Advantages in early recognition and treatment of psoriatic arthritis

Previously, the early diagnosis of psoriatic arthritis was not a priority, especially since there was an absence of drugs able to modify the course of the disease. The scenario has completely changed in the last few years as a result of the introduction of the anti-TNF-α-blocking agents, which control symptoms and signs of inflammation, and inhibit the progression of the structural joint damage. Recently, the CASPAR criteria have been proposed, which have demonstrated a sufficient performance in the early forms of the disease. In everyday clinical practice, these criteria can assist in recognizing early psoriatic arthritis, although the diagnosis should also be made if these are not met. To date, no evidence-based treatment strategies are available for early psoriatic arthritis. GRAPPA has recently proposed recommendations for the treatment of the various clinical manifestations of psoriatic disease. As part of these recommendations a grid was suggested for the degree of disease (mild, moderate and severe) for all the prevalent manifestations (peripheral arthritis, axial disease, enthesitis, dactylitis and skin and nail lesions). Such recommendations should also be followed for the management of early forms of psoriatic arthritis.

KEYWORDS: dactylitis ■ enthesitis ■ pharmacoeconomics ■ psoriasis ■ psoriatic arthritis ■ psoriatic disease ■ spondyloarthritis

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Psoriatic arthritis (PsA) is a heterogeneous chronic inflammatory disease characterized by a wide clinical spectrum and a variable course [1]. It can involve the peripheral joints, peripheral entheses, synovial sheaths of tendons, spine, skin and nails [1] and, occasionally, gut [2] and eye [3]. In addition, patients with PsA or psoriasis have an increased frequency of hypertension, hyperlipidemia, cardiovascular disease, insulin resistance, obesity, Type 2 diabetes and metabolic syndrome in comparison with the general population [4–7]. Recently, a new designation has been proposed with the aim to cover all these clinical situations: psoriatic disease [8–10].

Nowadays, PsA is classified in the spondyloarthritis (SpA) complex together with primary ankylosing spondylitis (AS), arthritis associated with inflammatory bowel disease, reactive arthritis and forms that fail to meet criteria for definite categories, which are labeled as undifferentiated SpA [11,12]. PsA shares with these diseases an association with the HLA B27 antigen, spinal involvement and extra-articular manifestations. In the past, PsA was considered a rare and mild disease. The prevalence of psoriasis in the general population has been estimated between 2 and 3%. The estimated prevalence of manifest PsA among patients with psoriasis has varied widely from 6 to 42%. A study from Sweden suggests that evident PsA occurs in about a third of patients with psoriasis [13]. If this is correct, then the prevalence of clinically evident PsA in the general population should be close to 1%. In the last 20 years, evidence has been gathered proving that PsA is deforming and destructive in 40–60% of patients with joint damage appearing in the first years of the disease course [14–22]. It is thought that approximately 20% of patients with PsA develop a serious destructive and disabling disease. Patients suffering from PsA have functional impairment, decreased quality of life and psychosocial disability, and are at increased risk of death compared with the general population [23,24].

Why should psoriatic arthritis be diagnosed early?

The diagnosis of PsA should be made in the early phases of the disease for three main reasons. The first, valid for every patient suffering from every disease, is the necessity to avoid unnecessary examinations and to avoid unhelpful and risky therapies [25]. Second, the major goals of the management (reduction of pain, improving function and quality of life, and inhibition of joint damage), can best be reached by early intervention [25–28]. Therapies for PsA have been inadequate till recently [29]. NSAIDs are useful in improving symptoms, but have no effect on the progression of radiographic joint damage. Local corticosteroid injections may be of great aid in patients with persistent mono- or oligo-arthritis,

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but systemic treatment is not supported by evidence. Traditional disease-modifying antirheumatic drugs (DMARDs), which are the second-line treatment, are employed in PsA to control symptoms, however there is no evidence that they slow the progression of the structural joint damage. The introduction of the TNF-α-blocking agents has changed the management of PsA. These drugs minimize signs and symptoms of inflammation, increase functional capacity and quality of life, and decrease the progression rate of the structural damage in peripheral joints [30–32]. The third reason is the reduction of costs of the disease [33]. Illness costs in PsA have been found to be high, even without the TNF-α inhibitors, and are not very different from those in other chronic inflammatory rheumatic diseases, such as rheumatoid arthritis (RA), AS and systemic lupus erythematosus [34–39]. A recent study from Hong Kong reported average annual direct and indirect costs of US$4141 and $3127 (2006), respectively [39]. Pain and function were significantly associated with costs, suggesting that treatments aiming to reduce pain and restore function are highly likely to decrease the costs incurred by patients with PsA. However, no patient was treated with TNF-α-blockers because these drugs are not within the Hong Kong government's reimbursement system and patients must pay for themselves to be treated with these drugs.

