NOVELTIES IN DERMATOLOGY

Psoriatic Arthritis: An Update

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Abstract Advances in our understanding of the pathogenesis of psoriatic arthritis and clinical aspects of the disease justify the present review. Studies have identified common inflammatory pathways related to the innate immune response, such as the IL-12/IL-23 axis, along with numerous genes that affect susceptibility to both diseases and influence phenotypic development. Interest has grown in biomarkers that can be used for early diagnosis or prognosis or to predict joint destruction and the response to treatment. Recent reports describe important differences between the effects of disease-modifying antirheumatic drugs and biologics on the process of new bone formation. Other issues that have been discussed include the need for reliable screening methods, particularly for early detection of oligoarticular arthritis, and for protocols to guide referral to specialists, especially in newly created multidisciplinary practices.

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Resumen En los últimos años se ha ampliado el conocimiento de aspectos clínicos y patogénicos de la artritis psoriásica, que justifican la presente revisión. Se han identificado vías comunes de activación de la respuesta inflamatoria relacionada con la inmunidad innata, como el eje IL12/IL23 y numerosos genes determinantes de la susceptibilidad a ambas enfermedades, y diferencias en el fenotipo. El desarrollo de biomarcadores de diagnóstico precoz, pronósticos y predictivos de la destrucción osteoarticular y la respuesta al tratamiento son también de interés creciente. Recientemente se han descrito también diferencias importantes en la respuesta sobre el proceso de neoformación ósea entre FAME y biológicos. Asimismo, se ha puesto de manifiesto la necesidad de disponer de métodos de cribado fiables, en especial para identificar precozmente las formas oligoarticulares, y establecer criterios de derivación prácticos que permitan ofrecer una atención especializada, principalmente en el contexto de unidades interdisciplinares de nueva creación.

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Psoriatic arthritis (PsA) is an inflammatory, progressive, and often destructive arthritis associated with psoriasis. Diagnosis can be difficult as the disease has a variety of presentations often indistinguishable from other joint diseases such as osteoarthritis and gout.

Severe arthritis can be observed in the absence of psoriasis while very mild arthritis may occur in patients with moderate or severe psoriasis. Thus, a high degree of clinical suspicion, screening of patients with psoriasis, and combined evaluation by dermatologists and rheumatologists are essential to arrive at a diagnosis.

Early diagnosis of the disease and a targeted treatment from the start may help prevent long-term complications, joint destruction, and patient dependence. The availability of biological agents has equipped the specialists responsible for treating this disease with the necessary tools for its treatment. It is therefore more important than ever that efforts are pooled to improve early diagnosis.

Progress in Understanding the Pathophysiology of Psoriatic Arthritis

Common Pathophysiologic Pathways for Skin and Joint Diseases

PsA is a musculoskeletal disease that occurs in association with psoriasis. Although some susceptibility genes are common to both diseases, there are also many genetic differences. The psoriatic phenotype appears to be mediated by the susceptibility allele HLA-C*06, giving rise to a clinical presentation in which skin involvement predominates, with limited and late joint involvement, whereas the allele HLA-B and above all the alleles HLA-B27 and HLA-B38 are associated with a clinical presentation with joint involvement, with onset at the same time as skin manifestations. The different epidemiological patterns of presentation of psoriasis and PsA suggest common mechanisms as well as mechanisms unique to each condition, with a complex mix of genetic and acquired factors. Most of the inflammatory pathways have already been reported in psoriasis and, using these as a basis, inflammatory models have been proposed for the joints. Thus, the presence of external factors acting on the epidermis could activate dendritic cells that migrate to regional lymph nodes where they could present antigens to naive T cells, which in turn could be activated to Th1 and Th17 cells by local production of interleukin (IL) 12/1L23. Expression of CCR4, CCR6, and CXCR3 on the surface of these lymphocytes may allow them to migrate from the vascular endothelium once more towards the epidermis, where they carry out an effector role to produce more inflammatory interleukins and chemokines able to recruit other inflammatory cells. Recently, investigators have reported CARD14 gene mutations which give rise to proteins present in the outermost layers of the epidermis with a capacity to constitutively activate nuclear factor kappa-B (NF-κB), thereby inducing the production of chemokines such as IL8. There is also an increase in the number of lymphocytes in the joints, triggering a local inflammatory response and inducing osteoclastogenic processes. This occurs through the receptor activator of NF-κB ligand (RANKL), the cytokine responsible for activating RANK, present in osteoclasts.

