Psoriatic arthritis. When the heterogeneity requires normality

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SUMMARY

Psoriatic arthritis (PsA) is characteristically associated with a large spectrum of disorders, some of which are peculiars, such as enthesopathy, dactilytis, osteitis and axial involvement. Due to the heterogeneity of its expression, definition and classification of PsA have been unsatisfactory until recent years, with consequences on the reliability of epidemiological studies. Other confounding factors for diagnosis and classification of PsA are the radiological changes, sometimes found in asymptomatic patients with psoriasis, and the frequent normality of acute phase response indices, in particular erythrocyte sedimentation rate and C reactive protein. All these aspects are frequently neglected and probably account also for the unsatisfactory response of PsA to traditional drugs, such as NSAIDs, steroids and DMARDs. Furthermore, these drugs showed only a partial ability to influence radiographic progression and psoriasis. The anti-TNF agents have demonstrated to be able to influence all the multiple aspects of the PsA disease and indeed, to slow radiographic progression and to improve patients' quality of life. This seems obtained with a convenient cost-effectiveness ratio.

Key words: *Psoriatic arthritis, psoriasis, biologic agents, arthritis*

The papers published in this monographic issue of *Reumatismo* by the main Italian experts represent the state-of-the-art in psoriatic arthritis (PsA) (1-7). We are grateful to all the contributing authors for their efforts in clarifying many relevant aspects of PsA, a very intriguing and complex disease. PsA has been classically defined as an inflammatory arthritis associated with psoriasis and with the negativity of rheumatoid factor (8). This short definition reflects only in part the large spectrum of disorders found in patients with psoriasis (9). In alternative, the term "psoriatic disease" was considered more appropriate in reflecting the large disease heterogeneity (10). However, in the absence of a satisfying definition, particular attention has been forwarded toward an adequate classification. The first classification proposed by Moll and Wright, although important in underlying the presence of different disease expressions, seems at present inadequate (8). Moll and Wright described 5 subgroups: predominant distal interphalangeal (DIP) joint disease, asymmetrical oligoarthritis, polyarthritis, spondylitis, and arthritis mutilans (8). It is now sufficiently ascertained that: DIP involvement may occurs in several patients with PsA; the distinction between oligoarticular and polyarticular disease is not useful since one form evolves into another and in both directions, and in addition, sometimes the number of affected joints (i.e. 5 or 6) makes difficult its fixed inclusion in one of these groups (9-11). Furthermore, the definition of axial disease may be in some cases problematic, since in comparison with ankylosing spondylitis (AS), the axial involvement of PsA may be less expressed, at least at the disease onset. Sometimes the inflammatory involvement of the spine may be clinically silent but can lead to ankylosis, although usually less severe than in classical AS (11); sacroiliitis, frequently less pronounced and unilateral than in AS, may be asymptomatic (11); a coarse syndesmophytosis, called tumoral enthesopathy, which can mimic diffuse idiopathic hyperostosis (12); more frequent involvement of cervical spine and/or relative sparing of the lumbar spine (11). Some recently well recognised characteristics of PsA, such as enthesopathies, osteitis and SAPHO, were not included in Moll and Wright classifica-

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tion. In addition, some features that may be considered almost pathognomonic of PsA, may result confounding for non experts, i.e.: the dactylitis/osteitis of the whole distal phalanx or onicopachidermoperiostitis (13); the involvement of the three joints of a single digit "monodigital arthritis" (9-11); the mixture of osteolysis and ankylosis; an asymptomatic erosive polyarthritis (14); the possibility, rarely found in other spondyloarthropathies (SpA), of a late onset after 60 years (15), sometimes associated with a pitting oedema (16). The interpretation of these aspects may be hard in presence of early disease. When 20 international experts were asked to classify 10 "paper cases" of patients with early arthritis, major differences were noticed between experts, especially when classifying a patient as PsA or not, although most experts declared to feel rather confident in their choices (17, 18).

Due to the heterogeneity of its expression, clinical experience is needed to avoid overdiagnosis or underdiagnosis of PsA. Patients with arthropathy or enthesopathy of various types, in presence of cutaneous psoriasis may be overdiagnosed as PsA. Conversely, in some others the diagnosis may be missed, especially in the absence of psoriasis, when other important hallmarks of PsA are misinterpreted. Other than for non-symptomatic radiological lesions, another reason for the late diagnosis in PsA is the frequent normality of acute phase response indices, in particular erythrocyte sedimentation rate (ESR) and C reactive protein (CRP), particularly in patients with axial involvement (4, 9, 19).

PsA confirms to be a very complex disease also for an appropriate classification. In this issue of *Reumatismo*, after having carefully analysed the eight different methods proposed until now to classify PsA, Marchesoni and Cantini (3) clearly state that the CASPAR classification (ClASsification criteria for Psoriatic ARthritis) is at present the most satisfactory and the preferres, as it has been obtained with an appropriate methodology and has been subsequently validated (20, 21). Furthermore, the CASPAR method is simple and can be easily used in daily clinical practice. Unfortunately, in patients with early PsA, the CASPAR criteria showed a relatively slow sensitivity (73.3%) (22), thus allowing Marchesoni and Cantini to suggest that these criteria are very good to classify PsA patients (very high specificity), while they should be used with caution in diagnosing patients with unknown early arthritis (3).