The cost–effectiveness studies on anti-TNF-α-blocking agents in PsA performed so far have demonstrated that these drugs are cost-effective for both the cutaneous and musculoskeletal manifestations of psoriatic disease [35,40–43]. Most of these studies have been carried out using data obtained from published international clinical trials [40–43] and one was carried out in a clinical practice setting [35]. In this study, 107 patients, from nine Italian rheumatology centers, with different forms of PsA showing inadeaquate response to conventional treatment, were administered anti-TNF-α agents, mainly etanercept [35]. Cost (expressed in Euros 2007) and utility (measured using EuroQoL) before and after the start of TNF-α therapy were evaluated with the purpose of estimating the incremental quality-adjusted life year (QALY) gained and of calculating the cost–effectiveness acceptability curve. The study was performed from the viewpoint of the community, the largest entity that can have a point of view and which includes the Italian third-party payer (the National Health System), patients and their families. After 12 months of anti-TNF-α therapy, there was a significant escalation of direct costs due to an increase of drug costs produced by anti-TNF-α agents that was only partially compensated by the reduction of indirect costs. In the last 6 months of 12 months of anti-TNF-α therapy, the direct costs increased by €5052, the costs for the Italian National Health System by €5044 and the social costs by €4638. However, a gain of 0.12 QALY produced a cost per QALY gained of €40,876 for the Italian National Health System and of €37,591 for the society. The acceptability curve demonstrated that there would be a 97% likelihood that anti-TNF-α therapy would be valued cost effective at the willingness-to-pay threshold of €60,000 per QALY gained suggested for Italy. One of the values of the Italian study was the demonstration that anti-TNF-α therapy is cost-effective in the short term in clinical practice.

How can psoriatic arthritis be diagnosed early?

There are no diagnostic criteria, only classification criteria for PsA [44]. Recently, new classification criteria, the Classification criteria for Psoriatic Arthritis (CASPAR) criteria, have been elaborated by experts from 30 worldwide rheumatologic centers (**Box 1**) [45]. A total of 588 patients with PsA and 536 controls suffering from other inflammatory joint diseases were evaluated. The new criteria showed a better specificity (98.7%) and sensitivity (91.4%) than those previously proposed. One value of the CASPAR criteria is that they permit the classification of the disease despite the lack of the typical psoriatic skin lesions if the characteristic features of PsA are present. Patients without skin lesions should necessarily have a first- or a second-degree relative with psoriasis. A major limitation of the CASPAR criteria could be the impossibility of their use in the classification of fresh-onset forms because these criteria were obtained from patients with long-lasting disease (mean disease duration: 12.5 years). Most recently, some study groups have evaluated the performance of the CASPAR criteria in cohorts of patients with early-onset PsA [22,46–48]. Chandran *et al.* have studied the performance of the CASPAR criteria at the first visit in 107 consecutive patients with early disease (disease duration: <2.5 years) and 181 with late disease (>2.5 years) [46]. A total of 106 (99.1%) of the first group and 176 (97.2%) of the second met the CASPAR criteria, indicating that these criteria can classify patients with early PsA. In the Swedish early PsA register, 134 of 183 patients with onset of symptoms within the last 2 years met the CASPAR criteria [22]. The low predictive value found was attributed to the

Box 1. The Classification Crieria for Psoriatic Arthritis criteria. Inflammatory articular disease (joint, spine or entheseal) with three or more points from the following five categories.

Psoriasis (one of a, b or c)
▪ **a.** Current psoriasis†: psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist
▪ **b.** Personal history of psoriasis: a history of psoriasis that may be obtained from patient, family doctor, dermatologist, rheumatologist or other qualified healthcare provider
▪ **c.** Family history of psoriasis: a history of psoriasis in a first- or second-degree relative according to patient report
Psoriatic nail dystrophy
▪ Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination
A negative test for rheumatoid factor
▪ By any method except latex, but preferably by ELISA or nephelometry, according to the local laboratory reference range
Dactylitis (one of a or b)
▪ **a.** Current: swelling of an entire digit ▪ **b.** History: a history of dactylitis recorded by a rheumatologist
Radiological evidence of juxta-articular new bone formation
▪ Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain x-rays of the hand or foot

†*Current psoriasis scores 2 whereas all other items score 1.*
Modified from Taylor W et al. [45].

incomplete radiological analysis that precluded the satisfaction of the criteria. In 44 patients with a disease duration of less than 12 months consecutively were examined in our outpatient clinic, the sensitivity of the CASPAR criteria was only 77.3% owing to the small proportion of patients meeting the radiologic criterion [47]. However, in the Italian multicenter study on early PsA in which 78 PsA patients and 68 suffering from other inflammatory arthritides with a disease duration of less than 12 months were studied, preliminary results showed sensitivity (91%) and specificity (97.1%) values similar to those of the CASPAR original paper [48].