Angiogenesis is an important component in the pathogenesis of both arthritis and psoriasis. Thus, tumor necrosis factor (TNF), IL8, IL18, and IL17 induce the production of vascular endothelial growth factor, Ang1, and Ang2, with the capacity to induce the formation of neovessels in the skin or synovium. Indeed, anti-TNF therapies have been shown to be effective at inhibiting this process in both domains.

IL12, IL23, and IL17 have been shown to play a part in the pathogenesis of arthritis and psoriasis, for example, through clinical trials conducted with their corresponding inhibitors, ustekinumab, ixekizumab, and brodalumab, respectively.

Genetics: Genotype-Phenotype Associations

In recent years, advances in our knowledge of the genes implicated in the pathogenesis of psoriasis and PsA have been made possible by the Genome Wide Association Scan (GWAS) studies. These have identified gene mutations implicated in the epidermal barrier (LCE3, GJB2, DEFB4) and genes involved in innate (TNFAIP3, TNIP1, NFKBIA, TYKZ, FXBXL19) and acquired (TRAF3IP2, IL23A, IL23R, IL4, IL13) immune response. Recently, 15 new susceptibility genes have been identified from a study of 10 588 patients with psoriasis and 22 806 controls. Some of the new genes identified are common to other autoimmune diseases and include genes implicated in the regulation of T-cell function (such as RUNX3, TAGAP, and STAT3). Other genes participate in innate immunity, including genes for interferon-mediated antiviral response (DDX58), macrophage activation (ZC3H12C), and NF-κB activation (CARD14 and CARM1). A model predictive of the risk of developing psoriasis has also been proposed using 10 susceptibility loci, which account for 11.6% of genetic variability.

In the case of pustular psoriasis, a homozygous mutation at IL36RN, a gene that encodes the IL36 receptor antagonist, gives rise to an inactive antagonist that cannot bind efficiently to its receptor, leading to an increase in secretion of proinflammatory cytokines.

Genotype-phenotype correlation studies have enabled the identification of associations between mutations in LCE3D and more severe psoriasis phenotypes, association between nail involvement and IL1RN, and the presence of PsA with mutations at the IFIH1 locus.

The search for specific susceptibility genes for PsA has confirmed the association of HLA-C, IL22B, IL23R, and TRAG3IP2 with PsA; of L28RA, TN1P1, IL23A, and RNF114 with psoriasis; and of new loci with both psoriasis and PsA (1p22, 5p13, 8q22, 14q12). GWAS studies have enabled a specific signal to be identified in the HLA-B/MICA region (Elder et al., unpublished results). HLA-B27, HLA-B38/39, TRAF3IP2, IL13 and some MICA alleles, among others, have been proposed as predisposing genes that can trigger PsA in individuals with psoriasis.

In the case of interaction with environmental factors, a negative correlation has been found between smoking and the development of psoriasis or PsA.
Pharmacogenetic studies are important for determining the capacity for response to a drug of an individual with a particular genotype. Polymorphisms associated with response to methotrexate (MTX), disease-modifying antirheumatic drugs (DMARD), and a range of biological agents have been identified. Such information can help optimize therapy.

Diagnostic and Prognostic Biomarkers in Psoriatic Arthritis

A biomarker is a characteristic that can be objectively measured and assessed as an indicator of a normal biological process, a pathological process, or a biological response to treatment. In the case of psoriasis, there is growing interest in determining prognostic biomarkers (severity, degree of development of PsA, extent of joint involvement in PsA, and development of cardiovascular disease), predictive biomarkers (response to treatment), and pharmacodynamics. The identification of biomarkers for PsA is important to enable early detection of patients with joint involvement and thus prevent progression. C-reactive protein (CRP) is a soluble biomarker of inflammation and cardiovascular risk. Levels are elevated in patients with psoriasis, PsA, and obese individuals. The use of etanercept decreases CRP levels significantly in patients of a normal weight with psoriasis and no associated PsA. Other soluble markers of PsA are IL6, which is elevated in patients with PsA regardless of CRP levels or erythrocyte sedimentation rate, and cartilage oligomeric matrix protein (COMP) as a marker of destruction of joint cartilage. RANKL and macrophage colony-stimulating factor have been identified as markers of bone erosion in PsA. The expression of dendritic cell-specific transmembrane protein in osteoclast precursors predicts progression to PsA in patients with psoriasis. In addition, the combination of the high-sensitivity CRP, osteoprotegerin (OPG), and MMP-3 soluble factors with the C-propeptide of type 2 collagen/collagen fragment neoepitopes Col2-3/4(long mono) ratio is useful for predicting which patients are at greatest risk of developing PsA. Metabolic syndrome has been found to be associated more frequently with patients with PsA, with adiponectin being the most relevant marker.

