



# ACTAS Dermo-Sifiliográficas

Full English text available at  
[www.actasdermo.org](http://www.actasdermo.org)



## SPECIAL ARTICLE

# Recommendations for the Coordinated Management of Psoriatic Arthritis by Rheumatologists and Dermatologists: A Delphi Study<sup>☆</sup>

J.D. Cañete,<sup>a</sup> E. Daudén,<sup>b</sup> R. Queiro,<sup>c</sup> M.D. Aguilar,<sup>d</sup> J.L. Sánchez-Carazo,<sup>e</sup>  
J.M. Carrascosa,<sup>f</sup> G. Carretero,<sup>g</sup> M.L. García-Vivar,<sup>h</sup> P. Lázaro,<sup>d</sup>  
J.L. López-Estebaranz,<sup>i</sup> C. Montilla,<sup>j</sup> J. Ramírez,<sup>a</sup> J. Rodríguez-Moreno,<sup>k</sup> L. Puig<sup>l,\*</sup>

<sup>a</sup> Servicio de Reumatología, Hospital Clínic de Barcelona e IDIBAPS, Barcelona, Spain

<sup>b</sup> Servicio de Dermatología, IIS-Princesa, Hospital Universitario La Princesa, Madrid, Spain

<sup>c</sup> Servicio de Reumatología, Hospital Universitario Central de Asturias, Oviedo, Spain

<sup>d</sup> Técnicas Avanzadas de Investigación en Servicios de Salud (TAISS), Madrid, Spain

<sup>e</sup> Servicio de Dermatología, Hospital General de Valencia, Valencia, Spain

<sup>f</sup> Servicio de Dermatología, Hospital Universitari Germans Trias y Pujol, Badalona, Barcelona, Spain

<sup>g</sup> Servicio de Dermatología, Hospital Universitario Doctor Negrín, Las Palmas de Gran Canaria, Spain

<sup>h</sup> Servicio de Reumatología, Hospital Universitario Basurto, Bilbao, Spain

<sup>i</sup> Servicio de Dermatología, Hospital Universitario Fundación Alcorcón, Alcorcón, Madrid, Spain

<sup>j</sup> Servicio de Reumatología, Hospital Universitario de Salamanca, Salamanca, Spain

<sup>k</sup> Servicio de Reumatología, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain

<sup>l</sup> Servicio de Dermatología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Received 14 April 2013; accepted 18 July 2013

Available online 20 March 2014

## KEYWORDS

Psoriatic arthritis;  
Clinical  
recommendations;  
Coordinated  
management

**Abstract** Psoriatic arthritis, a chronic inflammatory musculoskeletal disease that is associated with psoriasis, causes joint erosions, accompanied by loss of function and quality-of-life. The clinical presentation is variable, with extreme phenotypes that can mimic rheumatoid arthritis or ankylosing spondylitis. Because psoriasis usually presents before psoriatic arthritis, the dermatologist plays a key role in early detection of the latter. As many treatments used in psoriasis are also used in psoriatic arthritis, treatment recommendations should take into consideration the type and severity of both conditions. This consensus paper presents guidelines for the coordinated management of psoriatic arthritis by rheumatologists and dermatologists. The paper was drafted by a multidisciplinary group (6 rheumatologists, 6 dermatologists, and 2 epidemiologists) using the Delphi method and contains recommendations, tables, and algorithms for the diagnosis, referral, and treatment of patients with psoriatic arthritis.

© 2013 Elsevier España, S.L. and AEDV. All rights reserved.

<sup>☆</sup> Please cite this article as: Cañete JD, Daudén E, Queiro R, Aguilar MD, Sánchez-Carazo JL, Carrascosa JM, et al. Elaboración mediante el método Delphi de recomendaciones para el manejo coordinado (reumatólogo/dermatólogo) de la artritis psoriásica. Actas Dermosifiliogr. 2014;105:216–232.

\* Corresponding author.

E-mail address: [lpvig@santpau.cat](mailto:lpvig@santpau.cat) (L. Puig).

**PALABRAS CLAVE**  
Artritis psoriásica;  
Recomendaciones  
clínicas;  
Manejo coordinado**Elaboración mediante el método Delphi de recomendaciones para el manejo coordinado**

**Resumen** La artritis psoriásica es una enfermedad inflamatoria crónica que afecta al sistema musculoesquelético, se asocia a psoriasis y suele producir destrucción articular con pérdida de función y calidad de vida. Su presentación clínica es heterogénea, con extremos fenotípicos que pueden solaparse con la artritis reumatoide o la espondilitis anquilosante. La psoriasis suele preceder a la artritis psoriásica, y la consulta de dermatología es el lugar clave para su detección precoz. Muchos tratamientos utilizados en psoriasis también se utilizan en artritis psoriásica, por tanto las recomendaciones terapéuticas para la psoriasis deben realizarse teniendo en cuenta el tipo y la gravedad de la artritis psoriásica, y viceversa. El objetivo de este documento es establecer pautas para el manejo coordinado (reumatólogo/dermatólogo) de la artritis psoriásica. Ha sido elaborado mediante la técnica Delphi por un grupo multidisciplinar (6 reumatólogos, 6 dermatólogos y 2 epidemiólogos) y contiene recomendaciones, tablas y algoritmos para diagnóstico, criterios de derivación y tratamiento de la artritis psoriásica.

© 2013 Elsevier España, S.L. y AEDV. Todos los derechos reservados.

## Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disorder associated with psoriasis. The prevalence of psoriasis in the general population ranges from 0.1% to 2.8%<sup>1</sup> and between 6% and 42% of these patients also have arthritis.<sup>2</sup> In approximately 70% of cases, cutaneous symptoms precede the onset of joint disease, musculoskeletal symptoms precede skin disease in only 15% of cases, and both occur simultaneously in 15%.<sup>3</sup> The risk of PsA remains constant following initial diagnosis of psoriasis, and the prevalence reaches 20.5% after 30 years.<sup>4</sup> It has been estimated that the mean (SD) interval between the diagnosis of psoriasis and the onset of PsA is 17 (11) years.<sup>5</sup>

PsA was initially considered to be a milder disorder than rheumatoid arthritis, but its progressive course was subsequently shown to cause joint damage and loss of function comparable to that of rheumatoid arthritis.<sup>6</sup> Its clinical expression is very variable, and the disease can manifest as spondyloarthritis, peripheral arthritis, dactylitis, and enthesitis.<sup>7</sup> The most common presentation is oligoarticular peripheral arthritis, followed by the symmetric polyarticular variant, which is similar to the typical presentation of rheumatoid arthritis. The pure axial form, similar to ankylosing spondylitis, is much less common. Between 20% and 30% of patients develop both axial (sacroiliitis, spondylitis) and peripheral (arthritis) symptoms.<sup>8</sup> During the course of the disease, involvement may progress from oligoarticular to polyarticular disease and vice versa.

Moll and Wright<sup>9</sup> in 1973 were the first authors to consider PsA to be a separate clinical entity distinct from other rheumatologic diseases. They defined it as a rheumatoid-factor negative inflammatory arthritis associated with psoriasis. In 2006, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) developed the CASPAR criteria (CLASsification criteria for Psoriatic ARthritis).<sup>10</sup> One of the main advantages of this instrument is that it can be used to diagnose PsA in patients who do not have psoriasis and in patients with a positive rheumatoid factor. This characteristic, and the fact that it is quick and simple to apply, has made CASPAR the most widely used criteria for establishing a diagnosis of PsA.<sup>11</sup>

Owing to the association of PsA with psoriasis and the fact that, in most cases, joint involvement is preceded by skin disease, the dermatology consultation plays a key role in the early detection of PsA. However, the statistics reveal a somewhat depressing picture. A recent study showed that almost 30% of patients with psoriasis receiving dermatological treatment had undiagnosed PsA.<sup>12</sup> Thus, early diagnosis of PsA and prompt referral to a rheumatologist for treatment still represent a real challenge for dermatologists and there is evidence that prompt treatment of PsA can slow the progression of joint damage and the number of joints affected.<sup>13</sup>

Psoriatic onychopathy is a clinical predictor of PsA which has classically been associated with arthritis (80%-90% in PsA compared to 40%-50% in patients without arthritis).<sup>14</sup> Furthermore, although no correlation has been observed between the severity of psoriasis and PsA, an association has been found between the severity of psoriasis and the possibility of developing PsA.<sup>12</sup> The scalp, the retroauricular area, and the intergluteal cleft are the sites of psoriasis most often associated with PsA. An association has also been reported between obesity and the development of PsA.<sup>15-17</sup>

The diagnosis of PsA can be difficult in the dermatological consultation since, in addition to requiring close examination of the entheses, joints, and spine, it also requires imaging studies that are difficult to evaluate in this setting. However, assessment by a rheumatologist of all patients with psoriasis is not a viable option. The solution, therefore, is for the dermatologist to suspect a diagnosis of joint disease on the basis of a physical examination and the patient's medical history. A number of screening questionnaires have been developed to aid the clinician in establishing a suspected diagnosis of PsA in patients with psoriasis: the Psoriatic Arthritis Screening Evaluation (PASE),<sup>18</sup> the Psoriasis Epidemiology Screening Tool (PEST),<sup>19</sup> the Toronto Psoriatic Arthritis Screen (ToPAS),<sup>20</sup> the Psoriatic Arthritis Screening Questionnaire (PASQ),<sup>21</sup> and the Early ARthritis for Psoriatic patients (EARP) questionnaire.<sup>22</sup> However, the sensitivity and specificity of these instruments is well under 50% when the polyarticular forms of arthritis are excluded,<sup>12</sup> and no Spanish versions of these tools have yet been validated. Recent practical guidelines on the management of

comorbidity in patients with psoriasis<sup>23,24</sup> recommended the use of a simplified version of the CASPAR criteria adapted to the dermatological setting as a tool for diagnosing suspected PsA.<sup>10</sup> Patients with suspected PsA should be referred to a rheumatologist for confirmation of the diagnosis.

Clinical management of psoriasis and PsA should be coordinated because most of the systemic treatments used to treat psoriasis, such as disease-modifying antirheumatic drugs (DMARDs) and biologic therapy, are also used to treat PsA. Treatment recommendations should be made taking into consideration the type and severity of both conditions. The aim of this consensus document is to establish guidelines and criteria for the coordinated management of PsA by rheumatologists and dermatologists based on the recommendations of the clinical guidelines most widely used in Spain at this time<sup>23-32</sup>.

## Objectives

### General Aims

To establish a set of eminently practical recommendations on the management of PsA for both rheumatologists and dermatologists.

### Specific Aims

1. To review the tools for screening, assessment, and classification of PsA recommended in the main guidelines and to indicate those most appropriate for each specialty (rheumatology and dermatology) and clinical situation.
2. To develop diagnostic and treatment algorithms for the coordinated management of PsA by dermatologists and rheumatologists.
3. To establish guidelines and recommendations for the coordinated management of PsA.