The CASPAR criteria are not diagnostic criteria. In everyday clinical practice, the CASPAR criteria should be considered, but the diagnosis should also be made if these are not met. A diagnosis of early PsA should be considered every time a patient with psoriasis or a family history of psoriasis shows peripheral arthritis, especially if oligoarticular or involving the distal interphalangeal joints and/or peripheral enthesitis and/or tenosynovitis and/or dactylitis and/or inflammatory spinal pain [25].

The chronological definition of early PsA, taken from early RA, ranges from 6 to 24 months. In our early PsA clinic, to which dermatologists and general practitioners refer every patient with psoriasis suffering from musculoskeletal pain, we see with growing frequency patients with PsA of only a few months duration [25,47]. These patients are interesting for two reasons: they are often mono- oligo-symptomatic; they allow us to understand the exact chronology of the onset of events (i.e., knee synovitis as the first event, dactylitis after 5 days and heel enthesitis after 15 days). Such data cannot be obtained from patients with a disease duration of more than 1 year because they do not remember the exact time of the events of the early phases of their disease course.

Care should be taken in the differential diagnosis with other diseases, including osteoarthritis of the hand.

What is the role of the dermatologist in the early diagnosis of psoriatic arthritis?

In the majority of patients with PsA, the skin lesions appear before or at the same time as the musculoskeletal complaints. Therefore, the dermatologist has an exceptional opportunity to identify patients to be sent to the rheumatologist for an early diagnosis of PsA. However, a recent study from Germany, which analyzed 2009 patients with psoriasis from 13 dermatological hospitals and 129 dermatological private practices, showed that there are still a significant number of undiagnosed subjects suffering from PsA in developed

countries [49]. Actually, many dermatologists have time restrictions that make it impossible to have routine searching of musculoskeletal symptoms. With the aim of assisting the dermatologist, three screening tools have been proposed for the identification of the inflammatory manifestations of psoriatic disease to be filled in by the psoriatic patient in the dermatological waiting room or at home [50–52]. The three questionnaires differ in the number of questions, the population to be screened (patients with psoriasis in all three, but also the general population in one), sensitivity, specificity and positive- and negative-predictive values. None has been shown to be superior to the others. The GRAPPA group is studying this topic with the aim to propose the best tool [53]. It has been pointed out that a screening tool to be used in clinical practice should be different from an equivalent instrument for research purposes. The first should be highly sensitive while the second should be highly specific.

Can psoriatic arthritis have a subclinical course?

In the last few years, it has been established that each inflammatory lesion of PsA (joint synovitis, tenosynovitis, dactylitis, enthesitis, sacroiliitis and spondylitis) can develop without symptoms and signs being recognized by the patient and by the physician. Such patients can be considered as suffering from subclinical or occult PsA [54]. Their identification represents a further challenge for rheumatology.

In 1976, Harvie *et al.* studied 100 consecutive patients admitted to hospital due to severe psoriasis [55]. Erosions and sclerosis of the sacroiliac joints were found in 20 individuals, eight of whom were asymptomatic. De Filippis *et al.* evaluated by ultrasound the Achilles tendons and the flexor and extensor tendons of all fingers of both hands of 24 patients with psoriasis [56]. Abnormalities not detected at the clinical examination were found in 33% of cases. Recently, Gisondi *et al.* used ultrasound to investigate the presence of lower limb entheseal abnormalities in 30 patients with chronic plaque psoriasis without signs or symptoms of PsA, and in 30 control subjects [57]. The ultrasound findings were scored according to the Glasgow Ultrasound Enthesitis Scoring System (GUESS). Mean GUESS score was significantly higher in psoriatic patients compared with controls. Offidani *et al.* studied 25 asymptomatic patients with active nummular and/or plaque psoriasis without any arthritic signs and symptoms and 12 healthy control subjects by using MRI and standard radiographs [58]. Of the psoriatic patients, 68% showed at least a sign of arthritis (in particular capsular distension and periarticular bone edema) on MRI, while only 32% of the same group of patients were positive on standard x-rays. No control subject showed arthritic lesions. Two studies also evidenced that bone scintigraphy is able to disclose a subclinical joint involvement in more than 70% of patients with cutaneous psoriasis [59,60].

How should early psoriatic arthritis be treated?