Bone Remodeling in Psoriatic Arthritis

Rheumatoid arthritis (RA) is a model of local and systemic effects of joint inflammation in skeletal tissue. The 3 forms described are bone loss affecting the subchondral bone and bone at the joint margins, periarticular osteopenia adjacent to the inflamed joints, and generalized osteoporosis involving the axial skeleton. Although all these have common factors, different mechanisms are involved in their pathogenesis, and so the strategies for preventing these losses will also be different. OPG is an essential cytokine in osteoclast differentiation and a key factor in RA erosion. Different studies conducted to assess the involvement of OPG in RA showed osteoclast precursor cells in regions of bone where pannus had formed. OPG is also found in fibroblasts of the synovium and in activated T cells derived from synovial tissue. These synovial cells can contribute directly to the expansion of osteoclast precursors and to the formation and activation of osteoclasts in regions of bone erosion in RA.

In PsA, radiologic follow-up has shown that the apparent control of joint inflammation with drugs such as sulfasalazine or MTX does not prevent bone destruction, which must therefore be the result of uncontrolled inflammation. In contrast, studies with anti-TNF drugs, such as the IMPACT with infliximab, or the study reported by Mease et al. with etanercept, have shown sustained benefit in disease control including radiologic progression. There have also been studies of predictors or bone loss, such as axial involvement and those that show substantial inflammation on diagnosis, suggesting that a more aggressive therapeutic approach from the start is beneficial. The recent study by Finzel et al. aimed to describe the behavior of erosions and osteophytes in 41 patients with PsA treated with MTX or anti-TNF agents, using assessments with computed microtomography at baseline and after 1 year. The results showed that the osteophytes progressed in both groups, even though disease activity and erosions were controlled. This is the first evidence that pathologic bone formation is not affected by antirheumatic treatments.

Screening and Diagnosis

Prevalence of Psoriatic Arthritis in Patients with Psoriasis

Through cohort studies, it has been possible to show that the psoriatic phenotype is determined by the classic HLA-C*06 susceptibility gene, which is associated with a more penetrative cutaneous form of the disease with less joint involvement, whereas the HLA-B*27 haplotype induces simultaneous joint and cutaneous involvement, with equivalent penetration of the cutaneous and articular form. The clinical implication of these results is that there are 2 populations of patients with arthritis. One the one hand, there are patients with early joint involvement, who are usually seen by the rheumatologist. On the other, there are patients with predominantly skin involvement and late joint involvement. These patients are usually seen initially by dermatologists. For this reason, it is important that the dermatologist is able to make an early diagnosis of joint involvement in patients with skin manifestations with a view to reducing the long-term morbidity in these patients. According to Haroon et al., up to 29% of patients seen by dermatologists have undiagnosed PsA. Moreover, this situation is made worse by the limited sensitivity of the current screening methods (Psoriasis Epidemiology Screening Project [PEST], Psoriatic Arthritis Screening and Evaluation [PASE], and Toronto Psoriatic Arthritis Screen [ToPAS]), especially for the detection of oligoarticular forms. Thus, the development of the Early Arthritis for Psoriatic Patients (EARP) survey may be useful for visits to the dermatologist as it only has 10 questions and has been shown to be more sensitive than previous instruments.
Screening and Criteria for Referral of Psoriatic Arthritis

Given that psoriasis presents on average 12 years before clinical joint involvement in 84% of patients with PsA, it is important that dermatologists can apply screening methods to patients with psoriasis to enable early detection of patients with incipient joint involvement. The screening questionnaires are highly specific but have poor sensitivity and are not very useful beyond the polyarticular forms. In contrast, they are useful in patients with severe psoriasis and a greater risk of arthritis. In the CONTEST study, a comparison was made of the PEST/ToPAS/PASE tests with the CASPAR criteria in order to assess their capacity for detecting psoriatic joint disease. According to this study, the PEST and ToPAS methods seem to be slightly better than the PASE method, but the differences were not statistically significant. 16