### Methodology

A working group was set up comprising 12 clinical experts (6 rheumatologists and 6 dermatologists) and 2 epidemiologists with specific experience in developing clinical guidelines and consensus statements. The initiative was started by the 2 principal researchers (LP, dermatologist and JDC, rheumatologist), who each invited other physicians from their specialty who had appropriate experience and expertise in the subject to join the panel. Recently published recommendations on the management of PsA were reviewed.<sup>23-32</sup> These were identified in a nonsystematic way by the panelists. First drafts of the algorithms and the information on tools for the assessment, prognostic evaluation, and treatment of PsA were drawn up using as a starting point the consensus statement of the Sociedad Española de Reumatología (SER) on the use of biologic agents in the treatment of PsA and the consensus document on an integrated approach to comorbidity in patients with psoriasis published by the Working Group on Comorbidity in Psoriasis of the Spanish Academy of Dermatology and Venereology (AEDV).<sup>23,24,29</sup> These were then complemented by recommendations taken from the other documents reviewed,

especially when the initial information was ambiguous or insufficiently precise. The group of clinical experts directed and supervised all the phases of the study and participated in the formulation of the criteria based on expert opinion (those for which the published evidence was insufficient) and in the establishment of recommendations for the coordinated management of PsA.

The first draft of the document was submitted to the expert panel using the RAND/UCLA method (a modified Delphi process) and the panelists voted on the proposed recommendations using a scale of 1 to 9 (1 = totally disagree, 9 = totally agree). The recommendations to which more than 70% of the panelists assigned a score of 7 or higher were automatically included in the final document. The recommendations for which consensus (rate of agreement  $\geq 70\%$ ) was not achieved were reformulated and submitted to the panel for scoring in the second round of the process. If consensus was not achieved on the second round, the recommendation was deleted from the document.

Each one of the new recommendations developed by the expert panel includes a level of evidence rating, a grade of recommendation based on the system developed by the Centre for Evidenced-Based Medicine at the University of Oxford, and the rate of agreement, that is, the percentage of experts who assigned a score of 7 or higher.<sup>33</sup>

## Results

Tables 1 and 2 summarize the recommendations of the panel for screening, treatment, and coordinated follow-up of patients with PsA. Table 1 shows the recommendations for dermatologists and Table 2 the recommendations for rheumatologists.

### Screening for PsA in the Dermatology Clinic

Fig. 1 is a detailed algorithm showing the procedure that should be used by dermatologists to screen for PsA.

In the clinical examination of a patient with psoriasis, the dermatologist should include screening for PsA at regular intervals. This is particularly important in patients with risk factors for PsA, such as onychopathy, obesity, extensive skin disease ( $> 3$  areas affected by psoriasis), or involvement of sites such as the scalp and intergluteal cleft.

As mentioned in the publications of the AEDV Working Group on Comorbidity in Psoriasis,<sup>23,24</sup> the CASPAR criteria are difficult to apply in clinical practice outside the rheumatology office because they require diagnosis of inflammatory arthritis and radiographic evidence of juxtaarticular new bone formation (excluding osteophyte formation). To address this problem, the working group proposed criteria for referral to a rheumatologist based on a simplified version of the CASPAR criteria (Table 3). These modified criteria are indicative of suspected PsA rather than a confirmed diagnosis.

To apply this simplified adaptation of the CASPAR criteria, dermatologists must collect information on the presence or absence of the following signs and symptoms: inflammatory musculoskeletal pain (Table 4), current swelling of the peripheral joints (especially the knees, ankles, and the small joints of the hand), inflammatory or nocturnal pain

**Table 1** Recommendations for Dermatologists<sup>a</sup>

1. Dermatologists should regularly screen patients with psoriasis for PsA, paying particular attention in the presence of associated risk factors such as onychopathy, obesity, extensive skin involvement (> 3 areas affected by psoriasis), or involvement of sites associated with higher risk including the scalp and the intergluteal fold (LE, 5; GR, D; RA, 83%).
2. Dermatologists must explain to the patient that smoking and obesity can make it more difficult to manage psoriasis and may predispose them to psoriatic arthritis (LE, 5; GR, D; RA, 83%).
3. Dermatologists should screen for psoriatic arthritis at least once a year in patients receiving topical treatment for psoriasis and every 6 months in patients on systemic treatment and those with nail or intergluteal/perianal involvement (LE, 5; GR, D; RA, 83%).
4. PsA should be suspected in a patient with psoriasis in the presence of any of the following symptoms or circumstances: inflammatory pain or swelling in peripheral joints, inflammatory or nocturnal pain in the axial skeleton; evidence of enthesitis (especially in the Achilles tendon or plantar fascia); current dactylitis (defined as swelling of the entire digit); or prior history of dactylitis diagnosed by a rheumatologist (LE, 5; GR, D; RA, 100%).
5. If PsA is suspected, the dermatologist should refer the patient to a rheumatologist and provide a report including the PASI score, the percentage of affected BSA, and the current treatment regimen for psoriasis. This should be accompanied by a proposal for joint management of the patient's condition (LE, 5; GR, D; RA, 100%).
6. When a patient diagnosed with PsA is referred by a rheumatologist for assessment, the dermatologist must investigate the current presence of psoriasis, paying particular attention to the sites typically associated with PsA (nails, intergluteal/perianal region, scalp, etc.). If active psoriasis is confirmed, the rheumatologist should be informed. The report should include the current PASI score and BSA (%) and a proposal for joint management of the patient's condition (LE, 5; GR, D; RA, 100%).
7. Patients referred by a rheumatologist who do not have active psoriasis should be informed of the possibility that they will develop the skin disorder and the advisability of requesting a dermatology consultation if they should observe skin or nail lesions (LE, 5; GR, D; RA, 83%).
8. If a patient presents palmoplantar pustulosis and musculoskeletal pain, the dermatologist must investigate the skin lesions and refer the patient to the rheumatologist to complete the differential diagnosis with SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) (LE, 5; GR, D; RA, 92%).
- 9. The treatment plan for the patient with PsA should be devised jointly by the rheumatologist and the dermatologist taking into account the skin lesions as well as the involvement of peripheral and axial joints and entheses (LE, 5; GR, D; RA, 100%).**
10. Patients with controlled psoriasis who do not require additional monitoring related to their treatment regimen should be assessed once a year (LE, 5; GR, D; RA, 92%).
11. Both specialists should be involved in assessing the effectiveness of treatment (LE, 5; GR, D; RA, 92%).
12. Any decision to modify or continue treatment should be agreed by both specialists (5; GR, D; RA, 100%).
13. If the dermatologist confirms the presence of paradoxical psoriasis in a patient with PsA receiving biologic therapy, the patient should be prescribed the appropriate topical or systemic treatment depending on the severity or extension of the lesions. The rheumatologist should decide whether the biologic therapy should be continued, switched, or withdrawn depending on the severity of the cutaneous involvement and the response to the current treatment regimen (LE, 5; GR, D; RA, 100%).

Abbreviations: BSA, Body Surface Area; GR, grade of recommendation, LE, level of evidence; PASI: Psoriasis Area and Severity Index; PsA psoriatic arthritis; RA, rate of agreement.

<sup>a</sup> The recommendations highlighted in bold apply to both dermatologists and rheumatologists.

in the axial skeleton (Table 5) or zones of tendon insertion, especially on the heels (Achilles tendon) and soles of the feet (plantar fascia).<sup>34</sup> They must perform a visual inspection and exploration of suspect joints and entheses for redness, heat, limitation of mobility, swelling, and pain. The limbs should be examined to identify psoriatic onychopathy (nail dystrophy, onycholysis, pitting, or hyperkeratosis) or dactylitis ("sausage digits", that is, swelling of an entire digit).<sup>23</sup>

When a patient diagnosed with PsA is referred to the dermatologist, the skin specialist will perform a thorough examination to look for psoriasis, paying particular attention to the sites most often associated with PsA (nails, scalp, intergluteal region, etc.). The dermatologist should then provide the rheumatologist with a report on the patient's psoriasis, including a proposal for coordinated management of the two conditions.

Certain skin lesions—especially palmoplantar pustulosis associated with musculoskeletal pain (mainly when this is located in the anterior thorax, but also when it affects the dorsal spine or unilateral sacroiliac joint, or takes the form of a monoarthritis affecting a large joint)—require a differential diagnosis with SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis). The dermatologist will study the skin lesions and refer the patient to a rheumatologist, who will study and classify the type of musculoskeletal disease.

### Screening for PsA and Assessment of Prognosis in the Rheumatology Clinic

The algorithm in Fig. 2 shows the procedure that should be used by rheumatologists to screen for PsA.

**Table 2** Recommendations for Rheumatologists<sup>a</sup>

1. Application of the CASPAR criteria is recommended for the initial diagnosis of PsA in rheumatology when peripheral PsA is suspected. When axial PsA is suspected, these criteria should be complemented with sacroiliac radiography, exploration of vertebral mobility, and investigation of pain (**Table 6**) (LE, 5; GR, D; RA, 100%).
2. When axial PsA is suspected and the patient presents inflammatory lumbar pain and alternating buttock pain but the plain radiograph is normal or ambiguous, MRI is recommended (sacroiliac and/or lumbar spine) (LE, 5; GR, D; RA, 100%).
3. The initial prognostic assessment of PsA in rheumatology should include measurement of inflammatory activity, functional impairment, and structural damage. This assessment should include measurement of the parameters listed in **Tables 7 and 8** (LE, 5; GR, D; RA, 100%).
4. If the patient presents cutaneous lesions indicative of palmoplantar pustulosis in conjunction with musculoskeletal pain, the rheumatologist should include SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) in the differential diagnosis (LE, 5; GR, D; RA, 100%).
5. If PsA is confirmed in a patient who has not been diagnosed with psoriasis, the rheumatologist should refer the patient to a dermatologist for further examination and provide a clinical report on the PsA and a proposal for joint management of the patient's condition (LE, 5; GR, D; RA, 75%).
6. If PsA is confirmed in a patient diagnosed with psoriasis and no report on the patient's condition has been received from the dermatologist, the rheumatologist should request such a report, which should include information on the current PASI and BSA, as well as the treatment regimen. Once this information has been received, the rheumatologist will complete the prognostic assessment, classify the type of PsA, and decide on a treatment plan. The rheumatologist should send this information to the dermatologist together with a proposal for joint management of the patient's condition (LE, 5; GR, D; RA, 100%).
7. If a diagnosis of PsA is not confirmed in a patient with psoriasis and suspected PsA, an ultrasound study of entheses (Achilles, quadricipital, and rotulian) is recommended. In the presence of indicative abnormalities—such as altered echogenicity, erosion, calcification, and bursitis—not attributable to mechanical or occupational causes, the patient should be assessed by the rheumatologist every 6 months. If ultrasound findings are normal, the patient should be assessed again within 12 months (LE: 5; GR, D; RA, 92%).
8. This consensus document recommends the use of the treatment guidelines for PsA recommended by the SER, which are incorporated into the treatment algorithms shown in **Figs. 3 and 4** (LE, 5; GR, D; RA, 100%).
9. Systematic follow-up of patients with PsA is recommended. This should include the collection of social, occupational, clinical, and radiographic data as well as the results of laboratory analyses and information concerning response to treatment and toxicity. It should include measurement of the parameters listed in **Tables 7 and 8** (LE, 5; GR, D; RA, 100%).
- 10. The treatment plan for the patient with PsA should be devised jointly by the rheumatologist and the dermatologist taking into account the skin lesions as well as the involvement of peripheral and axial joints and entheses (LE, 5; GR, D; RA, 100%).**
- 11. Patients with controlled psoriasis who do not require additional monitoring related to their treatment regimen should be assessed once a year (LE, 5; GR, D; RA, 92%).**
12. Patients with PsA in whom assessment of treatment effectiveness, treatment adherence, or adverse effects is required and those who require specific monitoring should be followed up every 4 to 6 weeks for 3 to 4 months. (LE, 5; GR, D; RA, 75%).
13. Patients with PsA who present severe exacerbation, unexpected adverse effects to treatment, fever, or rapid deterioration in general health should be assessed as soon as possible and never later than 1 week (LE: 5; GR, D; RA, 92%).
14. The rheumatologist should refer to the dermatologist—for investigation of suspected paradoxical psoriasis—patients receiving treatment with biologic therapy who develop new skin lesions or present worsening of preexisting lesions (LE, 5; GR, D; RA, 100%).
- 15. Both specialists should be involved in assessing the effectiveness of treatment (LE, 5; GR, D; RA, 92%).**
- 16. Any decision to modify or continue treatment should be agreed by both specialists (LE, 5; GR, D; RA, 100%).**