Although it is generally recognized that early treatment may provide better results in the reduction of pain, improving function and quality of life, and inhibition of joint damage, few studies have been performed to test this assumption. Actually, it has not been demonstrated whether, as performed in RA, there is a window of opportunity in PsA for intervention at a phase of the disease course when tissue injury may still be reversible. Therefore, to date, no evidence-based treatment strategies are available for early PsA. However, recently, the GRAPPA group have suggested comprehensive recommendations, based on evidence from a literature review and consensus between rheumatologists and dermatologists, for the treatment of the various clinical manifestations of psoriatic disease [29,61–68]. Recently, two systematic reviews and meta-analyses of published randomized control trials (RCTs) examining the efficacy and safety of TNF-α inhibitors in the management of PsA were also published by Saad *et al.* [69] and Ravindran *et al.* [70]. In the second review, DMARDs were also considered.

One value of the GRAPPA recommendations is that a grid was suggested for the degree of disease (mild, moderate and severe) for all the prevalent manifestations (peripheral arthritis, axial disease, enthesitis, dactylitis and skin and nail lesions) [68]. Such recommendations should also be followed when approaching management of the early forms of PsA [27].

Peripheral arthritis

The treatment of patients with exclusively or prevalent peripheral arthritis include NSAIDs, intra-articular glucocorticoid injections, DMARDs and anti-TNF-α agents. An update on the treatment of peripheral arthritis has recently appeared [71].

NSAIDs

NSAIDs are widely used for the management of symptoms of peripheral arthritis. RCTs are limited but support their efficacy [72,73]. No study has assessed the efficacy of COX-2-specific inhibitors.

NSAIDs have no effect on psoriasis and there are descriptions of individual cases of aggravation of the skin lesions after the start of therapy [74,75].

Corticosteroids

Intra-articular corticosteroid injections can be very useful in the treatment of persistent mono- or oligo-arthritis if attention is paid to avoid injection through the overlying psoriatic lesions.

Although commonly utilized by rheumatologists, there are no RCT studies on systemic glucocorticoids in peripheral arthritis. Their use is not recommended and should be considered only in particular situations, and not chronically because of the risk of causing a flare of the skin disease on withdrawal [76].

Traditional DMARDs

Only four traditional DMARDs are recommended for the management of peripheral arthritis: methotrexate (MTX), leflunomide (LEF), sulphasalazine (SSZ) and cyclosporine (CsA).

Methotrexate

Despite evidence of efficacy only being provided by two small RCTs [77,78], MTX is probably the most extensively used DMARD in PsA because of its effectiveness on the skin and joint manifestations of psoriatic disease and its low cost. Three recent studies [79–81] and an editorial [82] have called new attention to the role of MTX in the management of PsA, especially in the early phase of the disease course. Scarpa and coworkers performed a 6-month RCT on 35 patients with early PsA on NSAID therapy [79]. In the first group, NSAID therapy was given alone during the initial 3 months and together with MTX in the following 3 months. The second group was administered NSAID/MTX combination therapy for the whole 6-month period. In both groups, there was a significant amelioration of all variables at 3 and 6 months. However, the second group showed a faster and more evident response only on the count of swollen and tender joints and/or entheses, suggesting partial and incomplete control of the pathogenetic process of PsA by MTX.

Chandran *et al.* have evaluated all patients treated with MTX for at least 24 months between 1994 and 2004 [80]. Patients had a shorter duration of disease and were administered higher doses of MTX compared with their previous study [83]. The progression of radiographic peripheral joint damage assessed by the Steinbrocker method and a 40% or higher reduction of actively inflamed joints were the primary outcome measures. At 24 months, the mean increase in radiographic damage score was 1.5 and the clinical outcome measure was met by 68% of patients. Compared with their previous study [83], there was a trend for a better clinical response and a milder progression of joint destruction, suggesting that MTX should be given earlier in the disease course when joint damage is mild and at higher doses.

Heiberg and coworkers compared the response to MTX monotherapy with anti-TNF-α agents within a real-life clinical setting in a longitudinal and observational study [81]. The adjusted changes of most parameters at 6 months were significantly larger in the anti-TNF-α group, suggesting a superior clinical improvement compared with MTX monotherapy.

Leflunomide

Leflunomide has been studied in three open studies [84–86] and in one double-blind, randomized, placebo-controlled trial [87]. In the latter, 191 patients with active PsA and psoriasis were randomized to receive LEF or placebo for 24 weeks. At the end of the study, 58.8% of the LEF-treated and 29.7% of the placebo-treated patients were classified as responders by the Psoriatic Arthritis Response Criteria (PsARC), which was the primary efficacy end point. A significantly higher proportion of patients achieved the ACR20 response criteria and had significant quality of life, target lesion and psoriasis area and severity index (PASI) score improvements. Treatment was relatively well-tolerated with a frequency of adverse events similar to that in RA. More patients on LEF than placebo had to be withdrawn from treatment due to side-effects. Malesci *et al.* have compared the safety profile of LEF and MTX in a 2-year retrospective analysis of PsA patients treated in daily clinical practice [86]. A total of 42 patients were treated with LEF and 44 with MTX. At 24 months, the cumulative survival rate of patients remaining on therapy was 54.9% for LEF and 57.0% for MTX ($p > 0.05$). LEF showed a manageable safety profile even through a higher discontinuation rate for toxicity than MTX (29.2 vs 10.8%; $p = 0.07$) was seen.