Another marker that has been considered as a method for detection of PsA is the degree of severity of psoriasis, as individuals with greater cutaneous involvement are those with subsequent joint involvement, although it should be remembered that the degree of skin involvement does not correlate with the severity of joint disease. 17 Other phenotype considerations are the presence of nail dystrophy, scalp lesions, or inverse psoriasis. 18

In any case, a patient should be referred to the rheumatologist when PsA is suspected for confirmation of diagnosis.

Diagnostic and Treatment of Early Psoriatic Arthritis

Disease progression is more marked in patients diagnosed more than 2 years earlier. 39 Therefore, early diagnosis of PsA is essential. Different studies show that the CASPAR classification criteria are more sensitive and specific than those of Moll and Wright for diagnosis of PsA. With these criteria, the disease can be classified despite the presence of rheumatoid factor and in absence of psoriasis if typical findings are present. Although their sensitivity is lower for established PsA, CASPAR criteria are valid as inclusion criteria for studies of early PsA. 40-43 Nevertheless, some patients with peripheral enthesitis as the only clinical manifestation may represent an undefined group of PsA in that they do not meet any of the classification criteria for spondyloarthropathy and are not well recognized in studies of PsA. 44

The use of diagnostic techniques such as bone scintigraphy can improve diagnosis in patients with early PsA and subclinical joint involvement. 45,46 Magnetic resonance imaging is more sensitive for soft tissues and bone inflammation than conventional X-rays and this technique may be relevant in the early diagnosis of inflammatory changes in the feet. 47,48 Finally, ultrasonography is a useful technique in the diagnosis and follow-up of enthesitis, which is under-diagnosed in some patients. 49

For an appropriate treatment, it is necessary to stratify the patients, establish the main manifestations, and determine disease severity. 50 Once this has been done, treatment guidelines are available based on systematic literature review and expert consensus. 24 From the economic point of view, both analgesics and nonbiologics decrease the expenditure due to disease in this group of patients. 52 Likewise, the use of anti-TNF agents in PsA with inadequate response to conventional treatment has shown acceptable results in terms of cost-effectiveness, 53 with good efficacy and no significant adverse effects. 54

Assessment and Follow-up of Psoriatic Arthritis

Different instruments have been developed to assess each of the clinical manifestations of PsA.

Recent studies have shown that peripheral joint damage is greater in RA than in PsA. However, quality-of-life and functionality measures show similar impact in both diseases. This has been attributed to skin involvement in patients with PsA. Therefore, assessment is not only necessary in clinical practice but also in clinical trials in PsA. 55 Different tools such as Psoriasis Area and Severity Index (PASI) and Psoriasis Severity Index (PSI) are available to objectively measure skin involvement. The modified Nail Psoriasis Severity Index (mNAPSI) is a validated tool for assessing nails. 56

Dactylitis can be measured by simply counting how many fingers are affected using grades of 0 to 3 according to severity, as was done in the IMPACT study. 57 In addition to this, the Leeds Dactylitis Index (LDI) is also useful in clinical trials. 58

For clinical enthesitis, in addition to the indices used in spondylitis, (Mander, Maastricht Ankylosing Spondylitis Enthesitis Score [MASES], Modified Gladman, Major/Berlin, Spondyloarthritis Research Consortium of Canada (SPARCC)), the Leeds Enthesitis Index (LEI), which includes 6 locations (epicondyle, femoral condyle and Achilles insertion on both limbs), has been developed for PsA. 59

For spinal assessments, measures validated for ankylosing spondylitis such as Bath AS disease activity index (BASDAI), Bath AS functional index (BASFI), and Bath AS radiology index (BASRI) are used. New specific measures, such as the Psoriatic Arthritis Spondylitis Radiology Index (PASRI) are also under development. 60

With regards the compound measures, recommended indices include the Psoriasis American College of Rheumatology (PsACR) score (which measures pain in 68 joints and inflammation in 66, with at least 3 of the following: acute phase reactants, patient pain assessment, physical assessment, and functional scale), 61,62 the Psoriatic Arthritis Joint Activity Index (PsAJAI) (which uses the same measures as for the PsACR but with a different weighting), and the Minimum Disease Activity (MDA) scale. 63 The Disease Activity Score (DAS) 28 is of note as an activity index (developed for RA, this is used in trials in psoriasis with multiple joint involvement) 64,65 and the Psoriatic Arthritis Disease Activity Score (PASDAS).