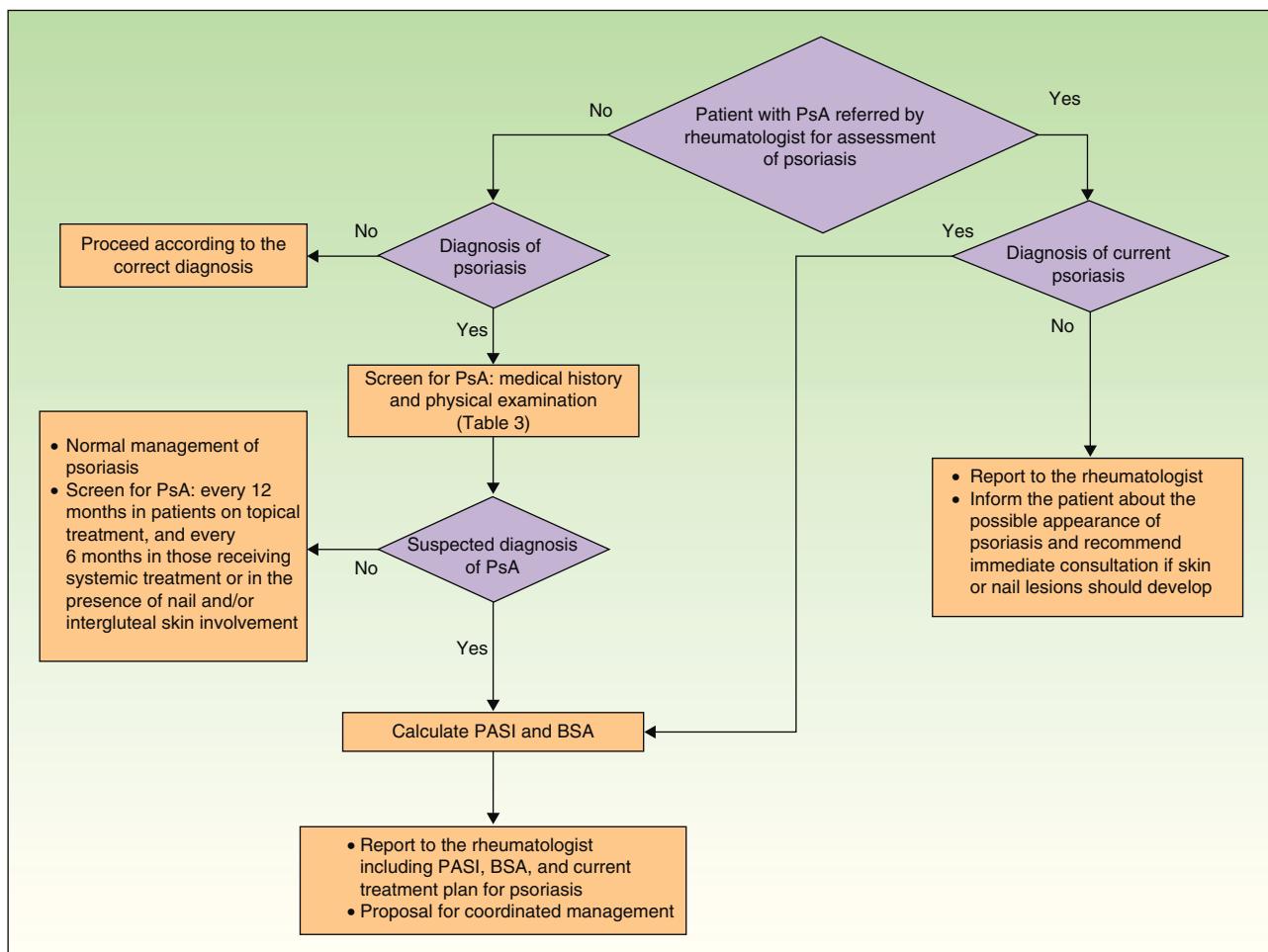
Abbreviations: BSA, body surface area; GR, grade of recommendation; LE, level of evidence; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; SER, Sociedad Española de Reumatología; RA, rate of agreement.

<sup>a</sup> The recommendations in bold face apply to both dermatologists and rheumatologists.

A suspected diagnosis of PsA may be established in the rheumatology consultation either in a patient with psoriasis referred by a dermatologist or in a patient (with or without psoriasis) who consults a rheumatologist for articular pain (joint or spine), dactylitis, and/or enthesitis. The CASPAR criteria (particularly when peripheral PsA is suspected),<sup>29</sup> together with sacroiliac radiography and assessment of vertebral mobility (to detect axial PsA),<sup>27</sup> can be useful in the initial diagnosis. **Table 6** lists the GRAPPA criteria for the diagnosis of axial PsA.<sup>27</sup> If enthesitis is suspected, Doppler

ultrasound and magnetic resonance imaging are useful to complement clinical examination of tendon, ligament, and capsular insertions for pain, inflammation, or tenderness on palpation or pressure.<sup>29</sup> Dactylitis, a condition found in between 16% and 48% of patients with psoriatic joint disease, is an indicator of the severity of PsA.<sup>35</sup> In some cases, isolated but recurrent episodes of dactylitis may be the only clinical manifestation of PsA.

SAPHO syndrome is one of the disorders the rheumatologist must include in the differential diagnosis. It is



**Figure 1** Screening for psoriatic arthritis in the dermatology office. PsA indicates psoriatic arthritis; BSA, % affected body surface area; PASI, Psoriasis Area and Severity Index.

an uncommon seronegative rheumatic condition associated with palmoplantar skin lesions of the pustulosis type that predominantly affects the sternocostal and sternoclavicular joints of the anterior chest wall, but can also give rise to sacroiliitis, dorsal vertebral involvement, and synovitis of the large joints. The features that distinguish SAPHO syndrome from PsA include the presence of hyperostosis, predominantly thoracic involvement, unilateral sacroiliac involvement, and nonerosive peripheral oligoarthritis.

**Table 3** Criteria for Suspected Diagnosis of Psoriatic Arthritis (PsA) (Based on a Simplified Version of the CASPAR Criteria).

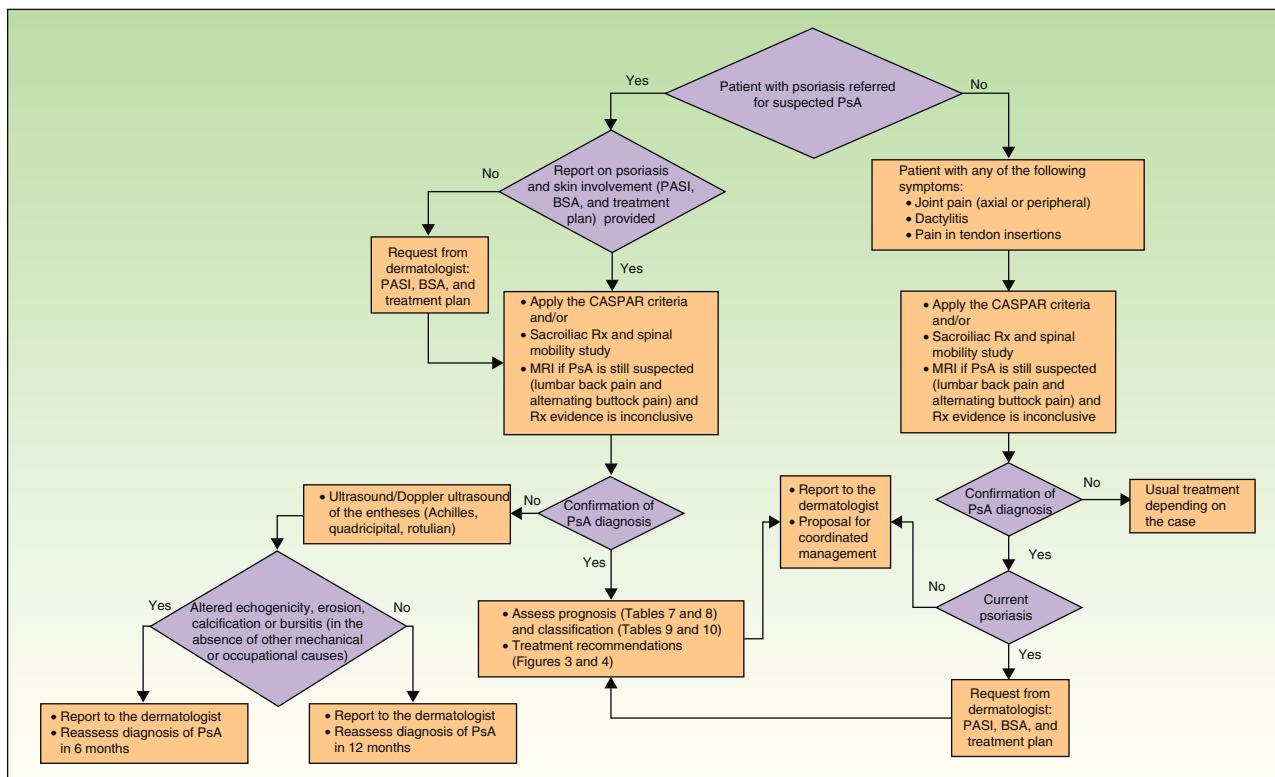
*Psoriatic arthritis should be suspected in patients with psoriasis who have any of the following signs or symptoms:*  
Inflammatory pain or swelling in peripheral joints  
Inflammatory or nocturnal pain in the axial skeleton  
Enthesitis (especially of the Achilles tendon or the plantar fascia)  
Dactylitis

Source: Daudén et al.<sup>23</sup>

If the diagnosis of PsA is confirmed, the rheumatologist should carry out the initial assessment and identify the clinical form. This initial assessment should include a medical history, physical examination, laboratory tests, radiography. Standardized and validated evaluation tools should be used to classify the condition: the DAS28 (Disease Activity Score based on 28 joint counts) to establish peripheral PsA involvement and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in the case of axial disease. The tools used should allow the clinician to measure inflammatory activity, function, and structural damage, as well

**Table 4** Characteristics of Inflammatory Pain in Peripheral Arthritis (Opinion of the Expert Panel).

Predominantly nocturnal, especially during the second half of the night  
Associated with significant morning stiffness (> 30-45 min)  
Alleviated or improved with activity and/or physical exercise  
Worsens with prolonged rest  
Usually improves with nonsteroidal anti-inflammatory treatment



**Figure 2** Screening for psoriatic arthritis in the rheumatology office. PsA indicates psoriatic arthritis; PASI, Psoriasis Area and Severity Index; BSA, % of body surface area affected; MRI, magnetic resonance imaging; Rx, radiography.

as the toxicity of treatment and response to therapy. Also of interest is the measurement of aspects—quality-of-life for instance—of vital interest to the patient. The results of this initial assessment will be used to establish criteria for remission and activity. **Table 7** summarizes the parameters that should be taken into consideration in the assessment of peripheral PsA. It includes the parameters that should be assessed initially and those that should be taken into account when evaluating response to non-steroidal anti-inflammatory (NSAID), DMARD, or biologic therapy. **Table 8** lists the parameters that should be assessed in axial PsA. Both tables include assessment of skin and nail involvement, which, if not provided, should be requested from the dermatologist together with a treatment plan for the skin disease.