Cyclosporine

No RCT comparing CsA with placebo exists. However, some published prospective control studies have compared CsA with other DMARDs [88–91].

A multicenter Italian study evaluated the 24-week efficacy and safety of CsA (3 mg/kg/day) versus SSZ and symptomatic therapy (ST) alone (NSAID, analgesic and/or prednisone ≤5 mg/day) in the treatment of PsA

with or without axial involvement [90]. Patients with CsA and SSZ were permitted to take a stable dose of ST. CsA was more effective than ST and SSZ in the treatment of PsA. However, the efficacy of CsA and SSZ on axial manifestations was not superior to that of ST. The efficacy of CsA on peripheral arthritis was apparent as early as the eighth week of treatment, while the effect of SSZ was evident only after 24 weeks.

In the study by Fraser and coworkers, 72 patients with active PsA with an incomplete response to MTX were randomized to receive either CsA or placebo [91]. Patients of the MTX/CsA arm had a significant improvement in swollen joint count, C-reactive protein, PASI and synovitis detected by ultrasound in comparison with the MTX/placebo group.

Another Italian study evaluated the effect of a 2-year CsA treatment on peripheral joint damage in PsA [92]. CsA was able to control the progression of radiological joint damage in 60% of the patients. Normal levels of the soluble IL-2 receptor after 6 months had a prognostic value for good radiological outcome.

Recently, we treated 11 patients with PsA with etanercept plus CsA, who had had a good response to etanercept for the rheumatological manifestations but not the skin lesions [93]. A significant improvement of psoriasis was obtained in these patients, avoiding the need to switch to another anti-TNF-α agent.

As far as the side-effects are concerned, the most common in the Italian study was a mild, reversible kidney dysfunction [90]. Therapy should be discontinued if the serum creatinine level is persistently elevated 30% above the baseline level.

Sulfasalazine

A systematic Cochrane review analyzed six RCTs comparing SSZ with placebo [94]. These studies have demonstrated a good clinical efficacy on peripheral arthritis of PsA [95–100]. The main limiting factor of SSZ is its gastrointestinal intolerance, accounting for a high rate of discontinuation. In the largest RCT to date, SSZ was more effective than placebo with a small size effect [99]. In the peripheral arthritis group, 59% of the patients in the active group and 42.7% of those in the placebo arm showed a clinical response.

In the Italian trial comparing SSZ, CsA and ST, no significant differences were found between SSZ and ST on tender and swollen joint count, joint pain, tenderness score, pain score and patient and physician global disease assessment [90]. In a case–control study, SSZ treatment showed partial beneficial effects over the control group and was associated with a high frequency of side-effects [101]. No change in the radiographic score was observed in both groups at 24 months.

TNF-α inhibitors

To date, four anti-TNF-α agents have been approved for the management of PsA: etanercept, infliximab, adalimumab and golimumab.

Etanercept

Two placebo-controlled randomized trials on etanercept in PsA have been completed [30,102]. The older study included 60 patients with active PsA and lasted 12 weeks [102]. A significantly higher percentage of patients treated with etanercept met the PsARC and ACR20 response criteria compared with patients treated with placebo. A significant response was also observed for the cutaneous lesions.

In the most recent study on 205 patients, those treated with etanercept were significantly more likely than placebo-treated patients to achieve both the PsARC (72 vs 31%) and ACR20 (59 vs 15%) criteria and to have better target lesion scores (32 vs 15%) after the first 12 weeks of treatment [30]. These results were maintained at 24 and 48 weeks. Besides, etanercept was able to slow radiographic evolution at 1 year. The modified total Sharp score was -0.03 units in the etanercept-treated patients and +1.00 unit in the placebo-treated patients. Of the 205 patients, 169 entered the open-label extension phase of the study. Of the patients originally randomized to etanercept, 68% achieved the ACR20, 84% the PsARC and 62% PASI50 after 2 years of therapy [103]. Patients originally on placebo had similar results after 12 weeks of etanercept treatment that were maintained at 48 weeks (63, 80 and 73%, respectively). Radiographic progression continued to be inhibited in the etanercept/etanercept patients (this group is is formed by patients who were on etanercept in both phases of the study; mean modified total Sharp score: -0.38 at 48 weeks) and was inhibited in the placebo/etanercept group when patients began receiving etanercept (mean adjusted change in modified total Sharp score: -0.22 from 1 to 2 years). Etanercept was well tolerated in these studies [30,102,103].

