA, as illustrated in **Table 4**. Cardiovascular disease represents the most important comorbidity in PsA, and a good therapeutic strategy should also take into account the increased cardiovascular risk of these patients, moreover the identification of patients at higher risk is crucial also to start the best monitoring and therapy [53]. Only two studies included in this systematic review investigated cardiovascular biomarkers. A study conducted on 11 patients with PsA in Norway studied aortic stiffness, carotid atherosclerosis and serum calprotectin, showing that calprotectin may represent a biomarker of aortic stiffness, while anti-TNFalpha treatments improve aortic stiffness and carotid atherosclerosis [54]. Another study showed that PTX-3 levels are higher in patients with inflammatory arthritis and cardiovascular disease [55].

Osteoporosis represents a major complication of chronic inflammation and frequently occurs in patients with PsA. BMD levels have been measured in three different studies suggesting that disease duration negatively correlates with BMD values, and that in general BMD is decreased in PsA [56, 57]. Bone metabolism markers are also correlated with PsA: CTX serum levels is correlated with disease duration while M-CSF and RANKL correlate with disease severity, i.e. erosions, joint space narrowing and osteolysis score, moreover TRAIL serum levels are increased in PsA and correlate with CRP [56-58].

Expert commentary.

As the results of our systematic literature review have illustrated, few biomarkers are currently available to assist clinical decisions in PsA diagnosis and management. With regard to PsA diagnosis, however all of the studies included analyzed patients with a pre-existing diagnosis and a selected population overall. Genetic studies may be helpful for detection of such disease, as the strong familial aggregation supports the evidence of a genetic predisposition. The major loci of interest have historically been the MHC region and HLA genes, which alleles, especially HLA-C*06, and HLA-B*27, which is carried by about 20-35% of patients [59], B*39 and B*07 that have been associated to PsA. HLA-B*27 is is also thought to have a pathogenic role in SpA development, and different theories have been proposed, mostly related to protein misfolding. Moreover, HLA antigens may also predict different clinical manifestations, as the HLA-B*27 allele is associated with a higher prevalence of axial disease, while HLA-B*38 and B*39 are linked to peripheral polyarthritis [60]. HLA-B*27 could be also used to discriminate different subsets of PsA, as it has been reported more frequently in patients with a late development of the skin condition, usually older than 40 years, but with a short interval between the two conditions, as well as dactylitis and uveitis [59]. Finally, HLA-B*27 is associated with a worse prognosis and disease progression [61]. In this context HLA-B*27 can be of particular help to discriminate patients with psoriasis more prone to develop PsA, or for early diagnosis in psoriasis when peripheral arthritis or inflammatory back pain are present. Another HLA antigen of interest is represented by HLA-Cw6*02, which is the antigen with the strongest association with psoriasis worldwide [62]. HLA-Cw6* is a marker for early development of psoriasis, positive family history and it is positive in nearly 100% of patients with psoriasis guttata [63]. PsA has been also associated with these antigen but with lower magnitude [64]. HLA-Cw6*02 evidence is limited for PsA, however patients carrying this allele may have a better response to ustekinumab, as suggested by recent studies [65]. Serum autoantibodies are a cardinal feature of most autoimmune diseases and frequently also chronic inflammatory conditions, and usually precede by years the development of the clinical disease [66]. SpA are classically considered

as seronegative, however, anti-MCVs antibodies have been observed in PsA [27] and RA-specific serum ACPA [67] are found in as many as 10% of patients with PsA or other inflammatory arthritis. In fact, ACPA are detected in about 1% of the generally population, more frequently at lower titers and in smokers [68, 69].

Currently, hsCRP represents the only routine biomarker, helpful for both. However, hsCRP is not specific to articular inflammation and levels are highly elevated also in infections, particularly bacterial. Only in one study included in this systematic literature review, hsCRP was found to be significantly higher in PsA than controls, and the levels are reduced with treatment [30], while predicting therapeutic response [70]. In clinical practice, the determination of hsCRP levels is highly disappointing, being elevated only in 50% of PsA cases [71], mainly in the elderly [72]. High levels of hsCRP may help however in the discrimination between PsA and psoriasis alone, in which hsCRP levels are usually within normal range, except in cases of severe skin disease [73-75]. Elevated levels of CRP may also predict radiographic progression [38]. On the other hand, clinicians are expected to consider that the coexisting metabolic conditions, which are frequently seen in PsA may also cause elevated hsCRP [76].

