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Early psoriatic arthritis: should we treat it in the same way as we treat rheumatoid arthritis?

Joint damage predicts functional limitation and mortality in psoriatic arthritis patients, but evidence from cohort studies supports the idea that early diagnosis and treatment are beneficial. Given the revolution in the treatment of rheumatoid arthritis, treating to targets and close control have become attractive concepts in the clinical management of psoriatic arthritis. The evidence in favor of the use of conventional disease modifying antirheumatic drugs is weak, but observational study results suggest that the early use of anti-TNF drugs should be encouraged. Ustekinumab and apremilast are useful alternatives for patients failing on previous anti-TNF therapy, and ampremilast can also be used for the first-line treatment of selected cases (i.e., patients who cannot tolerate other first-line treatments).

Keywords: biological drugs • psoriatic arthritis • tight control • treat to target

Fabiola Atzeni*[,1], Ignazio F Masala[2], Laura Boccassini[3] & Piercarlo Sarzi-Puttini[3]

[1]IRCCS Galeazzi Orthopedic Institute, Milan, Italy
[2]Orthopedic Unit, SantissimaTrinità Hospital, Cagliari, Italy
[3]Rheumatology Unit, L Sacco University Hospital, Via GB Grassi 74, 20127 Milano, Italy
*Author for correspondence:
Tel.: +39 02 39042489
Fax: +39 02 39043454
atzenifabiola@hotmail.com

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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Assess the diagnosis and clinical implications of psoriatic arthritis
- Distinguish treatment target criteria for psoriatic arthritis
- Evaluate traditional treatments of psoriatic arthritis
- Identify mechanisms of action of novel biologic agents that may be used to treat patients with psoriatic arthritis

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***CME author: Charles P. Vega, MD**, Clinical Professor of Family Medicine, University of California, Irvine*
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Authors & credentials:
***Fabiola Atzeni, MD, PhD**, IRCCS Galeazzi Orthopedic Institute, Milan, Italy*
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***Ignazio Francesco Masala, MD**, Orthopedic Unit, Santissima Trinità Hospital, Cagliari, Italy*
Disclosure: Ignazio Francesco Masala, MD, has disclosed no relevant financial relationships.
***Laura Boccassini, MD**, Rheumatology Unit, L. Sacco University Hospital, Milan, Italy*
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***Piercarlo Sarzi-Puttini, MD**, Rheumatology Unit, L. Sacco University Hospital, Milan, Italy*
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Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy of unknown etiology that affects as many as 30% of patients with psoriasis [1]. It belongs to the rheumatic disease family of the spondyloarthritis (SpA), which also includes entero-associated arthritis, reactive arthritis, ankylosing spondylitis and undifferentiated SpA [2], all of which are associated with arthritis of the axial skeleton, inflammatory back pain, uveitis, dermatological and gastroenterological involvement, and HLA-B27 [3]. Its various manifestations include mono-oligoarthritis, an erosive and destructive polyarthritis that is indistinguishable from rheumatoid arthritis [RA], spondyloarthropathy with axial involvement and enthesitis. Often progressively erosive joint destruction leads to cortical bone resorption (as in the case of RA), but it may be morphologically characterized by bony spurs known as enthesophytes [1]. All PsA patients must have psoriasis by definition and, although arthritis may precede psoriasis by many years, psoriasis usually appears before PsA. The very frequent nail lesions can help to distinguish patients with PsA from those with RA or psoriatic patients without arthritis as they occur in 40–45% of the latter, and in about 87% of PsA patients. It has recently been confirmed that PsA is a chronic inflammatory arthritis associated with increased cardiovascular mortality [3,4]. It is frequently associated with obesity, diabetes, dyslipidemia, hypertension, accelerated atherosclerosis, the risk of which may be increased by the chronic inflammatory state because of the unbalanced secretion of pro- and anti-inflammatory cytokines such as TNF-α, IL-1β, IL-10 and interferon [5]. Furthermore, in a 2-year prospective, observational study of 32 PsA patients classified on the basis of the CASPAR criteria and treated with anti-TNF drugs, Ramonda *et al.* [6] found that despite an improvement in the DAS 28/CRP score ($p < 0.0005$) and lower low-density lipoprotein cholesterol ($p < 0.013$) and triglyceride levels ($p < 0.036$), there was a significant increase in both mean intima-media thickness ($p < 0.0005$) and mean maximum intima-media thickness ($p < 0.0005$). These data suggest that although anti-TNF drugs can suppress inflammation and decrease disease activity, they cannot prevent the progression of atherosclerosis in PsA [6].