**Table 5** Characteristics of Axial Inflammatory Pain (Criteria of the GRAPPA Group).

Onset age < 45 y
Symptoms > 3 mo
Morning stiffness > 30 min
Insidious onset
Improved with exercise
Alternating buttock pain
May be accompanied by limitations in spinal mobility
Pain and limitation in movement typically less severe than in ankylosing spondylitis

Source: Ritchlin et al.<sup>27</sup>

The clinical form of PsA is classified on the basis of the results of this initial evaluation. For practical purposes, PsA can be classified according to the predominant component of the joint disease as predominantly peripheral PsA (with or without an axial component) or predominantly axial (with or without a peripheral component). For the purposes of prognosis and treatment, both forms are also stratified according to the level of clinical activity (clinical signs and symptoms and acute-phase reactants), structural damage, functional impairment, and impact on quality-of-life. For the practical purposes outlined in this document, **Tables 9 and 10** propose clinical classifications of peripheral and axial psoriatic arthritis based on the guidelines reviewed.<sup>27-29</sup>

Since the severity of PsA frequently does not correlate with that of psoriasis, the assessment must include a

**Table 6** Diagnostic Criteria for Axial Psoriatic Arthritis<sup>a</sup>

1. Inflammatory back pain: onset age < 45 y, symptoms > 3 mo, morning stiffness > 30 min, insidious onset, improved with exercise, alternating buttock pain
2. Limitation of motion of cervical, thoracic, or lumbar spine in sagittal and frontal planes
3. Unilateral sacroiliitis ≥ grade 2 on plain radiograph, syndesmophytes, MRI changes in sacroiliac joints of bone marrow edema, erosions, and joint space narrowing

Abbreviation: MRI, magnetic resonance imaging.

Source: Ritchlin et al.<sup>27</sup>

<sup>a</sup> Criteria 1 must be met plus at least 1 other.

**Table 7** Assessment of Peripheral Psoriatic Arthritis: Parameters to be Monitored and Recommended Instruments.

Parameters	Recommendation
Assessment of peripheral arthritis and/or enthesitis	Counts: SJC <sub>66</sub> , SJC <sub>28</sub> TJC <sub>68</sub> TJC <sub>28</sub> Dactylitis/enthesitis
Overall rating of pain in the last week by the patient	VAS or VNS (0-10)
Patient global assessment of disease activity	VAS or VNS (0-10)
Physician global assessment of disease activity	VAS or VNS (0-10)
Acute-phase reactants <sup>a</sup>	Erythrocyte sedimentation rate/C-reactive protein
Routine laboratory workup	Complete blood count, biochemistry
Composite index of disease activity in polyarticular PsA	Calculation of DAS28
Assessment of asthenia in the preceding week	VAS or VNS (0-10)
Assessment of functional capacity	Health Assessment Questionnaire
Assessment of quality-of-life with validated questionnaires	Generic (SF-36, SF-12, or EQ-5D), or specific (PsAQoL) questionnaires
Assessment of structural damage: diagnostic imaging <sup>a</sup>	Radiography of hands, feet, and other affected joints (once a year for the first 3-4 years). Calculation of the modified Sharp-van der Heijde Score for PsA. On the first assessment: radiography of sacroiliac joints to rule out asymptomatic axial disease. Radiography is not useful for early diagnosis, especially of enthesal involvement. Recently greater importance has been placed on the usefulness of ultrasonography, <sup>52,53</sup> magnetic resonance imaging, <sup>54,55</sup> scintigraphy, <sup>56</sup> and positron emission tomography <sup>57</sup> for early diagnosis during asymptomatic phases.
Assessment of skin and nail involvement <sup>a</sup>	PASI/NAPSI BSA (%)

Abbreviations: AP, anteroposterior; BSA, Body Surface Area; DAS28, Disease Activity Score; EQ-5D, European Quality of Life-5 Dimensions; ERS/CRP, erythrocyte sedimentation rate/C-reactive protein; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area Severity Index; PsAQoL, Psoriatic Arthritis Quality of Life Instrument; SF-36/12, Short Form-36/12 Health Survey; SJC, swollen joint count; TJC, tender joint count; VAS, visual analog scale; VNS, visual numeric scale.

Source: Ritchlin et al.,<sup>27</sup> Sociedad Española de Reumatología,<sup>28</sup> and Fernández-Sueiro et al.<sup>29</sup>

<sup>a</sup> These parameters should be included in the initial assessment, when disease activity is assessed, and when response to treatment with DMARD or biologic agents is evaluated. They are not required in patients receiving treatment with NSAIDs because that therapy is not expected to affect them.

dermatology report, which should include information on the patient's Psoriasis Area and Severity Index (PASI) score and the percentage of body surface area affected (% BSA), as well as the recommended treatment plan for the skin disease. The overall treatment plan should be developed jointly by the two specialists taking into account both joint and skin disease.

### Coordinated Treatment Plan (Rheumatologist and Dermatologist) for Psoriatic Arthritis

The goal of treatment in PsA is to achieve remission of the disease or, at least, minimum disease activity (Table 11). This implies achieving significant improvement in signs and symptoms, preserving functional capacity, maintaining a good quality-of-life, and controlling structural damage.<sup>29,36</sup> Tables 12–14 list the objectives for each treatment in peripheral and axial PsA.<sup>29</sup>

NSAIDs, alone or in combination with local injections of corticosteroids, are useful in mild peripheral PsA with skin

involvement that responds well to topical therapy (corticosteroids, vitamin D analogs) and UV-B or psoralen-UV-A phototherapy.

If the skin disease has not responded to earlier treatment or requires systemic therapy (Table 15), treatment with DMARDs (alone or in combinations) is recommended. In patients with moderate to severe peripheral PsA, DMARD treatment (monotherapy or in combinations) and even low dose corticosteroids are also recommended. If the patient also has skin disease, caution should be exercised with corticosteroid treatment, which may exacerbate psoriasis.<sup>27</sup> In PsA, biologic therapy is indicated when treatment with DMARDs has failed or is contraindicated or the patient is intolerant to such treatment. Fig. 3 presents a treatment algorithm for peripheral PsA based on the SER consensus statement on the use of biologic agents in PsA.<sup>29</sup> This algorithm includes criteria for treatment failure and recommendations for evaluating treatment.

DMARDs with proven efficacy in peripheral PsA include sulfasalazine, methotrexate, leflunomide, and cyclosporin A, although the most highly recommended of these in PsA are

**Table 8** Assessment of Axial Psoriatic Arthritis: Parameters to be Monitored and Recommended Instruments.

Parameters	Recommendation
Disease activity assessment	BASDAI (aggregate score)
Patient global assessment	VAS or VNS for the preceding week (0-10)
Global assessment of physical function	BASFI
Specific assessment of spinal mobility	BASMI
Assessment of fatigue, axial pain, and rigidity	BASDAI (pain, fatigue, and morning stiffness duration subscales with a VNS of 0-10)
Acute-phase reactants <sup>a</sup>	ERS/CRP
Routine laboratory workup	Complete blood count, biochemistry
Assessment of structural damage: radiography <sup>a</sup>	AP radiograph of the pelvis (sacroiliac and hips), AP and lateral radiograph of the lumbar spine and lateral view of the cervical spine Radiography is not useful for early diagnosis, especially of enthesal involvement. Recently greater importance has been placed on the usefulness of ultrasonography, <sup>52,53</sup> magnetic resonance imaging, <sup>54,55</sup> scintigraphy, <sup>56</sup> and positron emission tomography <sup>57</sup> for early diagnosis during asymptomatic phases.
Assessment of peripheral arthritis and/or dactylitis/enthesitis	Swollen peripheral joint count, dactylitis and/or enthesitis
Assessment of skin and nail involvement	PASI / NAPSI BSA (%)

Abbreviations: AP, anteroposterior; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BSA, Body Surface Area; ERS/CRP, erythrocyte sedimentation rate/C-reactive protein; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area Severity Index; VAS, visual analog scale; VNS, visual numeric scale.

Source: Ritchlin et al.,<sup>27</sup> Sociedad Española de Reumatología,<sup>28</sup> and Fernández-Sueiro et al.<sup>29</sup>

<sup>a</sup> These parameters should be studied as part of the initial assessment and whenever disease activity or response to treatment are evaluated.

**Table 9** Clinical Classification of Peripheral Psoriatic Arthritis<sup>a</sup>

#### No disease activity or in remission

*In polyarticular disease:* DAS28 < 2.4

*In oligoarticular disease (≤ 4 joints):*

No signs or symptoms of arthritis, enthesitis, or dactylitis

Physician's GDA using a VNS (0-10) < 1

Patient's GDA using a VNS (0-10) < 1

*No elevation of CRP or ERS*

*No impact on patient quality-of-life, work capacity, or leisure activities*

#### Mild activity

*In polyarticular disease:* DAS28 ≥ 2.4 and < 3.2

*In oligoarticular disease (≤ 4 joints):*

Signs and symptoms of arthritis/enthesitis/dactylitis

Physician's GDA using a VNS (0-10) < 4

Patient's GDA using a VNS (0-10) < 4 or elevated CRP or ESR

*Mild impact on quality-of-life, working capacity, and leisure activities*

#### Moderate to severe activity

*In polyarticular disease:* DAS28 ≥ 3.2

*In oligoarticular disease (≤ 4 joints):*

Signs and symptoms of arthritis, enthesitis, or dactylitis

Physician's GDA using a VNS (0-10) ≥ 4

Patient's GDA using a VNS (0-10) ≥ 4 or elevated CRP or ESR

*Moderate to severe impact on the patient's quality-of-life, working capacity, or leisure activities*

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DAS28, Disease Activity Score; CRP, C-reactive protein; pANAP, patient assessment of nocturnal axial pain; GDA, global assessment of disease activity; ESR, erythrocyte sedimentation rate; VNS, visual numeric scale.

<sup>a</sup> Proposed clinical classification of psoriatic arthritis for use in practice for the purposes described in this document.