As focused by Catanoso et al. in this issue of *Reumatismo* (1), the difficulties in appropriately define and classify PsA have hampered the epidemiological studies on this disease. Unfortunately, only a small number of epidemiological studies used the CASPAR criteria. The heterogeneity of the chosen criteria may explain the large discrepancies in the incidence (from 3,02 to 23,1 cases per 100,000 people) and prevalence (from 49,1 to 420 cases per 100,000 people) existing in the different studies (1). On the other hand, some differences may be genuine and reflect genetic or environmental factors.

The wide disease spectrum of PsA is probably determined by the relevant heterogeneity of the genetic predisposition along with the influence of environment factors. As underlined by Cauli and Mathieu in this issue of *Reumatismo* (2), the familial aggregation and inheritance of psoriasis and PsA are typical of complex multigenic diseases. Some environmental factors, including HIV infection, trauma, and psychological stress appear to increase susceptibility to development of PsA (23). Furthermore, patients with PsA have been found to have increased risk factors for cardiovascular disease including hypertension, dyslipidemia and insulin resistance (24-26).

As regards the cutaneous disease, type I psoriasis is characterized by an earlier onset (age <40 years) and by the association with the class I HLA-Cw6 allele (subtype Cw0602), while type II typically presents at an age >40 years and is not associated with Cw6 (27). HLA-Cw6 is the primary risk allele within the 300-kb region, called PSORS1 (Psoriasis susceptibility gene 1), containing multiple candidate susceptibility genes. Other HLA and HLA-related genes have been shown to be associated with

the disease. This is the case of B16 with its splits B38 and B39, which are in linkage disequilibrium with MICA-A9 gene, primarily associated with the symmetric polyarthritis (28). Another well known association is that between HLA-B27 allele and the axial form (spondylitis) (2).

Due to the heterogeneity of the disease spectrum, a correct clinical assessment is crucial, but not simple. In this issue of *Reumatismo*, Marchesoni and Cantini (3) have well focused difficulties and reliabilities of the subsequent measures in PsA. They underline as the assessment of PsA activity and response to the therapy should include the evaluation of peripheral arthritis, axial involvement, enthesitis, dactylitis, and psoriasis. As regards the joint assessment**,** OMERACT 8 recommended ACR response criteria using 68/66 tender/swollen joint. However, the Psoriatic Arthritis Response Criteria (PsARC) is at present the only outcome measure specifically designed for PsA and so subsequently used in several trial of traditional DMARDs and biologics in PsA. The very popular DAS28, although has been frequently utilised in several trials of biologics, does not seem adequate for PsA, since it does not include the evaluation of DIP and feet joints. The axial assessment in PsA is mainly based upon the scoring systems currently used for AS: BASDAI, BASFI, BASMI, and ASAS response criteria (29). Although currently applied to PsA patients, no methods to assess enthesitis developed and validated in patients with AS were designed for PsA, with the exception of the Leeds enthesitis index. Recently, a simplified dactylitis index, the Leeds dactylitis index (LDI) (30) has been proposed and adopted for clinical trial by OMERACT (31).

The role of biomarkers in PsA has been well elucidated by Bogliolo et al. in this issue of *Reumatismo* (4). They point out the difficulties to obtain specific markers for PsA able to adequately reflect the heterogeneous spectrum of articular manifestation and the variable disease course of PsA. Recently, 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 (32). An interesting observation was that on the value of anti cyclic cytrullinated peptides antibodies (ACPA), considered high specific for rheumatoid arthritis (RA).

Moreover, ACPA have been found also in PsA, with a proportion ranging from 5 to 16% (4). In these patients, ACPA seems useful in detecting those with an increased risk of erosion, requiring early DMARD treatment with conventional drugs or biological agents (33).

The role of imaging in PsA is increasingly relevant, and sometimes decisive for the diagnosis and for the therapeutic assessment. Spadaro and Lubrano have well underlined these aspects in this issue of *Reumatismo* (5). Imaging techniques to assess PsA include traditional radiography, ultrasonography (US), magnetic resonance imaging (MRI), computed tomography (CT) and bone scintigraphy (BS). The radiographic hallmark of PsA is the combination of destructive changes (joint erosions, tuft resorption, osteolysis) with bone proliferation (including periarticular and shaft periostitis, ankylosis, spur formation and non-marginal syndesmophytes).

Specific methods for radiographic assessment of joints, particularly in the context of clinical trials. The Bath Ankylosing Spondylitis Radiology Index (BASRI), the Stoke Ankylosing Spondylitis Spine Score (SASSS) and a new specific instrument, called PsA Spondylitis Radiology Index (PASRI) have been validated for assessing the radiologic axial involvement in established PsA (34, 35).