Furthermore, although radiographic damage may be less in PsA patients than in those with RA, it has a similar impact on functional ability and quality of life in patients with a comparable disease duration [7].

The aim of this review is to describe early PsA and the rationale for diagnosing and treating it in the same way as early RA.

Early psoriatic arthritis

A diagnosis of PsA within 6–24 months of the onset of the first articular episode indicates 'early PsA' [8], and recognizing the disease in this phase leads to better outcomes because established joint damage predicts both functional limitation and mortality [9,10]. In other words, as in the case of RA, there is a 'window of opportunity' for intervention at a stage when tissue injury may still be reversible.

Nevertheless, patients with PsA can develop early erosive disease: a study of patients within 5 months of symptom onset found that 27% developed erosive disease within 2 years, even though the majority had been treated with nonbiological disease modifying anti-rheumatic drugs (DMARDs) [11]. The findings of this study confirm that PsA is a chronic, progressive disease in the majority of patients and that, although they lead to clinical improvement, DMARDs have little effect on joint damage [11]. In a study of 35 patients with early PsA oligoarthritis taking NSAIDs on demand, who

were randomized to continue with full-dose NSAIDs for the following 3 months before adding methotrexate (MTX) for a further three, or to take a combination of NSAIDs and MTX for the entire 6–month period [12], it was found that the combined therapy lead to significantly better improvement in tender and swollen joint counts after the first 3 months, but there were no differences in patient global assessment, physician global assessment, visual analog scale (VAS) results, the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels at the end of the study period [12]. However, this study had the limitations of not using X-rays and the fact that it only included patients with oligoarthritis, and so its impact is difficult to define [12].

Tillett *et al.* [13] found that symptom duration for >1 year before diagnosis was significantly associated with an increased Health Assessment Questionnaire (HAQ) scores in 267 PsA patients. Similarly, Gladman *et al.* [14] showed that patients followed-up prospectively within 2 years of diagnosis had significantly less damage/radiographic progression than those first seen more than 2 years after disease diagnosis, thus suggesting that patients with PsA should be treated earlier [14]. Haroon *et al.* [15] found that more than 6 months before a first rheumatological examination was associated with the development of peripheral joint erosions (odds ratio [OR]: 4.25; $p < 0.001$) and worse HAQ scores (OR: 2.2; $p < 0.004$). A recent follow-up study of the Swedish Early Psoriatic Arthritis Register found that a short delay between onset of symptoms and diagnosis was an independent predictor of attaining minimal disease activity (MDA) after 5 years' follow-up [16]. In conclusion, although there are no randomized controlled trial (RCT) studies, data from cohort studies support the idea that early diagnosis and treatment are effective.

It is important to note severe arthritis can be observed in the absence of psoriasis, whereas very mild arthritis may occur in patients with moderate or severe psoriasis. Consequently, a high degree of clinical suspicion, the screening of patients with psoriasis and combined evaluations by dermatologists and rheumatologists are essential for diagnosis.

Treating to target & tight control in PsA

Given the revolution in the treatment of RA, treating to target has become attractive in the clinical management of many rheumatic diseases. This strategy involves treating patients aggressively enough to reach and maintain explicitly specified and sequentially measured goals, such as remission or low disease activity. In 2011, the EULAR published a literature review examining the evidence in favor of treating SpA to target [17]. Although the search did not reveal any trials comparing a treat-to-target approach with another or no strategy, it did provide indirect evidence regarding optimized treatment [17,18]. The review considered studies in which therapy was altered on the basis of achieving a target, including five involving PsA patients [16].

The protocols of three large RCTs of infliximab [19], adalimumab [20] and golimumab [21] included plans to escalate treatment if prespecified targets were not met. In the double-blind part of the adalimumab and golimumab trials, the patients could be randomized to increase therapy if they did not show a reduction in joint counts of respectively 20 [19] and 10% [20].