The DAS was used in studies of infliximab and etanercept, 66 although some authors do not recommend its use. 56

Among the new compound indices derived from the GRACE database, of particular note are the PASDAS (which attributes a weight to the usual outcome variables) 67 and the Arithmetic Mean of the Desirability Function (Arithmetic Mean of the Desirability Function [AMDF], which includes the PASI, Health Assessment Questionnaire [HAQ], PsA-specific Quality of Life [PsAQoL] as well as the usual measures).
In clinical practice, it is recommended to use the 68/66 number of painful and inflamed joints, skin assessment, assessment of dactylitis and enthesitis, spinal assessment if appropriate, and patient-reported assessments of function and quality of life.

Treatment: Optimization of Criteria, Goals, and Outcomes

Treatment Criteria and Goals

Treatment goals in PsA should focus on preventing pain and disability and maintaining quality of life, through the use of safe and ideally effective drugs in all aspects of the disease. The prevention of pain is linked to eliminating disease activity, that is, treating to target. Several different tools are available for measurement such as compound activity indices (Composite Psoriatic Disease Activity Index [CPDAI], PASDAS, AMQP), imaging criteria for ultrasound and magnetic resonance imaging, MDA, and remission measures.

To prevent disability, disease progression should be halted at a structural level, as measured using radiologic outcomes, with strict control of risk factors at a cardiovascular level (smoking habit, dyslipidemia, etc.). It is essential to start treatment early in the disease.

To assess the impact on quality of life, we can use questionnaires such as the Short Form (SF) 36, Dermatology Life Quality Index (DLQI), and Euroqol (EQ) 5D. We can also measure the impact on work, fatigue, or social integration.

In addition to the pharmacological therapies available, weight loss and smoking cessation are very effective patient-dependent treatments. With regards to the new therapies, one possibility would be to divide them according to their efficacy in osteolysis (anti-TNF, anti-RANKL, MTX, ustekinumab, ampremilast, anti-IL7, Janus Kinase [JAK] inhibitors) or bone formation (NSAIDs, Wnt pathway inhibitors), given that Wnt signaling is implicated in the process of bone formation, B-type natriuretic peptide [BNP] antagonist, anti-IL22 agents).

Update on Treatment of Psoriatic Arthritis

The currently approved treatments for the different presentations of PsA are NSAIDs, intraarticular steroids, DMARDs, and anti-TNF agents for peripheral arthritis; topical treatments, psoralsens, DMARDs, anti-TNF and anti-p40 agents for skin and nail involvement; NSAIDs, physiotherapy, and anti-TNF agents for axial involvement; and anti-TNF agents for dactylitis and enthesitis.27

In the European League Against Rheumatism (EULAR) recommendations for management of PsA, DMARDs are indicated in phases 1 and 2 of the disease and anti-TNF agents in phases 3 and 4.69

Traditional therapy is based on NSAIDs, corticosteroids, and DMARDs (sulfasalazine, MTX, leflunomide, cyclosporin, and antimalarial agents).62,70-72

Biological therapies that have shown to be effective according to both ACR and PASI include adalimumab, certolizumab, etanercept, golimumab, and infliximab.57,73,74

Some of the drugs that have been studied or are currently under study for PsA include IL1 inhibitors such as anakinra, which was not shown to be effective; inhibitors of costimulation of B and T lymphocytes such as alefacept o abatacept, which have a lower activity in the skin and poor results for patients who have failed anti-TNF therapy; anti-B-cell molecules, such as rituximab, which are reserved for special situations such as patients with concurrent lymphoma and PsA; phosphodiesterase 4 inhibitors, such as ampremilast, with good response in MTX-naive patients and a good safety profile; IL17 inhibitors, such as brodalumab, secukinumab, and ixekizumab, which have been shown to be effective essentially in skin and arthritis and only 39% of patients achieve ACR 20; IL6 inhibitors, such as tocilizumab, which do not show good results in PsA; IL12 and IL23 inhibitors such as ustekinumab, which obtain a good response in the skin and ACR 20 after 12 weeks in 43% of patients; and JAK I and II inhibitors, such as tofacitinib, which are approved for treatment of RA and are currently being investigated in phase 2 studies in PsA, with good results.