Lately, Anandarajah *et al.* have found a fast drop of osteoclast precursors and overall improvement in bone marrow edema on gadolinium-enhanced MRI in patients suffering from PsA treated with

etanercept giving reasons for the antierosive effect of anti-TNF-α therapy in PsA [104].

Infliximab

Two randomized, double-blind placebo-controlled trials, the first called Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT) [105] and the second IMPACT 2 [106], have assessed efficacy and safety of the chimeric monoclonal antibody infliximab in PsA.

The IMPACT trial admitted 104 patients with active PsA (at least five tender and swollen joints) refractory to at least one DMARD [105]. At week 16, a significantly higher percentage of patients on infliximab (65%) met ACR20 in comparison with 10% of patients on placebo. The percentage of infliximab-treated patients remained high during the 50 weeks of the study. Patients from the placebo group achieved an ACR response rate at week 50, similar to those of patients originally treated with infliximab after the crossover to infliximab at week 16. Comparable results were seen with the secondary end points: ACR50, ACR70, PsARC and PASI. Radiographic joint damage progression was slowed during the 50 weeks [31]. The long-term open-label extension phase of this study over 2 years showed continuous improvement of skin and joint symptoms, inhibition of radiographic progression and a positive benefit–risk ratio [107].

IMPACT 2 included 200 patients with active PsA refractory to DMARD therapy [106]. The primary end point was the ACR20 and secondary end points included PsARC, PASI, enthesitis and dactylitis. At week 14, 58% of patients on infliximab and 11% of those on placebo achieved an ACR20 response and 77% of infliximab patients and 27% of placebo patients achieved PsARC (both $p < 0.001$). These results were preserved during the 24 weeks of the study. Fewer patients on infliximab had enthesitis and dactylitis than those on placebo. Infliximab enhanced physical function and health-related quality of life [108]. The drug retained a high degree of clinical efficacy during the 12 months of therapy [109] and reduced radiographic joint damage progression as early as 6 months after the start of therapy and in the subsequent 6 months [110]. Treatment with infliximab was well-tolerated in both trials.

Adalimumab

The efficacy of adalimumab in comparison with placebo in the treatment of active PsA was first evaluated in Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT), a 24-week RCT [32]. A total of 315 patients who were moderate-to-severe PsA intolerant or not responsive to NSAIDs were randomized to receive 40 mg of adalimumab or placebo subcutaneously every other week for 24 weeks. At week 24, 57% of the patients treated with adalimumab achieved an ACR20 response versus 15% of the patients in the placebo group. Among patients with psoriasis involving 3% or more of body surface area at baseline, PASI75 was achieved at week 24 by 59% of adalimumab-treated patients and 1% of the placebo-treated patients. Patients treated with adalimumab had a reduced progression of radiographic joint damage (mean change in modified Sharp score: -0.2) in comparison with the patients on placebo (mean change in modified Sharp score: +1.0) and a significant improvement in the disability and quality of life measures. Of the 315 patients, 285 were afterwards admitted to the 120-week open-label extension phase of the trial [111,112]. Compared with the 24-week double-blind phase, improvements in joint and skin diseases and inhibition of radiographic progression were retained in the majority of patients during the 2 years of treatment. Adalimumab was generally safe and well tolerated all through the study.

The results of ADEPT were confirmed by another 12-week placebo-controlled RCT involving patients refractory to previous DMARD therapy [113]. A recent prospective placebo-controlled RCT has evaluated the influence of adalimumab treatment on synovial tissue [114]. A marked reduction in T-cell infiltration and MMP-3 expression was evident in patients treated with adalimumab, suggesting that these factors could be used as biomarkers in future studies on PsA.

Golimumab

Golimumab, a human monoclonal antibody with high specificity and affinity for the soluble and transmembrane TNF-α, is the fourth anti-TNF-α-blocker approved for the management of PsA.

In Golimumab – a Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody (GO-REVEAL) study, 405 adult patients suffering from PsA and with at least three swollen joints were randomized to receive golimumab 50 mg, golimumab 100 mg or placebo subcutaneously every 4 weeks for 20 weeks [115]. At week 14, the ACR20 response (the primary end point) was achieved by 48% of patients on 50 mg, 45% on 100 mg and 9% on placebo ($p < 0.001$). Of those patients who had at least 3% of body area affected by psoriasis at baseline, 40% on golimumab 50 mg, 58% on 100 mg and 3%

on placebo had at least 75% improvement of the PASI ($p < 0.001$). A significant improvement was also seen for the other major secondary end points, including physical function, quality of life, nails, enthesitis and dactylitis. The efficacy of golimumab was sustained during the 24 weeks and the safety profile was good.