In the IMPACT-2 study of 15 patients, the dose could be increased to 10 mg/kg after 38 weeks in those who failed to respond or in whom the drug lost its effect during the course of the study [19]. Nine of the 15 patients achieved an ACR 20 response by week 38, five of whom also achieved an ACR 20 response at week 54, but none of the six patients who had failed to respond by week 38 achieved an ACR 20 response after dose escalation to 10 mg/kg [19]. Twelve of the patients were included in the psoriasis area severity index (PASI) analysis, five of whom achieved PASI 75 by week 38 and maintained it at week 54; the seven patients who did not achieve PASI 75 by week 38 were also unable to achieve it after dose escalation [19]. The ADEPT analyses showed clinical efficacy and inhibition of structural progression in patients treated with a standard or increased dose of adalimumab [20]. The use of subcutaneous golimumab at doses of 50 and 100 mg administered every 4 weeks significantly improved active PsA and associated skin disease; both doses led to similar results in the arthritis endpoints, but the number of patients achieving the psoriasis endpoints was higher in the 100 mg dose group [21].

A study of anti-TNF agents in only 16 PsA patients escalated infliximab therapy by shortening the interval between doses if the patients did not achieve a 30% reduction in active joint counts [22], and the last study was a study of the efficacy of sulfasalazine, in which doses could be increased if the patients did not achieve a 40% reduction in the number of active joints after 3 months [23]. In brief, all of these studies showed that changing dosing is an alternative when full efficacy is not achieved.

The EULAR task force defined the treatment target as remission or low disease activity. Minimal disease activity was defined as meeting five of the following seven criteria: a tender joint count of ≤1; a swollen joint count of ≤1; a PASI score of ≤1 or a BSA score of ≤3; a patient pain VAS score of ≤15; a patient global disease activity VAS score of ≤20; an HAQ score of ≤0.5 and a tender entheseal point count of ≤1 [24]. The MDA criteria were specifically developed with the idea of investigating the benefits of treating to target, and were used in the Tight

Control in PsA (TICOPA) study, a UK multicenter, open-label, randomized, controlled, parallel group trial of 206 patients with early PsA [25]. The patients were randomized 1:1 to receive 48 weeks' standard care (selected by their physicians, with patient encounters every 12 weeks), or intensive management (i.e., MTX; if MDA was not achieved, MTX plus salazopyrin; if this combination failed, MTX plus cyclosporin or leflunomide; and, if this failed, first-line anti-TNF agents followed by second-line anti-TNF drugs second line, with patient encounters every 4 weeks). The patients assigned to the intensive management group followed a strict treatment protocol in which dose continuation or escalation was determined by means of an objective assessment of the MDA criteria [25]. After 48 weeks, significantly more patients in the intensive management group had achieved ACR20 (the primary outcome), ACR50 or ACR70 responses. The odds of achieving an ACR20 response after 48 weeks were significantly higher in the tight control arm (OR: 1.91; p = 0.0392), as were the odds of achieving an ACR50, ACR70 or PASI75 response. There were also benefits in terms of patient-reported outcomes, including physical function (HAQ), quality of life and improvements in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores in the case of the patients with axial disease. Although there were no differences in terms of enthesitis, dactylitis, nail involvement or radiographic progression between the two groups, the study showed that treating to target and tight control can improve outcomes and are therefore effective in managing PsA [25,26].

Treatment

NSAIDs & disease modifying antirheumatic drugs

The aims of treating PsA are to alleviate disease signs and symptoms, inhibit structural damage and maximize the patients' quality of life. NSAIDs are often sufficient to treat mild PsA, and local intra-articular injections of corticosteroids may be used if only a few joints are involved. However, neither of these treatments affect the development of structural joint damage, and the findings of observational studies indicate that the same is true of DMARDs, although there is a lack of RCTs evaluating their impact on PsA [26,27]. However, the guidelines still recommend traditional DMARDs (methotrexate, leflunomide or sulfasalazine) for 3–6 months as the first step in the treatment of peripheral arthritis in PsA. The rationale for this and the extended period of exposure to DMARDs, may be due to the positive experience of many rheumatologists using these drugs, the findings of observational studies and the lack of any evidence that a relatively brief delay of 3 or 6 months in starting drugs of more proven efficacy has a substantial negative impact on long-term disease progression, disability or the quality of life [28,29].