**Table 10** Clinical Classification of Axial Psoriatic Arthritis<sup>a</sup>

<b>No disease activity or remission</b>
<i>BASDAI &lt; 2, and/or no impact on patient quality-of-life, work capacity, or leisure activities</i>
<b>Mild or moderate activity</b>
<i>BASDAI &gt; 2 and &lt; 4 Physician's GDA using a VNS (0-10) ≥ 2 and &lt; 4 At least one of the following criteria: pANAP using a VNS (0-10) ≥ 2 and &lt; 4 Patient's GDA using a VNS (0-10) ≥ 2 and &lt; 4 Slightly elevated CRP or ESR Slight to moderate impact on quality-of-life, working capacity, and leisure activities</i>
<b>Moderate to severe activity</b>
<i>BASDAI ≥ 4 Physician's GDA using a VNS (0-10) ≥ 4 At least one of the following criteria: pANAP using a VNS (0-10) ≥ 4 Patient's GDA using a VNS (0-10) ≥ 4 Moderately elevated or high CRP or ESR values Moderate to severe impact on the patient's quality-of-life, working capacity, and leisure activities</i>

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; GDA, global assessment of disease activity; ESR, erythrocyte sedimentation rate; pANAP, patient assessment of nocturnal axial pain; VNS, visual numeric scale.

<sup>a</sup> Proposed clinical classification of psoriatic arthritis for use in practice for the purposes described in this document.

methotrexate and leflunomide because of their risk-benefit profile.<sup>29</sup> However, since methotrexate is the first-line choice among DMARDs in psoriasis, it is the recommended treatment in patients who have both psoriasis and PsA.<sup>37</sup>

**Table 12** Treatment Goals in Predominantly Peripheral Psoriatic Arthritis.

In polyarthritis (>4 joints)	<p>Following correct administration of NSAID or nonbiologic DMARD:<sup>a</sup> DAS28 &lt; 3.2 and/or MDA has been achieved</p> <p>Following correct administration of a biologic treatment:<sup>b</sup> Desirable: DAS28 &lt; 2.6 Acceptable: DAS28 &lt; 3.2 or a decline of 1.2 in relation to the preceding assessment and/or MDA</p> <p>Complete disappearance of inflammation, and/or MDA</p>
In oligoarthritis and monoarthritis	Radiographic progression of joint disease
In polyarthritis and monoarthritis the therapeutic goal is not achieved if any of the following apply:	Marked functional impairment or significant impairment of quality-of-life or work activity Uncontrolled or recurrent extra-articular manifestations (recurrent uveitis, bowel disease, etc.) Extensive skin involvement An increase in acute phase reactants

Abbreviations: DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; MDA, minimal disease activity; NSAID, non-steroidal anti-inflammatory drug.

Source: Ritchlin et al.<sup>27</sup> and Fernández-Sueiro et al.<sup>29</sup>

<sup>a</sup> Correct administration of nonbiologic DMARD treatment implies treatment with one or more DMARDs for at least 3 months, during at least 2 of which the patient must receive the full dose (except when the dose is limited by intolerance or toxicity).

<sup>b</sup> Correct administration of biologic treatment involves maintaining the recommended dose for at least 3 to 4 months.

**Table 11** Minimal Disease Activity: Criteria for Peripheral Psoriatic Arthritis.

<i>A state of minimal disease activity is assumed if at least 5 of the following criteria are met:</i>
1. TJC ≤ 1
2. SJC ≤ 1
3. PASI ≤ 1 or BSA ≤ 3%
4. pPA using a VNS (0-10) ≤ 1.5
5. Patient GDA using a VNS (0-10) ≥ 2.5
6. HAQ ≤ 0.5
7. Number of painful entheses ≤ 1

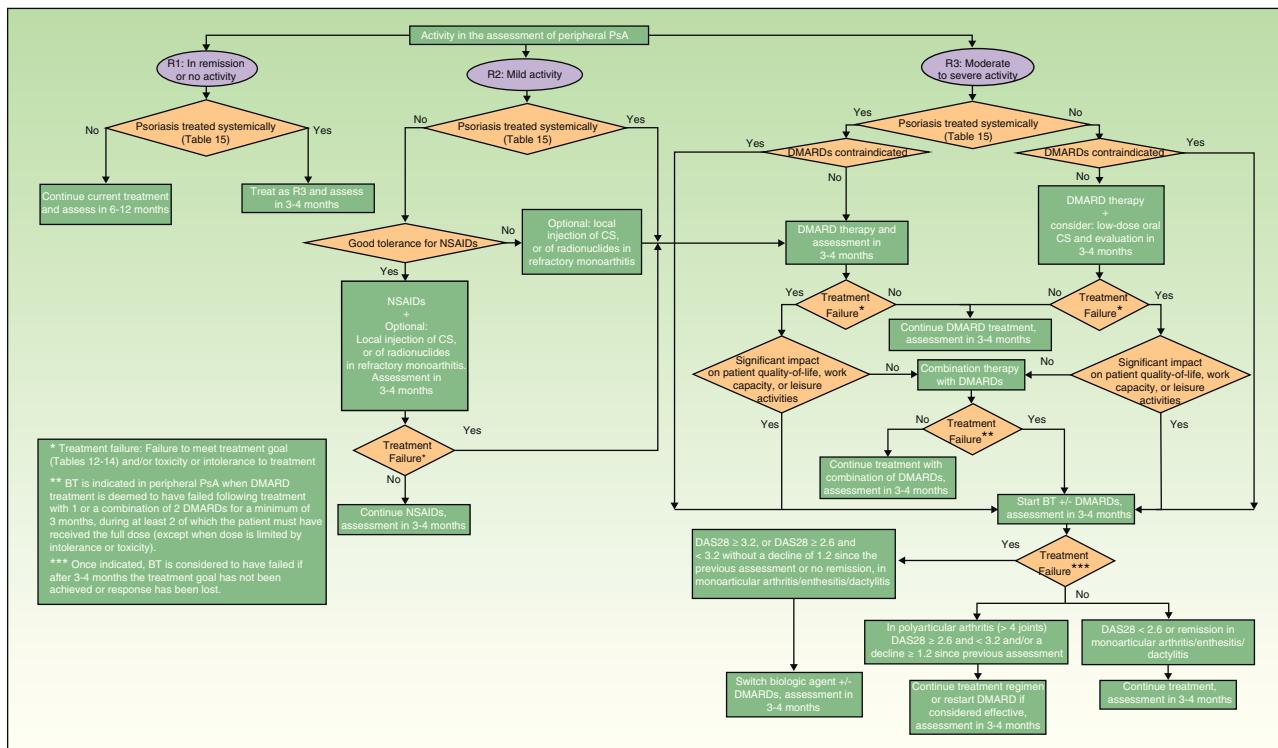
Abbreviations: BSA Body Surface Area; GDA, global assessment of disease activity; HAQ, Health Assessment Questionnaire; PASI Psoriasis Area Severity Index; pPA, patient pain assessment; SJC swollen joint count; TJC: tender joint count; VNS, visual analog score.

Source: Coates et al.<sup>58</sup>

The treatment regimens for DMARDs in PsA are summarized in Table 16.

In predominantly peripheral PsA, treatment with biologic therapy should be considered when an adequate response has not been obtained following treatment with DMARDs (monotherapy or a combination regimen) for at least 3 months, during at least 2 of which the patient must receive the full dose (except when the dose is limited by intolerance or toxicity).<sup>29</sup>

Treatment with NSAIDs and physiotherapy are the first-line treatment in mild to moderate axial PsA when the skin disease does not require treatment with DMARDs or biologic therapy. However, since DMARDs have not been shown to be effective in axial PsA, biologic therapy is recommended when NSAID treatment fails to produce an adequate response or when the skin condition is refractory to topical therapy or requires systemic therapy. In predominantly axial PsA, biologic therapy is considered when treatment has failed with at least 2 NSAIDS having proven



**Figure 3** Treatment algorithm for peripheral psoriatic arthritis. NSAID indicates nonsteroidal anti-inflammatory drugs; DMARD, disease-modifying antirheumatic drug; CS corticosteroids; BT, biologic therapy.

anti-inflammatory effect. In each case, the NSAID must have been administered for at least 4 weeks at the maximum recommended or tolerated dose, except when there are contraindications to NSAIDs or evidence of toxicity.<sup>29</sup> The treatment algorithm for axial PsA, also based on the SER consensus statement, is presented in Fig. 4.<sup>29</sup>

Four biologic agents are currently approved by the regulatory agencies for the treatment of the signs and symptoms of active PsA refractory to conventional therapies (Table 17): adalimumab, etanercept, golimumab, and infliximab (Fig. 5).

There is currently insufficient evidence from direct comparisons to support the use of one biologic agent rather than another in the treatment of PsA.<sup>38</sup> Consequently the choice of treatment depends on the physician's criteria, the particular circumstances of each patient, and the structure, antigenicity, and mechanisms of action of the different biologic therapies.<sup>39</sup> In the databases of international registers and in observational studies, it appears that etanercept may be associated with longer drug survival than other anti-TNF agents in patients with PsA.<sup>40-42</sup>

If within 3 to 4 months of starting biological therapy no response has been obtained (in polyarticular PsA, a DAS28 higher than 3.2 or between 2.6 and 3.2 without a decline of 1.2 points over the previous assessment) or if the initial response has been lost, there is no evidence to support a change in the dose of the current biologic agent. Thus, an alternative treatment strategy should be considered, that is, a switch to another biologic agent. If the response is acceptable (in polyarticular PsA, DAS28 between 2.6 and 3.2 and/or a decrease of 1.2 points compared to the previous value), treatment should be continued with

the possible addition of a DMARD. If the treatment goal has been achieved, treatment should be continued and response assessed in 3 to 4 months.<sup>29</sup>