Finally, with regard of monitoring of comorbidities, clinicians should be aware of the incidence of such in PsA population and know the most appropriate test to perform when screening. In this view, we propose the use of serum markers of bone resorption and DEXA for osteoporosis [56-58] as well as testing for cardiovascular risk factors, knowing that traditional risk scores may underestimate the real risk.

We are aware that our systematic literature review has limitations: firstly, we decided to include only PsA and to exclude studies on SpA, that may sometimes incorporate also patients with the psoriatic forms of axial disease; second, our research question did not include imaging biomarkers, which have not been clearly identified yet, and we believe that serum and synovial biomarkers may allow disease stratification and targeted therapies, thus allowing a better management of PsA.

Five-year view.

Biomarkers represent a major part of the research agenda in all fields of medicine, including rheumatology, particularly considering the search for tools to personalized medicine [77, 78]. In the case of PsA, the early diagnosis and especially the detection of psoriasis patients with susceptibility to develop the joint disease is crucial to change the disease course and start effective treatments soon, while also reducing the risk of developing complications and comorbidities. The Group for Research and Assessment of Psoriasis and PsA (GRAPPA) has developed and is actively pursuing a large effort to detect PsA biomarkers. These should fulfill the key features of the OMERACT (Outcome Measures in Rheumatology Clinical Trials) filter, i.e. truth, discrimination, and feasibility [75, 79-81]. Clinical research of GRAPPA is mainly focused on finding a soluble biomarker for radiographic progression and the analysis of comorbidity biomarkers, specifically cardiovascular and articular, in a psoriasis inception cohort [82]. We herein expect that in the future a soluble biomarker will be identified and act both as a prognostic factor and as a disease activity measurement, particularly considering the availability if high-throughput platforms for the analysis of microRNA, epigenomics, proteomics, and transciptomics [83, 84]. However, the identification of a biomarker is challenging and time consuming [85], and new techniques are approaching to help finding multiple biomarkers simultaneously, as multiple reaction monitoring mass spectrometry platform for the measurement of peptides. We encourage the development of shared data and sample biobanks that may allow the validation of the proposed biomarkers with an accepted study design [86]. This may well be obtained also with the collection of unique populations such as representative families, naïve patients with different clinical phenotypes, or monozygotic twins discordant and concordant for psoriasis and PsA [87].

Another important issue in the search for PsA discovery that we expect to be better characterized in the future is the possibility to stratify PsA patients by their synovial tissue histology and fluid assessment at diagnosis, thus allowing a more personalized therapeutic approach. The identification of a proband cytokine in particular patients could help to determine their susceptibility to treatment,

295 and, in case of mono or olygoarticular disease, targeted intra-articular injections into the affected
296 joints, as *Fiocco* et al demonstrated reduced CD45+ MNC infiltration, and IL-6 and IL-1beta levels
297 in synovial fluid of after intra-articular etanercept [88]. In this view, the possibility of obtaining a
298 synovial sample at disease diagnosis to characterize the inflammation process could help deciding
299 the best treatment for every patient.
300 Finally, more biomarkers are emerging for new biologic agents and small molecules that are
301 approved or under investigation for PsA and psoriasis [89] and may allow a better allocation of
302 resources. Most of the studies have been conducted on skin psoriasis and their reproducibility in
303 PsA is not confirmed. Once again, we submit that the availability of well-established series of
304 patients and samples at different stages of disease and treatments may make this approach feasible
305 in the near future.
306

Key issues.

1. No serum biomarker for psoriatic arthritis diagnosis has been identified.
2. There are few features that can help discriminate psoriasis patients that will develop psoriatic arthritis, particularly HLA-B*27.
3. Few biomarkers are reliable disease activity measurements, and hsCRP represent one of these, even if with many limitations and also being elevated only in half of the patients.
4. Comorbidities are a major concern in psoriatic arthritis, especially cardiovascular and psychiatric, no biomarker is yet available to identify patients at higher risk.
5. New biomarkers are in the pipeline but the identification and validation is time-consuming and challenging, new techniques are required to accelerate the process.
6. Synovial biomarkers could be of particular help to stratify patients depending on their functional status and thus to choose the best therapeutic approach for every patient leading to personalized medicine.
7. As new molecules for PsA treatment are approaching, research agenda should focus also on identifying markers for these therapies.
8. Anti-MCVs are present in PsA but are not specific for the disease, as ACPA for RA.
9. HLA Cw6 is of limited use in PsA, different from skin psoriasis.