Anti-TNF drugs

Studies have shown that PsA patients have high TNF levels in synovial fluid and the synovium, and that anti-TNF agents (infliximab, etanercept, adalimumab) are effective in reducing active joint inflammation and the progression of radiographic damage; efficacious against skin manifestations, enthesitis and dactylitis; and significantly improve function and the patients' quality of life [30]. It is also presumed that they are as effective on the spine as they are in patients with ankylosing spondylitis [31]. One of the main differences between using anti-TNF drugs in patients with PsA and using them in patients with RA is that they can be used as monotherapy in PsA. All of the *post hoc* analyses of RCTs comparing anti-TNF monotherapy with combined MTX treatment have shown that there is no difference in efficacy [32–34]; however, registries show that drug survival is longer in patients on combination therapy [35]. No head-to-head studies have compared anti-TNF drugs in the treatment of PsA, but there have been attempts to determine their relative efficacy by means of observational studies and analyses of well-controlled single trials [36]. Most research suggests that improvements in the joint manifestations of PsA, regardless of the drug. However, some patients with severe PsA are (or become) resistant or experience adverse events and require alternative treatment [37,38].

Ustekinumab

Ustekinumab, which is approved for the treatment of adults with active PsA in the USA and Europe, is a fully human monoclonal antibody that blocks the activity of p40, a protein subunit shared by IL-12 and IL-23 that consequently neutralizes the biological activity of both [37–39]. It has been shown that it decreases the cutaneous mRNA expression of IL-23p40, IL-23p19 and IFN-γ. IL-23 levels are clearly high in psoriatic lesions, as indicated by the increased levels of the mRNA of the p19 and p40 subunits, but not the mRNA of the p35 subunit of IL-12, which suggests that IL-23 plays a more dominant role than IL-12 in psoriasis [40].

Ustekinumab also inhibits IL-12- and IL-23-induced secretion of IFN-γ, IL-17A, TNF-α, IL-2 and IL-10, and is generally safe and well tolerated [39–42].

Two large and well-designed, placebo-controlled trials involving 927 patients with active PsA despite previous treatment with conventional therapy evaluated the efficacy and safety of subcutaneously administered ustekinumab 45 or 90 mg at week 0, week 4 and then

every 12 weeks (PSUMMIT I and PSUMMIT II), and found that 24 weeks' active treatment was significantly more effective in inducing ACR20 and PASI 75 responses and improving enthesitis and dactylitis, radiographic progression and HAQ-Disability Index (HAQ-DI) scores [41,42]. PSUMMIT II also included 180 patients with previous exposure to anti-TNF drugs in whom ustekinumab led to ACR20 and PASI75 response rates of respectively 35.6 and 47.1% by week 24, as against 14.5 and 2.0% in the placebo group ($p < 0.01$ for both) [42]. The long-term evaluations showed that ustekimumab was clinically efficacious and inhibited radiographic progression up to week 100 with and without concomitant MTX, and there were only rare serious infections or cardiovascular events [41,42].

IL-17 inhibitors

IL-17 is an inflammatory cytokine secreted by Th17 T and other cells that has been found in psoriatic plaques and inflamed entheses [37–39]. Three IL-17 inhibitors, all of which improve skin psoriasis, are currently undergoing advanced clinical testing: two IL-17A mAbs (secukinumab and ixekizumab) and one (brodalumab) against IL-17 receptor A (IL-17RA).

A Phase IIb RCT of secukinumab showed that 81% of the patients achieved PASI 75 responses and 57% a PASI improvement after 12 weeks' treatment (as against only 9% treated with placebo), and a randomized dose-finding study of ixekizumab showed significant PASI improvements in >77% of the treated patients (as against 8% in the placebo group) [37,38].

Secukinumab, a fully human monoclonal antibody against IL-17A, has intravenous and subcutaneous formulations. It received its first approval for the treatment of psoriasis and psoriatic arthritis in adults inadequately responding to systemic therapies (other than biological agents) in Japan on 26 December 2014, and was approved in the USA and Europe for the treatment of patients with moderate-to-severe plaque psoriasis in early 2015 [43].

The results of the Phase III randomized, placebo-controlled FUTURE 1 and 2 trials showed that secukinumab is efficacious in treating PsA. The FUTURE 1 trial randomized 606 patients to intravenous secukinumab 10 mg/kg (weeks 0, 2 and 4) followed by 75 or 150 mg subcutaneously every 4 weeks, or placebo using the same schedule [44,45]. The week 24 ACR20 response rates were 51 and 50% in the secukinumab 75 and 150 mg groups, and 17% in the placebo group ($p < 0.0001$ for both secukinumab groups vs placebo). The FUTURE 2 trial randomized 397 patients to subcutaneous secukinumab 75, 150 or 300 mg or placebo administered weekly for 5 weeks, and then every 4 weeks. The week 24 ACR20 response rates were respectively 29, 51 and 54% in the secukinumab 75, 150 and 300 mg groups, and 15% in the placebo group ($p < 0.05$ for the 75 mg group vs placebo, and $p < 0.0001$ for the 150 and 300 mg groups vs placebo) [45].