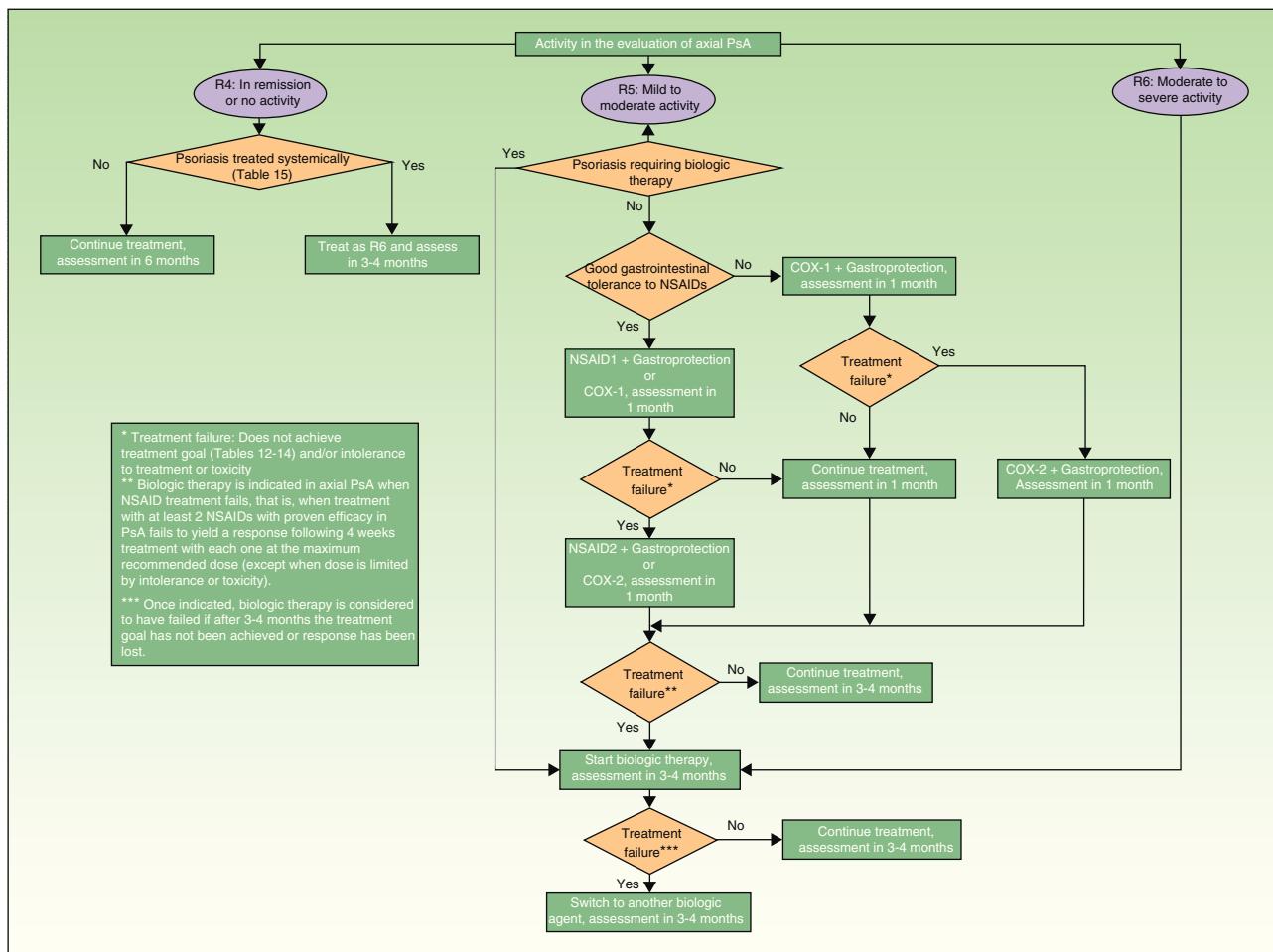
There is currently insufficient evidence in patients with PsA receiving biologic therapy whose condition is in remission to support a recommendation for reducing the dose or prolonging the interval between doses, although a reduction in treatment intensity can be considered on a case-by-case basis.<sup>29</sup> Some authors have published their experience with dose reduction in this setting.<sup>43</sup> This topic is currently considered to be a priority research target.<sup>36</sup>

## Coordinated Management (Rheumatologist and Dermatologist) of Psoriatic Arthritis

As there is very little information in the literature concerning the monitoring and follow-up of patients with PsA,<sup>44-46</sup> recommendations are based on expert opinion.

As a general rule, the rheumatologist is in charge of the management of PsA, but the dermatologist who detects signs or symptoms indicative of a worsening of PsA should refer the patient to the rheumatologist. The dermatologist will also agree with the rheumatologist any change in the patient's treatment that might directly affect the course of PsA (in particular changes in DMARD or biologic therapy). Likewise, the rheumatologist will agree with the dermatologist on any change in therapy that might directly affect the course of psoriasis (in particular changes in DMARD or biologic therapy).

The assessment undertaken by the rheumatologist on follow-up of patients with PsA will be shorter and more



**Figure 4** Treatment algorithm for axial psoriatic arthritis. PsA indicates psoriatic arthritis; NSAID, nonsteroidal anti-inflammatory drug; COX-1, cyclooxygenase-1 selective inhibitor; COX-2, cyclooxygenase-2 selective inhibitor.

specific than the initial evaluation; the findings of the physical examination, complete blood count, routine biochemistry, CRP, and ESR together with an assessment of prognosis should all be recorded in the patient's clinical records. The follow-up visit provides an opportunity to assess the activity of PsA and to evaluate adherence and response to treatment and identify any adverse effects.

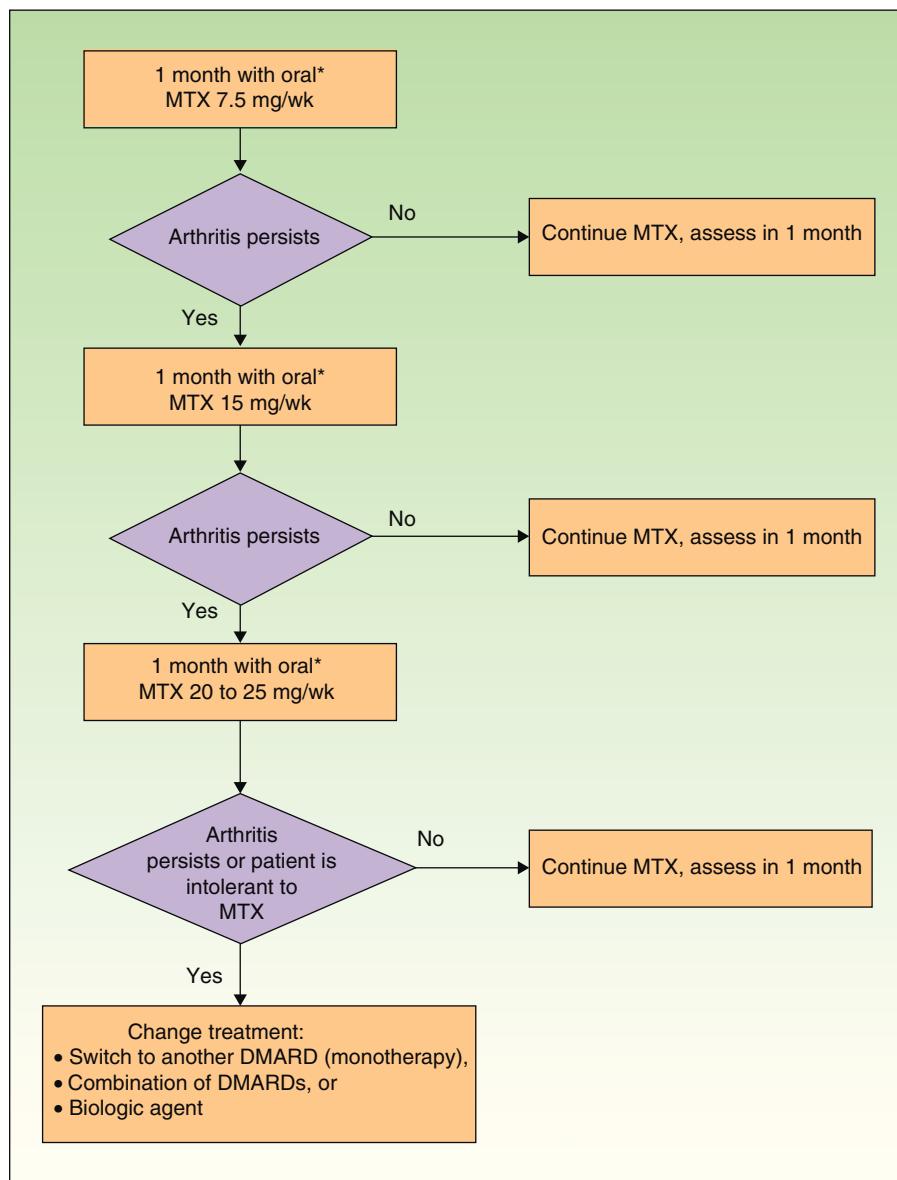
Tables 7 and 8 list the parameters that should be assessed and the recommended instruments for use in the follow-up of PsA. In order to assess disease activity, objective data will be collected and recorded, including tender and swollen joint counts, the presence of dactylitis or enthesitis, and the physician's global disease assessment. At the same time subjective data will be collected, including the patient's assessment of disease activity and pain during the preceding week using a visual numeric scale (VNS). The results of laboratory tests indicative of inflammation, such as CRP and ESR, will also be recorded together with an assessment of the impact of the disease on the patient's social and working life (asthenia, functional capacity, quality-of-life). It may also be useful to record information on the use of symptomatic treatments. Use of the DAS28 to assess treatment response is recommended in polyarticular forms in spite the limitations of the instrument. Although the DAS28 was developed specifically to assess rheumatoid arthritis, the

rheumatologist's familiarity with its use and the fact that the calculator can measure response to treatment make it an attractive tool for monitoring polyarticular forms of PsA in routine practice. The BASDAI is the recommended method for assessing treatment response in axial PsA. Monitoring aimed at identifying adverse effects to therapy should include complete blood count and routine biochemistry in addition to the specific tests required for each drug.

The results of skin and nail assessment should also be recorded, especially in moderate to severe psoriasis. The patient should be referred to a dermatologist for a report on PASI and BSA scores and to obtain a proposed treatment plan if this is considered clinically necessary.

Radiographs of symptomatic joints must be obtained during patient follow-up. Anteroposterior radiographs of the hands and feet should be obtained if the PsA is polyarticular. These should be obtained annually for the first 3 to 4 years after onset, after which the frequency will depend on disease activity.

If the disease is well controlled and not acute and the patient does not require special monitoring related to the drug regimen or other circumstances, follow-up visits should be scheduled every 6 to 12 months. When it is necessary to establish the effectiveness of a therapeutic intervention or monitor compliance, or when the clinical



**Figure 5** Protocol for rapid escalation of methotrexate. MTS indicates methotrexate; DMARD, disease-modifying antirheumatic drug. \*If oral treatment is ineffective or not tolerated by the patient, parenteral administration may be considered.

situation demands more frequent consultations, follow up visits should be scheduled every 4 to 6 weeks for up to 4 months after start of treatment or stabilization of symptoms.

Biologic therapy occasionally triggers a paradoxical reaction that can provoke an exacerbation of existing lesions or de novo psoriasis in patients with no prior skin involvement. These flares of psoriasis associated with biologic therapy can appear within days of the start of anti-TNF therapy or after years of treatment. The most common presentation is palmoplantar psoriasis, either pustular or hyperkeratotic. The choice of treatment in such cases will depend on the extent of the lesions and their response to topical treatment. Tolerable lesions with a BSA of less than 5% to 10% should be treated topically with corticosteroids, keratolytic agents, or vitamin D analogs. If the condition does not improve, switching to another biologic agent or discontinuation of

biologic therapy should be considered. If the lesions are tolerable but the BSA is greater than 5% to 10% or the patient has palmoplantar involvement, a switch to another biologic agent and the addition of topical therapy with occlusive corticosteroids in combination with phototherapy, acitretin, and/or a DMARD (MTX or cyclosporin A) may be considered; if the problem does not improve, a switch to another biologic agent or discontinuation of biologic therapy should be considered. When the lesions are more severe or the patient finds them intolerable or wishes to discontinue the treatment regimen, biologic therapy should be discontinued and topical treatment initiated. The rheumatologist should refer to the dermatologist any patients receiving treatment with biologic therapy who develop skin disease or experience worsening of existing lesions.<sup>47,48</sup> If de novo psoriasis develops or existing psoriasis is exacerbated, the dermatologist will propose an appropriate treatment plan to the

**Table 13** Treatment Goal in Predominantly Axial Psoriatic Arthritis.

<b>Following a correctly administered course of treatment with NSAID.<sup>a</sup></b>
<i>If no increase in acute phase reactants is observed and all of the following criteria are met:</i>
1. BASDAI $\geq 4$
2. Physician's GDA $< 4$
3. Patient's GDA using a VNS (0-10) $< 4$
4. pANAP using a VNS (0-10) $< 4$
<b>Following a correctly administered course of biologic treatment<sup>b</sup></b>
<i>The 3 following criteria must be met:</i>
1. BASDAI: a 50% or 2-point decrease relative to the previous assessment
2. Physician's GDA: a 50% or 2-point decrease with respect to the previous assessment
3. A reduction of 50% in at least one of the following measures if they were previously elevated:
Patient's GDA using a VNS (0-10), if the previous score was $\geq 4$
pANAP using a VNS (0-10), if the previous score was $\geq 4$
ESR and/or CRP, if the previous values were elevated

Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GDA, global assessment of disease activity; NSAID, nonsteroidal anti-inflammatory drugs; pANAP, patient assessment of nocturnal axial pain; VNS, visual numeric scale.