Figure 1. Flowchart of the selection process.

Table 1. Articles included: biomarkers of psoriatic arthritis diagnosis.

Author (Reference)	Year	Region	PsA patients, n (F%)	Biomarker investigated	Methodology	Main results
Bosè, F. [24]	2014	Italy	30 (33.3)	IL-2 expression by anti-CD3 stimulated PBMC	Comparison of cytokine secretion profile of circu-lating T cells in patients with PsA, patients (30) with cutaneous psoriasis (21) and blood donors (26)	Increased expression in PsA patients compared to psoriasis
Butt, C. [23]	2007	Canada	258 (48.5)	VEGF, FGF1, FGF2 and EGF polymorphisms	Genotyping of PsA (258) and ethnically matched controls (154) using Sequenom chip-based MALDI-TOF mass spectrometry platform	Protective role of the T allele VEGF in +936
Chandran, V. [29]	2010	Canada	26 (53.8)	IL-12, IL-12p40, IL-17, TNFSF14, MMP-3, RANKL, OPG, COMP, CPII, C2C, C1-2C, hsCRP	Serum analysis in PsA (26), psoriasis (26) and healthy volunteers (26)	hsCRP, MMP-3, OPG, CPII-C2C ratio differentiate patients with PsA and psoriasis
Chandran, V. [19]	2013	Canada	678 (57)	HLA alleles	DNA genotyping for HLA alleles on 678 PsA	HLA-C*12/B*38, HLA-B*27 and HLA-

					and healthy controls (688)	C*06/B*57 are more frequently associated with PsA
Chandran, V. [22]	2014	Canada	678 (57)	KIR2D, KIR3D gene polymorphisms	DNA genotyping on 678 PsA, psoriasis (369) and healthy controls (688)	KIR2DS gene polymorphism associated with PsA
Chou, CL. [26]	2010	Taiwan	13 (38.5)	Anti-agalactosyl IgG antibody	Serum analysis of PsA (13), AS (30), RA (22), and healthy controls (25)	Present in inflammatory arthritis (including RA)
Dalmady, S. [27]	2013	Hungary	46 (52.1)	Antibodies targeting mutated citrullinated vimentin (anti-MCVs)	ELISA analysis in PsA (46), psoriasis (42) and in 40 healthy controls	Higher levels of anti-MCVs in PsA than psoriasis
Eder, L. [21]	2011	Canada	555 (41.5)	IL13 gene polymorphism	Genotyping of the rs20541 and rs848 single nucleotide polymorphisms of PsA (555), psoriasis (342) and healthy controls and database biobank (217)	If present increases susceptibility for PsA in psoriasis patients
Eder, L. [18]	2012	Canada	178 (-)	HLA-B and HLA-C	Family-based association study on PsA (178), psoriasis (30) and first degree relatives (561) by	HLA-B27, HLA-B38, HLA-B39 and HLA-C12 are potential genetic markers in patients with

					genotyping	Psa compared to psoriasis
Firuzi, O. [34]	2008	Italy	16 (31.2)	SH and CO groups in sera and synovial fluid	Sera and synovial fluid analysis on PsA (16), RA (18) and OA (15)	SH serum levels were higher in PsA than RA and lower than OA, SH synovial fluid levels were lower in PsA and RA compared to OA
Jensen, P. [31]	2013	Denmark	42 (57.1)	Plasma YKL-40	Level measurement on PsA (42), and psoriasis (48)	Plasma YKL-40 is increased in PsA, but not in psoriasis
Maejima, H. [28]	2010	Japan	15 (33.3)	ACPA	Serum analysis of PsA (15), psoriasis vulgaris (15), psoriasis pustolosa (3)	Predictor of server and erosive PsA
Maejima, H. [32]	2014	Japan	12 (33.3)	Moesin, stress induced phosphoprotein-1	Serum analysis of PsA (12), psoriasis (31) and healthy controls (31) first by two-dimensional immunoblotting, then by dot blot analysis	May differetìntiate PsA from psoriasis
Perez-Alamino, R. [33]	2014	USA	81 (46.9)	ACPA	Serum analysis of PsA (81) patients	More severe disease, erosive, and polyarticular