Subcutaneous brodalumab doses of 140 and 280 mg led to 12–week ACR20 responses in respectively 36.8 and 39.3% of PsA patients (18.2% in the placebo group).

However, further longer-term studies are necessary to define the effects of IL-17 inhibitors on the various manifestations of PsA [38].

Apremilast

Apremilast is an oral inhibitor of phosphodiesterase 4, the main phosphodiesterase expressed in immune cells that degrades cAMP into AMP [38,46]. This increases the intracellular levels of cAMP, which partially inhibit the expression of inflammatory cytokines IL-12, IL-23, TNF-α and IFN-γ and increase the expression of anti-inflammatory IL-10. The encouraging results and mild adverse reactions observed in Phase II clinical trials led to it being used in Phase III studies of its effects on PsA, and the preliminary results of the PALACE-1 study confirmed its clinical efficacy and safety [46,47]. It was therefore approved by both the US FDA and EMA for the treatment of PsA, and is recommended in patients with active PsA, depending on local licensing conditions [46,47].

PALACE 1 (504 patients), 2 (484 patients) and 3 (505 patients) [48–50] were pivotal Phase III multicenter RCTs with two active-treatment groups that randomized their approximately 1500 PsA patients previously treated with DMARDs and/or biological therapy 1:1:1 to receive apremilast 20 mg twice daily (b.i.d.), apremilast 30 mg b.i.d. or placebo for 16 weeks. Apremilast was associated with significantly higher ACR20 response rates (the primary endpoint) than placebo [48–50] and, in all three studies, the patients who had been treated with apremilast from the beginning maintained their responses for up to 52 weeks. The secondary endpoints, which included swollen and tender joint counts, Maastricht Ankylosing Spondylitis Enthesitis Scores (MASES), dactylitis counts, Short Form-36 (SF–36) Physical Function and Physical Component Summary scores, the HAQ-DI, Disease Activity Score (DAS28) and PASI scores, were also reached. More patients receiving apremilast 20 mg b.i.d. (31%) and 30 mg b.i.d. (28%) achieved an ACR20 response than those receiving placebo who had been previously exposed to biological agents (5%), although the differences were not statistically significant.

Recent trials have shown that ustekinumab and apremilast are useful alternatives for patients failing on

other anti-TNF drugs, and that apremilast can also be used as first-line therapy in selected cases (those who cannot tolerate other first-line treatments).

JAK inibitors

The Janus family of intracellular kinases consists of tyrosine-protein kinase 2 (TYK2), JAK1, JAK2 and JAK3, which interact with various members of the STAT family to modulate gene transcription downstream of a number of cell surface cytokine and growth factor receptors. Tofacitinib is an oral inhibitor of JAK3, JAK1 and (to a lesser extent) JAK2. As a JAK3 inhibitor, it blocks cytokines such as IL-2, IL-4, IL-15 and IL-21, whereas its ability to block JAK1 and JAK2 inhibits signaling by IFN-γ, IL-6 and (to a lesser extent) IL-12 and IL-23 [51]. It is known to block the effects of IL-6 and type I interferons on synovial fibroblasts, and it also led to positive results in Phase II studies of psoriasis [52]. Twelve weeks' treatment with tofacitinib 2, 5, or 15 mg b.i.d. significantly improves moderate-to-severe plaque psoriasis [53]. Approved for the treatment of RA in various countries, in combination with MTX or other nonbiological DMARDs, it improves ACR20, ACR50 and ACR70 responses, DAS28 scores and the quality of life and probably inhibits the progression of structural damage in patients with moderate to severe active RA who have failed to respond to treatment with traditional DMARDs or anti-TNF drugs [54]. Topical preparations of tofacitinib have been also tested in psoriasis patients, and were found to be well tolerated and efficacious in improving chronic plaque psoriasis in a Phase II study [55]. Further studies of tofacitinib in psoriasis and PsA are ongoing, and other JAK inhibitors (baricitinib, decernotinib, filgotinib, INCB-039110, GLPG0634) are being evaluated in RA in Phase II studies. Baricitinib, a JAK1/JAK2-selective inhibitor, has also been evaluated in psoriasis patients [52].