Source: Ritchlin et al.<sup>27</sup> and Fernández-Sueiro et al.<sup>29</sup>

<sup>a</sup> Correct administration of NSAID therapy implies treatment with at least 2 different NSAIDs having proven anti-inflammatory effect for at least of 4 weeks each at the maximum recommended or tolerated dose, except when there is evidence of toxicity or a contraindication to NSAIDs.

<sup>b</sup> Correct administration of biologic treatment involves maintaining the recommended dose for at least 3 to 4 months.

rheumatologist, taking into account the severity and extent of the skin involvement.

Communication between the primary care physician, dermatology and rheumatology should be prompt and efficient.

## Discussion

In recent years, there has been a growing interest in the study of PsA and its consideration as a separate clinical

**Table 14** Treatment Objective After Correct Administration<sup>a</sup> of Biologic Treatment in Dactylitis and/or Enthesitis.

<i>If after proper treatment all of the following are improved:</i>
Functional impairment
Pain
Signs of inflammatory activity
Work disability
Quality-of-life

Source: Ritchlin et al.<sup>27</sup> and Fernández-Sueiro et al.<sup>29</sup>

<sup>a</sup> Correct administration of biologic treatment involves maintaining the recommended dose for at least 3 to 4 months.

**Table 15** Indications for Systemic Treatment in Psoriasis.

*Systemic therapy is indicated in any of the following situations:*

- Disease is not controlled with topical therapy and/or phototherapy
- PASI > 10
- Extensive disease: BSA > 5%-10%
- Rapid worsening of disease
- Involvement of visible areas
- Functional impairment (palmoplantar or genital involvement)
- Subjective perception of severity (DLQI > 10)
- Extensive erythroderma or pustular psoriasis
- Presence of psoriatic arthritis

Abbreviations: BSA, Body Surface Area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area Severity Index.

Source: Puig et al.<sup>37</sup>

entity from other forms of spondyloarthritis. Its association with psoriasis, the involvement of peripheral joints, the presence of dactylitis, and the peculiarities of its axial involvement compared to ankylosing spondylitis make it advisable to consider PsA as a separate and distinct disease requiring specific assessment and management.

Recent publications include 2 review articles on PsA written for dermatologists<sup>49,50</sup> and numerous guidelines and recommendations for its management, some addressed mainly to rheumatologists<sup>27-31</sup> and others to dermatologists.<sup>23-26</sup> Recent publications of the Working Group on Comorbidity in Psoriasis<sup>23,24</sup> address the role of the dermatologist and deal with the diagnosis of PsA and the referral of these patients to a rheumatologist. They do not, however, discuss in depth the role of the dermatologist in the management of PsA or how rheumatologists and dermatologists should work together to decide on the most appropriate treatment regimen in each case and evaluate treatment response taking into account the clinical features of both psoriasis and PsA.

The authors of the multicenter CALIPSO study undertaken a few years ago in Spain observed substantial differences in the clinical management and follow-up of patients with PsA depending on whether they were treated in rheumatology or dermatology clinics.<sup>51</sup> Those authors considered that these differences were indicative of a lack of consensus on

**Table 16** Peripheral Psoriatic Arthritis: Initial Regimen (First 3 Months) for Each DMARD.

DMARD	Regimen
MTX	7.5 mg/wk. If remission is not achieved within 1 mo, increase according to rapid escalation regimen
LEF	20 mg/d (if patient is intolerant: 10 mg/d)
SSA	2-3 g/d
Ciclosporin A	3-5 mg/kg/d (in the case of adverse effects, maximum tolerated dose)

Abbreviations: LEF, leflunomide, MTX, methotrexate, SSA, sulfasalazine.

Source: Fernández-Sueiro et al.<sup>29</sup>

**Table 17** Dosage and Route of Administration of Biologic Therapies Approved for the Treatment of Psoriatic Arthritis. First 52 Weeks of Treatment.

Active Substance	Trade Name	Dosage as per Summary of Product Characteristics	Route of Administration
Adalimumab	Humira	40 mg every 2 wks	s.c.
Etanercept	Enbrel	25 mg twice weekly 50 mg each wk	s.c.
Golimumab	Simponi	50 mg each mo	s.c.
Infliximab	Remicade	5 mg/kg at wks 0, 2, and 6, and every 8 wks thereafter	i.v.
Ustekinumab*	Stelara	45 mg at wks 0, 4, and every 12 wks thereafter. 90 mg may be used in patients with a body weight > 100 kg.	s.c.

Abbreviations: i.v., intravenous; s.c. subcutaneous.

\* Ustekinumab (Stelara), alone or in combination with methotrexate, has recently been approved for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological DMARD therapy has been inadequate.

the correct approach in PsA and recommended the development of standardized practice guidelines covering the diagnostic protocols, classification, management of symptoms and treatment, and criteria for referral between the two specialties. The present document was drawn up to address this problem and to complement existing guidelines and consensus statements by providing specific recommendations aimed at unifying the criteria and improving the coordinated management of PsA by dermatologists and rheumatologists.

The fact that the present document is not based on a systematic review of the literature does not constitute a limitation. The review was performed to identify the customary and accepted tools for the diagnosis, assessment, and therapeutic management of PsA, which were then used as a framework to support the project. They provided the structure for the recommendations made by the panelists for coordinated management of PsA.

The recommendations are based solely on expert opinion. To make them more robust we used a strict criterion based on clear consensus among the panelists (at least 70% endorsement with the 3 highest categories). Moreover, the panel was made up of both rheumatologists and dermatologists and the recommendations were endorsed by both groups. Thus, it is hoped that these recommendations will prove useful in the coordinated management of PsA.

In conclusion, this document contains recommendations and guidelines for improving the coordinated management of PsA between dermatologists and rheumatologists. It will be of particular interest and benefit to dermatologists because of the key role they play in the early diagnosis and referral of patients with PsA and in assessing any skin involvement to provide the information needed to establish a prognosis and devise a treatment plan for these patients.

## Ethical Disclosures

**Protection of Human and Animal Subjects.** The authors declare that no experiments were performed on humans or animals for this investigation.

**Confidentiality of Data.** The authors declare that no private patient data are disclosed in this article.

**Right to Privacy and Informed consent.** The authors declare that no private patient data are disclosed in this article.

## Funding

This work was carried out with independent financing from Pfizer S.L.U.

## Conflicts of Interest

The authors whose names are indicated in parentheses have received remuneration for expert consulting, participation in clinical trials, or conferences from the companies listed below: Abbvie (Juan de Dios Cañete, Esteban Daudén, Gregorio Carretero, Lluís Puig, José Luis Sánchez-Carazo, and José Luis López-Estebaranz); Celgene (Juan de Dios Cañete, Esteban Daudén, and Lluís Puig); Janssen-Cilag (Juan de Dios Cañete, Esteban Daudén, Gregorio Carretero, Lluís Puig, and José Luis López-Estebaranz); MSD and/or MSD-Schering-Plough, and/or Merck Serono (Juan de Dios Cañete, Esteban Daudén, Gregorio Carretero, Lluís Puig, José Luis Sánchez-Carazo, and José Luis López-Estebaranz); Pfizer and/or Wyeth and/or Pfizer-Wyeth (Juan de Dios Cañete, Esteban Daudén, Gregorio Carretero, Lluís Puig, José Luis Sánchez-Carazo, and José Luis López-Estebaranz); Amgen (Esteban Daudén and Lluís Puig); Astellas (Esteban Daudén); Boehringer (Lluís Puig); Centocor Ortho Biotech Inc (Esteban Daudén and Lluís Puig); Galderma (Esteban Daudén); Glaxo and/or GSK (Esteban Daudén); Leo Pharma (Esteban Daudén, Gregorio Carretero, and Lluís Puig); Novartis (Esteban Daudén, Gregorio Carretero, and Lluís Puig), and VBL (Lluís Puig).

The other authors declare that they have no potential conflicts of interest in relation to the content of the present article. All of the authors consider that they have acted with total independence with respect to the drafting of this article.

## Acknowledgments

In memory of Dr. José Luis Fernández Sueiro, the rheumatologist who pioneered collaboration between dermatologists and rheumatologists in the study and management of psoriatic arthritis.