Ramonda, R. [30]	2013	Italy	43 (21)	VEGF, MMP-3, PTX, hsCRP	Serum analysis of PsA (43) and healthy controls (n not known)	MMP-3, VEGF, hsCRP are higher in PsA than in controls
Szodoray, P. [25]	2007	Norway	43 (55.8)	IL-10, IL-13, IFNalpha, EGF, VEGF, CCL3, (MIP-1alpha), CCL4 (MIP1beta), CCLII, FGF, G-CSF	Serum analysis by multiplex cytokine assay of PsA (43) and healthy blood donors (25)	Discriminated Psa from healthy individuals
Winchester, R. [20]	2012	Ireland	359 (-)	HLA B and C alleles	Four cohort of patients with PsA (359) and psoriasis (214), divided in discovery and validation, population derived controls (1000) and healthy controls (119)	HLA-C*06 is associated with psoriasis and HLA-B*27 with PsA

Table 2. Articles included: biomarkers for psoriatic arthritis disease activity.

Author	Year	Region	PsA patients, n (W%)	Biomarker investigated	Methodology	Main results
Chiu, YG. [38]	2010	USA	29 (-)	CD16	Flow cytometry analysis on PBMC and monocytes from PsA (29), psoriasis (29), RA (8) and healthy controls (16)	Intermediate levels of CD16 may suggest a transitional state of OCP during osteoclastogenesis and higher erosions
Eder, L. [39]	2013	Canada	203 (39.4)	Adiponectin, leptin, insulin	Serum analysis of PsA (203) and psoriasis (155)	Adiponectin associated with joint count and biologic use
Hansson, C. [35]	2014	Sweden	65 (49.2)	Serum calprotectin, hsCRP, selected cytokines	Serum analysis of PsA (65) and healthy controls (31)	Calprotectin correlated with a more sever disease (polyarthritis)
Helliwell, PS. [36]	1991	UK	36 (33.3)	Cytidine deaminase activity, CRP, ESR and histidine	Serum analysis of PsA (36)	ESR was found to be the best correlate for disease activity
Madland, TM. [37]	2007	Norway	119 (49.7)	Serum calprotectin, S100A12, ESR, hsCRP	Serum analysis of PsA (119)	Calprotectin and S100A12 are inferior to CRP for disease activity but predict better radiographic changes
Peled, M. [40]	2015	USA	20 (30)	Programmed death-1	Flow cytometry,	PD1 inversely correlated

		ELISA, Western Blot and RAP1 activation assay analysis of PsA (20) and healthy controls (15)	with DAS28, strongly correlated with joint count but not CRP levels and PASI

Table 3. Articles included: biomarkers for psoriatic arthritis therapy response.

Author	Year	Region	PsA patients, n (W%)	Biomarker investigated	Methodology	Main results
Cauza, E. [45]	2006	Austria	9 (44.4)	COMP	Serum levels measurement on PsA (9)	Short-term infliximab therapy decreases COMP
Chandran, V. [51]	2013	Canada	40 (27.5)	COMP, hsCRP, MMP-3, RANKL, OPG, TNFSF14, C2C, C1-2C, CPII, CS-846	Serum levels measurements on PsA (40) before and after anti-TNFalpha treatment	MMP-3 reduction lively to achieve response, reduction in COMP lower odds of achieving response
De Simone, C. [49]	2014	Italy	48 (43.7)	Circulating endothelial cells levels	Serum levels measurement on PsA (48), and healthy subjects (50)	CECs after etanercept decreased significantly
Fiocco, U. [41]	2010	Italy	14 (-)	Synovial effusion, synovial fluid, synovial tissue biomarkers in knees	Synovial fluid analysis, synovial biopsy with immunohistochemistry on PsA (14)	Synovial effusion and synovial fluid biomarkers are associated with efficacy of IA injection of etanercept
Lebre, MC. [44]	2012	Netherlands	11 (-)	IL-20 in synovial tissue and skin	Immunohistochemistry of skin and synovial biopsies of PsA (11) and RA (10)	IL-20 decreased in the skin of PsA patients after alefacept, while it did not decrease in synovium