Comparison & switching among TNF-α-blockers

In the meta-analysis by Saad *et al.* there were no differences in efficacy of the first three available anti-TNF-α agents (infliximab, ertanercept and adalimumab) in comparison with placebo as measured by PsARC and ACR20, ACR50 and ACR70 response criteria [69]. It has been suggested that in clinical practice patients should be free to choose between the flexibility of subcutaneous self-injections or bimonthly intravenous injections [116].

Similarly to patients with RA and AS, patients with PsA failing one of the TNF-α inhibitors because of adverse events or inefficacy can gain advantages from switching to another anti-TNF-α agent [117].

Therapeutic approach

The disease of patients with exclusively or prevalent peripheral arthritis should be stratified according to the GRAPPA categories of 'mild', 'moderate' and 'severe' [68]. In addition, risk factors associated with a poor prognosis related to disease progression and damage should be identified. These include: a high number of joints with effusion, involvement of more than five joints, a high level of past medication and the presence of damaged joints either clinically or on x-rays, loss of function and reduced quality of life [118].

Patients with mild disease, especially in the absence of risk factors for disease progression, should be treated with NSAIDs or intra-articular glucocorticoid injections. Those not responding to this first level should be given DMARDs. Patients with moderate and severe disease should be treated with traditional DMARDs. The choice of the first DMARD should be made individually. Combination therapy with different DMARDs should be reserved to patients failing to respond to a single DMARD or to those showing joint damage progression despite treatment. Patients unsuccessfully treated with at least one DMARD should be treated with TNF-α-blocking agents. As addressed before, all three presently currently available anti-TNF-α agents (infliximab, etanercept and adalimumab) are equally effective for the treatment of peripheral arthritis and for the reduction or prevention of joint damage [69,116]. Golimumab seems to be equally effective but data on its action on joint damage progression are forthcoming. Patients with a poor prognosis could be treated with anti-TNF-α drugs without trying a DMARD. In addition, the prescription of anti-TNF-α agents before DMARDs should be more common in the near future because it has been demonstrated that anti-TNF-α therapy is already cost-effective in the first year of therapy [35]. However, it should be explained to the patients, especially those with axial involvement, that although TNF-blockers prevent erosion, they do not prevent ankylosis and bone formation.

Axial disease

Axial involvement is frequent in PsA and it is seen on radiographs of 30–50% of cases. Differences found with primary AS include asymmetric sacroiliitis, asymmetric and nonmarginal syndesmophytes, and a more frequent involvement of the cervical spine [119]. Clinically, patients with psoriatic spondylitis complain of less pain and have less limitation of movement than patients with primary AS [119]. Despite these differences, the International Spondyloarthritis Interobserver Reliability Exercise (INSPIRE) study has shown that measures used to assess spinal mobility in primary AS are also reliable for psoriatic spondylitis [120]. GRAPPA has agreed by consensus that the recommendations proposed by ASAS and EULAR for the management of primary AS [121] should also be used for psoriatic spondylitis [68].

Therapeutic approach

Patients with mild-to-moderate disease should receive education, initiate exercise treatment and be given NSAIDs. In patients with increased gastrointestinal risk, a selective COX-2 inhibitor or a nonselective NSAID plus a gastroprotective agent could be used. Simple analgesics and corticosteroid injections in the sacroiliac joints could be useful. The use of systemic corticosteroids and DMARDs, such as SSZ and MTX, for axial disease is not supported by evidence. Patients with moderate-to-severe disease failing to respond to this therapy should be considered for anti-TNF-α therapy. Insufficient data support the use of bisphosphonates such as pamidronate for the management of active axial involvement [122]. These drugs can be useful for the treatment of osteoporosis in PsA patients.

Peripheral enthesitis

Peripheral enthesitis is a frequent clinical manifestation of PsA and SpA [123]. Entheses of the

lower limbs are more frequently involved than those of the upper limbs and heel enthesitis is the most frequent. Peripheral enthesitis produces pain but may also be asymptomatic and only revealed by imaging techniques such as ultrasonography, especially if combined with power Doppler [57] and MRI [124]. It may also be the only clinically apparent manifestation of the disease [125]. Entheseal pain may be mild but also severe and disabling. GRAPPA has developed criteria for 'mild', 'moderate' and 'severe' enthesitis.

Therapeutic approach

Although widely used in peripheral enthesitis, NSAIDs and local steroid injections have not been evaluated in controlled trials or in case series. SSZ and MTX were found to be effective on enthesitis in controlled studies in PsA [99] and AS [126] patients, respectively. In placebo-controlled trials on anti-TNF-α drugs, peripheral enthesitis improved in patients on the active treatment [32,105,106,113].