Different drugs have been shown to be effective in different domains of PsA such as enthesitis and dactylitis, but their ability to act on bone proliferation phenomena, which appear to be key in the pathogenic process, is not known.

Therapeutic Optimization of Psoriasis and Psoriatic Arthritis.

Recently, several articles have been published that report on new alternatives in the management of patients with psoriasis and/or PsA, as well as on combination treatments of new drugs. These combinations are discussed below.

Anti-TNF Agents

The combination of MTX with anti-TNF agents has been proposed as a good method for achieving better response in patients with severe or moderate psoriasis. In the study of simultaneous treatment with MTX and etanercept compared with etanercept and placebo,75 PASI75 was reached by a significantly greater proportion of patients treated with etanercept and placebo, both at week 12 and week 24. The proportion of patients with PASI50 and PASI70 was also greater in the combination group at weeks 12 and 24. Moreover, the improvements achieved at week 12 were maintained at week 24, when the etanercept dose was reduced. The safety and tolerability profile was acceptable in both treatment groups.

Combination treatment of adalimumab and MTX is able to reduce the immunogenicity of this anti-TNF agent, obtaining better outcomes with combination compared to adalimumab as monotherapy.75,76

In the cases of patients with psoriasis in treatment with infliximab who lose response, there is also the possibility of combining with conventional systemic therapies such as MTX. In the study conducted by Baranaukaitė et al.,77 the efficacy of infliximab plus MTX was compared with that of MTX alone. The authors reported PASI50 in 97.1% in patients treated with combination compared with 54.3% in those treated with MTX alone. In some cases, the addition of low doses of MTX (<7.5 mg week) is considered a good option.
for decreasing the rate of anti-infliximab antibodies and prolonging clinical efficacy.  

The use of anti-TNF agents in patients with RA has also been associated with a reduction in cardiovascular events, as well as a decrease in the number of myocardial infarctions in patients with psoriasis.

**Ustekinumab**

Ustekinumab has recently been shown to be effective and safe in the treatment of palmoplantar psoriasis in an open-label study, with a physician global assessment (PGA) score of 0 or 1 in 38% of patients at week 16. Of these, 6 of 9 patients (60%) reached the primary outcome at a dose of 90 mg, whereas only 1 patient of 10 achieved the outcome at a dose of 45 mg. The assessment at 24 weeks showed improvements in PGA score in 36%, while 56% had an improvement in DLQI and 33% in pain scores.

The use of ustekinumab in PsA was assessed in the PSUMMIT 1 and 2 trials. In the PSUMMIT 1 trial, patients who had previously been treated with DMARD received ustekinumab while the PSUMMIT 2 trial enrolled patients who had previously been treated with anti-TNF agents. Ustekinumab showed good results both for arthritis and psoriasis outcomes, although in the case of arthritis, the response occurred more slowly than in patients with psoriasis. In the assessment of treatment response in patients with dactylitis and enthesitis, both conditions improved with use of ustekinumab 45 mg and 90 mg.

**Janus Kinase Inhibitors**

Oral JAK inhibitors, such as tofacitinib, have been shown to be effective in the treatment of severe psoriasis in a double-blind, placebo-controlled study in which the efficacy of tofacitinib was assessed at 12 weeks, using a dose of 2 mg, 5 mg, and 15 mg twice daily. The results of the study showed that 25% of patients achieved PASI75 at 12 weeks with a dose of 2 mg, 40% with 5 mg, and 67% with 15 mg. Among the most frequent adverse effects were headache, which was reported more frequently at all 3 doses. The use of tofacitinib can induce anemia and neutropenia during the first 4 weeks of treatment, increased low-density lipoprotein and high-density lipoprotein cholesterol, increased muscle creatine kinase, and increased risk of infections, as seen in the phase 2 clinical trial.