Mullan, RH. [46]	2007	Ireland	17 (59)	C2C, C1,2C, CPII	Serum analysis of PsA (17), RA (45)	Short-term changes in collagen degradation biomarkers following biologic therapy predict better long-term clinical and radiologic outcomes
Pedersen, SJ. [47]	2010	Denmark	17 (-)	IL-6, VEGF, YKL-40, MMP-3, total aggrecan	Serum analysis on PsA (17), AS (32), and healthy volunteers	These biomarkers decrease in anti-TNF responders
Peters, MJ. [50]	2010	Netherlands	126 (34.9)	Adiponectin	Serum levels of PsA (126)	Adiponectin levels did not decrease after anti-TNF treatment
Pontifex, EK. [42]	2011	Ireland	25 (60)	Immunohistochemical staining of synovial biopsies for CD3, CD68, FVIII; MRI synovitis	Immunohistochemistry of synovial biopsies of PsA (25)	CD3 and CD68 changes were higher in responders
Strober, B. [90]	2008	USA	151 (36.4)	CRP	Retrospective analysis of levels in PsA (151) and psoriasis (501)	Etanercept decreased CRP levels in PsA
van Kuijk, AWR. [43]	2009	Netherlands	24 (37.5)	Synovial cell infiltrate, cytokines and metallo-proteinases expression	Immunohistochemical analysis of synovial biopsies of PsA (24)	T cell infiltration and MMP-13 reduction after adalimumab therapy
van Kuijk, AWR. [48]	2010	Netherlands	24 (37.5)	Serum CPII, PINP, MIA,		MMP-3 decrease tih

Wagner, C. [52]	2013	-	100 (-)	MMP-3, C2C, COMP, OC, NTX-1, ICTP Biomarker and protein profiling (total 92 markers)	Serum analysis of PsA (100)	adalimumab therapy while MIA increase Golimumab is effective in modulating markers of inflammation, bone metabolism, and metabolic factors in PsA

Table 4. Articles included: biomarkers for psoriatic arthritis comorbidities.

Author	Year	Region	PsA patients, n (W%)	Biomarker investigated	Methodology	Main results
Angel, K. [54]	2012	Norway	11 (-)	Aortic stiffness, carotid atherosclerosis, calprotectin	Assessments of aortic stiffness (aortic pulse wave velocity, aPWV), CIMT, and plasma calprotectin of PsA (11), RA (25) and AS (19)	Anti-TNF improved aortic stiffness and carotid atherosclerosis, calprotectin may be a marker of aortic stiffness
Borman, P. [56]	2008	Turkey	18 (80)	DEXA and bone turnover markers	Serum analysis and DEXA of PsA (18) and psoriasis (29)	Disease duration negatively correlated with BMD values and serum CTX levels
Dalbeth, N. [58]	2010	New Zealand	38 (42)	Dkk-1, M-CSF, OPG, RANKL, DEXA, plain joints X-rays	Serum analysis PsA (38), with psoriasis (10), and healthy controls (12), DEXA and X-ray only in PsA	M-CSF and RANKL correlated with erosions, joint space narrowing and osteolysis score
Hofbauer, LC. [57]	2006	Germany	116 (49.1)	Markers of bone turnover, DEXA, serum TRAIL, OPG	Serum levels and BMD of PsA (116), and controls from the	BMD is decreased in PsA, TRAIL serum levels are increased and correlate

					TRAIL cohort (90)	with CRP
Hollan, I. [55]	2010	Italy	-	PTX-3		CAD patients had higher levels of PTX-3

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Reference annotations.

* = of interest

** = of special interest

Financial & competing interests disclosure.

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

APPENDIX

Terms searched for the systematic literature review.

MEDLINE: Mesh terms “psoriatic arthritis” and “serum/genetic and synovial biomarkers”

EMBASE: Emtree “psoriatic arthritis” and “serum/genetic and synovial biomarkers”

COCHRANE: free words search for “psoriatic arthritis” and “serum/genetic and synovial biomarkers”

Inclusion criteria:

- Clinical trials investigating biomarkers in PsA
- Age of participants >18
- English language
- Full text availability through our bibliotecary services
- Abstract including PsA and serum, genetic and synovial biomarkers.