Mild peripheral enthesitis can be treated with NSAIDs, activity modification, supportive and accommodative orthoses, physiotherapy and local steroid injections. Moderate cases can be treated with SSZ and/or MTX and severe forms with anti-TNF-α agents.

Dactylitis

Dactylitis or 'sausage-shaped' digit is a hallmark clinical manifestation of SpA and is especially frequent in PsA, occurring in 16–48% of patients [127]. Dactylitis is due to a combination of flexor tenosynovitis, articular synovitis, enthesitis and soft-tissue edema [128]. Like peripheral enthesitis, dactylitis can be the only clinically apparent manifestation of PsA [125]. GRAPPA has developed criteria for 'mild', 'moderate' and 'severe' dactylitis.

Therapeutic approach

No controlled trial has evaluated the use of NSAIDs and local corticosteroid injections for dactylitis. DMARDs such as SSZ, CsA and LEF have shown some efficacy. Of the three available TNF-α inhibitors, infliximab and adalimumab have been studied in dactylitis. In the IMPACT [105] and IMPACT 2 [106] trials, there was a significant improvement of dactylitis in the active group compared with the placebo group. In the two placebo-controlled trials on adalimumab there was a significant improvement of dactylitis in the adalimumab group compared with placebo [32,113].

Mild dactylitis should be treated with NSAIDs and corticosteroid local injections. Moderate or unresponsive forms could benefit from DMARDs (SSZ, CsA, MTX and LEF). Patients with severe or resistant forms should be administered anti-TNF-α agents.

Psoriasis & nail disease

Management of skin and nail lesions are beyond the scope of this review. The reader is directed to the systematic reviews on the topics by GRAPPA [65–67] and the recently published guidelines for the treatment of psoriasis with biologics [129].

Conclusion

Until recently, the early diagnosis of PsA has not been a priority, especially given the absence of drugs able to modify the disease course. The scenario has completely changed with the introduction of the TNF-α-blockers. These drugs are more effective than traditional DMARDs on symptoms and signs of the disease, improve function and quality of life, and inhibit the structural damage in peripheral joints [30–32].

Diagnostic criteria for PsA are lacking. Recently, new classification criteria called CASPAR have been proposed [45]. These criteria have been shown to be sufficiently valid in the classification of the early forms and can assist in recognizing the early PsA, but the diagnosis should also be made if these are not met. Since in the majority of patients the skin lesions precede or appear simultaneously with the musculoskeletal manifestations, dermatologists are in the best position to screen patients with psoriasis for an early diagnosis of PsA. Some screening tools have been suggested for the identification of the musculoskeletal manifestations of psoriatic disease to be filled in by the patient with psoriasis in the dermatology waiting room or at home [50–52].

After making the diagnosis the patient should be treated effectively. To date, no evidence-based strategies are available for early PsA. While awaiting the results of RCTs specifically addressing this topic, patients should be treated according to the recommendations suggested by GRAPPA [68]. These require the staging of the musculoskeletal disease with the aim of establishing the prevalent disease manifestation (peripheral arthritis, peripheral enthesitis, axial involvement and dactylitis) and the degree of the disease (mild, moderate or severe).

Future perspective

The introduction of anti-TNF therapy has changed the management of PsA. To date, the recommendations proposed for the use of

TNF-blockers affirm that these drugs should be used after the failure of traditional drugs. Consequently, the early forms of PsA can be treated with these drugs only with a delay, making early recognition of the disease less useful. If in PsA there is a window of opportunity for intervention at a stage when tissue injury may still be reversible, the early use of TNF-α inhibitors should result in a great benefit for the patient. This scenario is highly likely to happen in the near future. One possible criticism to this approach is the heterogeneous clinical spectrum of PsA, which include self-limiting forms. Also, the early self-limiting forms could benefit from the early treatment with anti-TNF-α agents that could be administrated only for a short period of time, avoiding the negative aspect of the high costs of long-term treatment.

Financial & competing interests disclosure

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

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

Executive summary

- Psoriatic arthritis (PsA) should be diagnosed early because the major goals of management (i.e., reduction of pain, improvement of function and inhibition of joint damage) can best be reached by early intervention.
- The introduction of the TNFα-blocking agents has changed the management of PsA. These drugs minimize signs and symptoms of inflammation, increase functional capacity and quality of life, and decrease the progression rate of the structural damage in peripheral joints. In the randomized control studies performed so far there were no more adverse events in the treatment groups than in the placebo groups.
- There are no diagnostic criteria but only classification criteria for PsA. Recently, new classification criteria, the CASPAR criteria, have been proposed that can assist in recognizing early PsA. However, the diagnosis also should be made if these are not met.
- To date, no evidence-based treatment strategies are available for early PsA. GRAPPA has recently proposed recommendations for the treatment of all forms of PsA, which should also be followed when approaching the management of the early forms.

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