**Ampremilast**

Ampremilast is a phosphodiesterase 4 inhibitor that has been shown to be effective in the treatment of moderate and severe psoriasis in a randomized, placebo-controlled, clinical trial. The doses used in the study were 10, 20, and 30 mg, administered twice a day. PASI75 at 6 weeks was attained in 6% in the placebo group, in 11% in the group treated with 10 mg, in 29% in the group treated with 20 mg, and in 41% in the group treated with 30 mg; the differences obtained were significant in the groups treated with 20 and 30 mg compared to the placebo-treated group. Among the noteworthy adverse effects were nausea, diarrhea, and headache.

The use of ampremilast in PsA has been compared with placebo with good outcomes; ACR 20 was obtained in 45.5% of patients treated with ampremilast 20 mg twice a day, in 35.8% of those treated with 40 mg/day, and in 11.8% of those treated with placebo.

**Anti-IL17 Drugs**

Secukinumab is an anti-IL17 antibody that has been shown to be effective in the treatment of PsA with good outcomes in a randomized placebo-controlled trial in which the use of secukinumab was associated with an ACR 20 in 39% of patients at week 6. The drug is well tolerated and has a low rate of adverse effects. Currently, other IL17 inhibitors have been shown to be effective in psoriasis (ixekizumab and brodalumab), but as yet no data are available on their efficacy in PsA.

**Cardiovascular Risk in Psoriatic Arthritis**

As is the case for RA, PsA is considered a disease of high cardiovascular risk, with a higher incidence of subclinical atherosclerosis and cardiovascular mortality. It is therefore important to detect cardiovascular risk factors in patients with PsA using risk tables adapted from the general population. Stratification of patients according to their cardiovascular risk enables intervention to reduce the impact risk factors may have in patients with PsA. In the European population, the Systematic Coronary Risk Evaluation (SCORE) tables can be used, with additional noninvasive measures such as carotid ultrasound able to further assist in predicting the actual cardiovascular risk in these patients.

**Experience in Multidisciplinary Units for Patients With Psoriatic Arthritis**

In a study conducted by dermatologists and rheumatologists published by Reich et al., 612 of the 1511 patients with psoriasis reported joint pain and of these 612, 422 were referred to rheumatologists, who confirmed PsA in 312 of them. This figure represents 20% of patients diagnosed with psoriasis.

The use of tools for the confirmation of diagnosis has been shown to improve the ability to detect joint involvement. Thus, the physical examination (which detected 10% peripheral involvement and 10% axial involvement) and the use of imaging techniques such as joint ultrasound and radiology increased that percentage to 60%. In conclusion, these authors advocate participation of both specialties in diagnosis and therapeutic decision making.

**Conclusions**

PsA is a type of progressive inflammation arthritis that is associated with psoriasis and that often leads to functional deterioration in affected patients. In recent years, numerous articles have been published on the pathogenetic mechanisms of psoriasis and PsA. Of particular note among the common mechanisms is the participation of TNF, IL12, IL23, and IL17, as well as the formation of neovessels in the joints. Moreover, activation of osteoclastogenesis occurs in PsA through activation of RANK by RANKL. Thus, in PsA, bone remodelling is a key phenomenon in which OPG participates.
The early detection of joint symptoms in patients with psoriasis is important because joint disease is reversible if appropriate treatment is initiated early; recently, anti-TNF agents have been used to reverse bone remodelling in PsA, something that cannot be achieved with MTX or sulfasalazine.

The early detection of PsA and referral to the rheumatologist are basic initiatives to prevent delays in starting treatment. Screening tools such as EARP can be of use in everyday clinical practice if validated in Spain. The existence of common pathogenetic mechanisms also facilitates using the same approach for psoriasis and PsA, as shown in the most recent clinical trials conducted with anti-IL12/IL23 agents.

Given the association of PsA and psoriasis with greater cardiovascular risk, there is a need for awareness and screening on the part of dermatologists and rheumatologists for such risk factors in patients, with a view to detect them and intervene early.

The high percentage of patients with psoriasis who present with initial forms of PsA undetected by dermatologists means it is important for those dedicated to the management of patients with psoriasis to learn about joint disease. Thus, collaboration between dermatologists and rheumatologists who work in multidisciplinary units for the management of patients with psoriasis and/or PsA would allow efforts to be optimized and their units to become centers of excellence, training, and reference. It would therefore be possible to make an early diagnosis of joint involvement, avoiding long-term sequelae and deterioration in quality of life of patients, and also to optimize the patient’s treatment once diagnosis has been made.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.adengl.2013.10.013.

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