Ultrasonography (US) has an increasing role in the evaluation of PsA. Power Doppler (PD) US is useful to assess musculoskeletal (joints, tendons, entheses) and cutaneous (skin and nails) involvement, to monitor efficacy of therapy and to guide steroid injections at the level of inflamed joints, tendon sheaths and entheses (36, 37). Given this, US scores for SpA enthesseal involvement have been developed (37).

Magnetic resonance imaging (MRI) has greatly improved the early diagnosis and objective monitoring of the disease process in PsA. Furthermore, MRI has allowed to explain the relationships between enthesitis, synovitis (or the synovio-entheseal complex) and osteitis or bone oedema in PsA (38, 39). Computed tomography (CT) has little role in assessment of peripheral joints, but it may be useful in assessing elements of spine disease. CT accuracy is similar to MRI in assessment of erosions in sacroiliac joint involvement, but CT is not as effective in detecting synovial inflammation (5). In specific sites (i.e. sternoclavicular joints) CT could be complementary to other techniques (5, 40, 41). Although bone scintigraphy could yield a more accurate evaluation of enthesoarticular involvement and distribution in patients with early PsA, it lacks specificity and is now replaced by US and MRI techniques (42, 43). In particular scintigraphy of the sacroiliac joints is not considered in decision tree on diagnosing axial SpA (43).

In this issue of *Reumatismo*, Lubrano and Scarpa (6) update the treatment strategies with the so called "conventional" therapy, mainly including non steroidal antiinflammatory drugs (NSAIDs) and classical disease-modifying anti-rheumatic agents (DMARDs). Most aspects are in accordance with the 2010 update of the Italian Society for Rheumatology recommendations on the use of biologic therapy in the treatment of PsA, which has taken into account the treatment strategies using NSAIDs and classical DMARDs showing, in particular, that they still represent the first choice for patients with PsA with peripheral arthritis (44).

Although NSAIDs are taken by the majority of PsA patients, few studies have evaluated their efficacy, including the more recent Cox-2 inhibitor which, when assessed in AS, showed the ability to slow the radiological progression. The introduction of the new biological agents have stimulated a re-evaluation of the role of DMARDs in PsA. Although the evidence for its efficacy on the broad spectrum of the disease (skin, nail, peripheral joint, axial, enthesitis, dactylitis) is poor, methotrexate (MTX) is the most used (45). According with the conclusions of a recent Italian study in a setting of PsA patients of everyday clinical practice, MTX might be considered the non-biologic DMARDs of choice for the treatment of peripheral PsA condition (46). This preferential activity on the peripheral arthritis is also shared by other DMARDs evaluated in PsA, including sulphasalazine, cyclosporin A, and leflunomide (46-52).

The modern treatment strategy with biologic agents has been pointed out by D'Angelo et al. in this issue of *Reumatismo* (7). There are few doubts that anti-tumor necrosis factor α (TNFα) agents have shown the greatest treatment efficacy to date in the various aspects of PsA. These drugs moderate signs and symptoms of inflammation, improve QoL and functional status, and inhibit the progression of structural destruction in peripheral joints (7).

Four of the currently available TNFα blockers (infliximab, etanercept, adalimumab, golimumab) have been studied in randomized controlled trials (RCTs) and in observational post-marketing studies with consistent evidence supporting their safety and efficacy in patients with PsA (53). Together with their ability to act on the various clinical features of PsA, they also showed effects on dactylitis, enthesitis, fatigue, function and quality of life (7, 53, 54). Additionally, anti-TNF therapies are the first with proven efficacy in slowing down or halting radiographic progression (54, 55).

Several international and national recommendation sets are currently available for PsA management. Among these, GRAPPA (56) and EULAR (57) recommendations address all pharmacological therapies while the Italian Society of Rheumatology recommendations were designed to help Italian rheumatologists in everyday clinical practice management of PsA patients (44).

All these recommendations propose that anti-TNF therapies should be reserved for patients with active disease and in general include quite similar criteria for starting the biologic agent in each pattern of presenta-

tion of PsA, i.e. peripheral arthritis, axial disease, enthesitis and dactylitis (44, 56, 57). Active disease was generally defined as one or more tender and inflamed joint and/or tender enthesis point and/or dactylitic digit and/or inflammatory back pain.

Despite their relevance, cost-effectiveness of biologic agents have been scarcely considered in PsA. The Psoriatic Arthritis Cost Evaluation (PACE), an Italian cost-of-illness study on TNFα inhibitors in patients with PsA refractory to traditional DMARDs, demonstrated that anti-TNFα agents, although more expensive than conventional drugs, reduce disease activity and improve function and quality of life and are therefore able to reduce direct and indirect costs due to PsA (48). Other studies are in accordance with this observation, confirming that anti-TNFα blocking agents are cost-effective on the various clinical manifestation of PsA (59).

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