## References

1. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. *J Investig Dermatol Symp Proc.* 2004;9:136–9.
2. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: Epidemiology, clinical features, course, and outcome. *Ann Rheum Dis.* 2005;64 Suppl 2:ii14–7.
3. Anandarajah AP, Ritchlin CT. The diagnosis and treatment of early psoriatic arthritis. *Nat Rev Rheumatol.* 2009;5: 634–41.
4. Christophers E, Barker JNWN, Griffiths CEM, Daudén E, Milligan G, Molta C, et al. The risk of psoriatic arthritis remains constant following initial diagnosis of psoriasis among patients seen in European dermatology clinics. *J Eur Acad Dermatol Venereol.* 2010;24:548–54.
5. García-Díez A, Ferrández-Foraster C, Vanalocha-Sebastián F, Lizán-Tudela L, Badía-Llach X, Sellers-Fernández G. What characterizes the severity of psoriasis? Results from an epidemiological study of over 3,300 patients in the Iberian region. *Dermatology.* 2008;216:137–51.
6. Sokoll KB, Helliwell PS. Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. *J Rheumatol.* 2001;28:1842–6.
7. Kavanaugh AF, Ritchlin CT. Systematic review of treatments for psoriatic arthritis: An evidence based approach and basis for treatment guidelines. *J Rheumatol.* 2006;33:1417–21.
8. Bruce IN. Psoriatic arthritis: clinical features. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weissman MH, editors. *Rheumatology.* Philadelphia: Mosby-Elsevier; 2008. p. 1165–75.
9. Moll J, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum.* 1973;3:55–78.
10. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: Development of new criteria from a large international study. *Arthritis Rheum.* 2006;54:2665–73.
11. Torre Alonso JC. Utilidad y aplicación en la práctica clínica de los criterios CASPAR. *Reumatol Clin.* 2010;6 Suppl 1:18–21.
12. Haroon M, Kirby B, FitzGerald O. High prevalence of psoriatic arthritis in patients with severe psoriasis with suboptimal performance of screening questionnaires. *Ann Rheum Dis.* 2013;72:736–40.
13. Gladman DD, Thavaneswaran A, Chandran V, Cook RJ. Do patients with psoriatic arthritis who present early fare better than those presenting later in the disease? *Ann Rheum Dis.* 2011;70:2152–4.
14. Ash ZR, Tinazzi I, Gallego CC, Kwok C, Wilson C, Goodfield M, et al. Psoriasis patients with nail disease have a greater magnitude of underlying systemic subclinical enthesopathy than those with normal nails. *Ann Rheum Dis.* 2012;71:553–6.
15. Li W, Han J, Qureshi AA. Obesity and risk of incident psoriatic arthritis in US women. *Ann Rheum Dis.* 2012;71: 1267–72.
16. Love TJ, Zhu Y, Zhang Y, Wall-Burns L, Oggie A, Gelfand JM, et al. Obesity and the risk of psoriatic arthritis: A population-based study. *Ann Rheum Dis.* 2012;71:1273–7.
17. Cañete JD, Mease P. The link between obesity and psoriatic arthritis. *Ann Rheum Dis.* 2012;71:1265–6.
18. Husni ME, Meyer KH, Cohen DS, Mody E, Qureshi AA. The PASE questionnaire: Pilot-testing a psoriatic arthritis screening and evaluation tool. *J Am Acad Dermatol.* 2007;57:581–7.
19. Ibrahim GH, Buch MH, Lawson C, Waxman R, Helliwell PS. Evaluation of an existing screening tool for psoriatic arthritis in people with psoriasis and the development of a new instrument: The Psoriasis Epidemiology Screening Tool (PEST) questionnaire. *Clin Exp Rheum.* 2009;27:469–74.
20. Gladman DD, Schentag CT, Tom BD, Chandran V, Brockbank J, Rosen C, et al. Development and initial validation of a screening questionnaire for psoriatic arthritis: The Toronto Psoriatic Arthritis Screen (TOPAS). *Ann Rheum Dis.* 2009;68: 497–501.
21. Peloso PM, Behl M, Hull P, Reeder B. The Psoriasis and Arthritis Questionnaire (PAQ) in detection of arthritis among patients with psoriasis. *Arthritis Rheum.* 1997;40 Suppl 9:S64.
22. Tinazzi I, Adami S, Zanolini EM, Caimmi C, Confente S, Girolomoni G, et al. The early psoriatic arthritis screening questionnaire: A simple and fast method for the identification of arthritis in patients with psoriasis. *Rheumatology.* 2012;51:2058–63.
23. Daudén E, Castañeda S, Suárez C, García-Campayo J, Blasco AJ, Aguilar MD, et al. Grupo de Trabajo en Comorbilidades Asociadas a la Psoriasis. Abordaje integral de la comorbilidad del paciente con psoriasis. *Actas Dermosifiliogr.* 2012;103 Suppl 1:1–64.
24. Daudén E, Castañeda S, Suárez C, García-Campayo J, Blasco AJ, Aguilar MD, et al. Clinical practice guideline for an integrated approach to comorbidity in patients with psoriasis. *J Eur Acad Dermatol Venereol.* 2012.
25. Menter A, Gottlieb A, Feldman SR, van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol.* 2008;58:826–50.
26. Gottlieb A, Korman NJ, Gordon KB, Feldman SR, Lebwohl M, Koo JYM, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 2. Psoriatic arthritis: Overview and guidelines of care for treatment with an emphasis on the biologics. *J Am Acad Dermatol.* 2008;58:851–64.
27. Ritchlin CT, Kavanaugh A, Gladman DD, Mease PJ, Helliwell P, Boehncke W-H, et al. Treatment recommendations for psoriatic arthritis. *Ann Rheum Dis.* 2009;68:1387–94.
28. Sociedad Española de Reumatología (SER). ESPOGUIA. Guía de Práctica Clínica sobre el manejo de los pacientes con Espondiloartritis. Madrid: SER; 2009. cited 2013 Aug 22. Available from: [http://www.ser.es/practicaClinica/Guias\\_practica-clinica/Guias\\_finalizadas.php](http://www.ser.es/practicaClinica/Guias_practica-clinica/Guias_finalizadas.php)
29. Fernández-Sueiro JL, Juanola-Roura X, Cañete-Crespillo JD, Torre-Alonso JC, García de Vicuña R, Queiro-Silva R, et al. Documento SER de consenso sobre el uso de terapias biológicas en la artritis psoriásica. *Reumatol Clin.* 2011;7:179–88.
30. Machado P, Bogas M, Ribeiro A, Costa J, Neto A, Sepriano A, et al. 2011 Portuguese recommendations for the use of biological therapies in patients with psoriatic arthritis. *Acta Reumatol Port.* 2012;37:26–39.
31. Gossec L, Smolen JS, Gaujoux-Viala C, Ash Z, Mar-Ortega H, van der Heijde D, et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis.* 2012;71:4–12.
32. National Clinical Guideline Centre (NCGC). Psoriasis: Assessment and Management of Psoriasis. Clinical Guideline: Methods, Evidence and Recommendations. London: NCGC; 2012.
33. Centre for Evidence Based Medicine (CEBM) [Internet]. Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009). Oxford: CEBM; 2012. cited 2013 Aug 22. Available from: <http://www.cebm.net/index.aspx?o=1025>
34. Tinazzi I, Mcgonagle D, Biasi D, Confente S, Caimmi C, Girolomoni G, et al. Preliminary evidence that subclinical

- enthesopathy may predict psoriatic arthritis in patients with psoriasis. *J Rheumatol.* 2011;38:12.
35. Brockbank JE, Stein M, Schentag CT, Gladman DD. Dactylitis in psoriatic arthritis: A marker for disease severity. *Ann Rheum Dis.* 2005;64:188–90.
36. Smolen JS, Braun J, Dougados M, Emery P, Fitzgerald O, Hellier P, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: Recommendations of an international task force. *Ann Rheum Dis.* 2013.
37. Puig L, Bordas X, Carrascosa JM, Daudén E, Ferrández C, Hernanz JM, et al. Consensus document on the evaluation and treatment of moderate-to-severe psoriasis. Spanish psoriasis Cite in Spanish. [Documento de consenso sobre la evaluación y el tratamiento de la psoriasis moderada/grave del Grupo Español de Psoriasis\* de la Academia Española de Dermatología y Venereología]. *Actas Dermosifiliogr.* 2009;100:277–86.
38. Gladman DD. Adalimumab etanercept and infliximab are equally effective treatments for patients with psoriatic arthritis. *Nat Clin Pract Rheumatol.* 2008;4:510–1.
39. Migliore A, Buzzi E, Broccoli S, Laganà B. Indirect comparison of etanercept, infliximab, and adalimumab for psoriatic arthritis: Mixed treatment comparison using placebo as common comparator. *Clin Rheumatol.* 2012;31:193–4.
40. Saad AA, Ashcroft DM, Watson KD, Hyrich KL, Noyce PR, Symmons DP. Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: Observational study from the British Society of Rheumatology Biologics Register. British Society for Rheumatology Biologics Register. *Arthritis Res Ther.* 2009;11:R52.
41. Carmona L, Gómez-Reino JJ. Survival of TNF antagonists in spondylarthritis is better than in rheumatoid arthritis. Spanish registry BIOBADASER. *Arthritis Res Ther.* 2006;8:R72.
42. Esposito M, Giunta A, Mazzotta A, Zangrilli A, Babino G, Bavetta M, et al. Efficacy and safety of subcutaneous anti-tumor necrosis factor-alpha agents, etanercept and adalimumab, in elderly patients affected by psoriasis and psoriatic arthritis: An observational long-term study. *Dermatology.* 2012;225:312–9.
43. Cantini F, Niccoli L, Cassarà E, Kaloudi O, Nannini C. Sustained maintenance of clinical remission after adalimumab dose reduction in patients with early psoriatic arthritis: A long-term follow-up study. *Biologics.* 2012;6:201–6.
44. Mease PJ. Assessment tools in psoriatic arthritis. *J Rheumatol.* 2008;35:1426–30.
45. Mease PJ, Antoni CE, Gladman DD, Taylor WJ. Psoriatic arthritis assessment tools in clinical trials. *Ann Rheum Dis.* 2005;64 Suppl 2:ii49–54.
46. Salliot C, Dernis E, Lavie F, Cantagrel A, Gaudin P, Wendling D, et al. Diagnosis of peripheral psoriatic arthritis: Recommendations for clinical practice based on data from the literature and experts opinion. *Joint Bone Spine.* 2009;76:532–9.
47. Santos-Juanes J, Galache C. Reacciones cutáneas psoriasisiformes durante el tratamiento con etanercept. *Actas Dermosifiliogr.* 2010;101 Supl 1:106–10.
48. Collamer AN, Guerrero KT, Henning JS, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: A literature review and potential mechanisms of action. *Arthritis Rheum.* 2008;59:996–1001.
49. López-Ferrer A, Torrente-Segarra V, Puig L. Artritis psoriásica: lo que el dermatólogo debe saber (parte 1). *Actas Dermosifiliogr.* 2010;101:578–84.
50. López-Ferrer A, Torrente-Segarra V, Puig L. Artritis psoriásica: lo que el dermatólogo debe saber (parte 2). *Actas Dermosifiliogr.* 2010;101:742–8.
51. López-Estebaranz JL, Zarco-Montejo P, Escalas-Tabernert J, García-Rodríguez M, García-Llorente JF, García-Calvo C. Manejo de la artritis psoriásica en España: estudio Calipso. *Actas Dermosifiliogr.* 2010;101:629–36.
52. Gutierrez M, Filippucci E, de Angelis R, Salaffi F, Filosa G, Ruta S, et al. Subclinical enthesal involvement in patients with psoriasis: An ultrasound study. *Semin Arthritis Rheum.* 2011;40:407–12.
53. De Simone C, Calderola G, d'Agostino M, Carbone A, Guerrero C, Bonomo L, et al. Usefulness of ultrasound imaging in detecting psoriatic arthritis of fingers and toes in patients with psoriasis. *Clin Dev Immunol.* 2011;2011:390726.
54. McGonagle D, Gibbon W, O'Connor P, Green M, Pease C, Emery P. Characteristic magnetic resonance imaging enthesal changes of knee synovitis in spondylarthropathy. *Arthritis Rheum.* 1998;41:694–700.
55. Emad Y, Ragab Y, Gheita T, Anbar A, Kamal H, Saad A, et al. Knee enthesitis and synovitis on magnetic resonance imaging in patients with psoriasis without arthritic symptoms. *J Rheumatol.* 2012;39:1979–86.
56. Raza N, Hameed A, Ali MK. Detection of subclinical joint involvement in psoriasis with bone scintigraphy and its response to oral methotrexate. *Clin Exp Dermatol.* 2008;33:70–3.
57. Takata T, Taniguchi Y, Ohnishi T, Kohsaki S, Nogami M, Nakajima H, et al. (18)FDG PET/CT is a powerful tool for detecting subclinical arthritis in patients with psoriatic arthritis and/or psoriasis vulgaris. *J Dermatol Sci.* 2011;64:144–7.
58. Coates LC, Fransen J, Hellier PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis.* 2010;69:48–53.