Exclusion criteria:

- Clinical trials regarding biomarkers in diseases different from PsA
- Children age, as PsA is a rare entity in these patients
- Languages different than English, due to the lack of financial possibilities to traduce the articles
- Abstract or poster presentations from meetings, as some are incomplete results and are subsequently reported in future studies
- Duplicates, identified through Endnote

Data extraction form.

Author: _____

Year: _____

Geographical region: _____

PsA patients (n, F vs.M%): _____

Controls: _____

Study design: _____

Biomarker investigated: _____

GENETIC ☐ SYNOVIAL ☐ SERUM ☐

Main methodology: _____

Main results: _____

Quality assessment (NOS) *

Selection Criteria	
Adequate case definition	
Representativeness of the cases	
Selection of controls	
Definition of controls	
Comparability	
Controls for diagnosis/age and sex	
Exposure	
Ascertainment of the exposure	
Method of ascertainment	
Non response rate	

Appendix Table 1. Detailed Risk of Bias Results Using the Newcastle–Ottawa Scale for Assessing Quality for Case Control Studies

Study, Year (Reference)	Selection Criteria				Comparability	Exposure		
	Adequate case definition	Representativeness of the cases	Selection of controls	Definition of controls	Controls for diagnosis/age and sex	Ascertainment of the exposure	Method of ascertainment	Non response rate
Angel, 2012 [54]	A*	B	B	B		D	A*	C
Borman, 2008 [56]	A*	B				A*		A*
Bosè, 2014 [24]	A*	A*	B	B	B*	E	A*	C
Butt, 2007 [23]	A*	A*	A*	A*	B*	D	A*	C
Cauza, 2006 [45]	A*	B				A*		C
Chandran, 2010 [29]	A*	A*	B	A*	B*	D	A*	C
Chandran, 2013 [51]	A*					D		C
Chandran, 2013 [19]	A*	B	B	A*	A*	D	A*	C
Chandran, 2014 [9]	A*	B	B	A*	A*	D	A*	C
Chiu, 2010 [38]	A*	B	B	B		D	A*	C
Chou, 2010 [26]	A*	A*	B	A*	A*	D	A*	C
Dalbeth, 2010 [58]	A*	B	B	A*		D	A*	C
Dalmady, 2013 [27]	A*	A*	A*	A*		D	A*	C
De Simone, 2014 [49]	A*	B	C	B	B*	D	A*	C
Eder, 2011 [21]	A*	A*	A*	A*		D	A*	C
Eder, 2012 [18]	A*	B	B	B		D	A*	C
Eder 2013 [39]	A*	A*	B	A*		D	A*	C

Fiocco, 2010 [41]	A*	B				D		
Firuzi, 2008 [34]	A*	B	C	B		D	A*	C
Hansson, 2014 [35]	A*	A*	C	A*	B*	D	A*	C
Helliwell, 1991 [36]	A*	B				D		
Hofbauer, 2006 [57]	A*	B				D		
Hollan, 2010 [55]	A*	A*	B	A*		D	A*	C
Jensen, 2013 [31]	A*	A*	B	B		D	B	C
Lebre, 2012 [44]	B	B	B	A*		D	A*	C
Madland, 2007 [37]	A*	B				D		
Maejima, 2010 [28]	A*	B	B	A*		D	A*	C
Maejima, 2014 [32]	A*	B	B	A*		A*	A*	C
Mullan, 2007 [46]	A*	B	B	A*		D	A*	C
Pedersen, 2010 [47]	A*	B	B	A*		D	A*	C
Peled, 2015 [40]	A*	B	B	A*	B*	D	A*	C
Perez-Alamino, 2014 [33]	A*	B				D		
Peters, 2010 [50]	B	B	B	A*		D	A*	C
Pontifex, 2011 [42]	A*	B				C	A*	C
Ramonda, 2013 [30]	A*	B	B	A*	B*	D	A*	C
Strober, 2008 [90]	A*	A*	B	B	A*	D	A*	C
Szodoray, 2007 [25]	A*	A*	B	A*	B*	D	A*	C
van Kujik, 2009 [43]	A*	A*				D		
van Kujik, 2010 [48]	A*	A*				D		
Wagner, 2013 [52]	A*	A*				D		
Winchester, 2012 [20]	A*	A*	B	A*	B*	D	A*	C