Conclusion

The early detection of joint symptoms in patients with psoriasis is important because joint disease is reversible if appropriate treatment is promptly started, and anti-TNF drugs have recently been used to reverse bone remodeling in PsA patients (which is not possible with MTX or sulfasalazine). The evidence for using conventional DMARDs to manage PsA is weak, but this may be a viable approach if exposure is limited to 3–6 months. However, the early use of anti-TNF drugs should be encouraged.

Preliminary evidence supports the role of treat-to-target strategies in PsA. In order to achieve MDA consistently, patients need to be seen regularly and treated aggressively, and treatment may be even more intense if the target is remission. However, as not all patients are suitable for this approach, experts agree that MDA is a valid, feasible and acceptable target.

There is still an urgent need for guidelines concerning the early diagnosis and management of PsA, but as PsA and RA are both systemic diseases with extra-articular manifestations and comorbidities (such as metabolic syndrome, etc.), PsA should be diagnosed and treated using the same strategy as that used to treat RA in order to prevent disability and increase survival. However, as has been shown in RA patients [56], PsA patients with comorbidities may not experience the same degree of benefit as those without comorbidities, and this needs to be evaluated carefully before treating any PsA patient.

Future perspective

Interesting innovative views of early PsA come from registry and other long-term studies, basic research and many currently ongoing or planned studies. However, national and international registries are necessary in order to provide information about early PsA and the efficacy and safety of all of the new drugs that are useful in clinical practice, and improve our understanding of the quality of life and working ability of PsA patients. Furthermore, the effects of biological and nonbiological agents on PsA should be evaluated in further studies not only based on the use of radiography, but also on the use of ultrasonography and magnetic resonance which seem to be sensitive in detecting early joint involvement.

Authors' contributions

F Atzeni conceived the idea and drafted the manuscript. IF Masala, L Boccassini and P Sarzi-Puttini helped in drafting the manuscript and research of the literature. All of the authors read and approved the final manuscript.

Executive summary

- Preliminary evidence supports the role of treat-to-target strategies in psoriatic arthritis (PsA).
- The early use of anti-TNF drugs should be encouraged.
- Ustekinumab and apremilast are useful alternatives for patients with anti-TNF drug failure.
- Early detection of joint symptoms in patients with psoriasis is important because joint disease is reversible if appropriate treatment is started early.
- Early detection of PsA and referral to a rheumatologist are basic steps to prevent delays in starting treatment.
- Preliminary evidence supports treating PsA in the same way as rheumatoid arthritis.

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Early psoriatic arthritis: should we treat it in the same way as we treat rheumatoid arthritis?

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.					
	1	**2**	**3**	**4**	**5**
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. You are seeing a 55-year-old woman recently diagnosed with psoriatic arthritis (PsA). What should you consider regarding this diagnosis and its clinical implications?
   - ☐ **A** PsA affects approximately 5% of patients with psoriasis
   - ☐ **B** Arthritis usually precedes skin lesions among patients with PsA
   - ☐ **C** Nail lesions are not helpful in differentiating PsA from rheumatoid arthritis
   - ☐ **D** Erosive disease can develop early despite treatment with nonbiologic disease-modifying antirheumatic drugs (DMARDs)
2. You consider treatment for this patient. Which of the following is not part of the treatment target criteria according to the European League Against Rheumatism (EULAR) task force?
   - ☐ **A** Stabilization of erosive joint disease for at least 1 year
   - ☐ **B** Tender joint count of 1 or less
   - ☐ **C** Swollen joint count of 1 or less
   - ☐ **D** Patient pain visual analog scale score of 15 or less
3. Which of the following statements regarding routine treatment of PsA is **most** accurate?
   - ☐ **A** Nonsteroidal anti-inflammatory drugs are insufficient to treat even mild PsA
   - ☐ **B** Methotrexate or sulfasalazine can be used to treat peripheral arthritis for 3 to 6 months
   - ☐ **C** Anti-tumor necrosis factor (TNF) agents are ineffective in preventing joint erosion
   - ☐ **D** Anti-TNF agents should not be used as monotherapy in PsA
4. Which of the following novel biologic agents potentially applicable to PsA is correctly matched with its mechanism of action?
   - ☐ **A** Ustekinumab → inhibition of Janus kinase 1 (JAK1) and JAK3
   - ☐ **B** Secukinumab → interleukin-17 (IL-17) inhibition
   - ☐ **C** Tofacitinib → blocks p40
   - ☐ **D** Apremilast → IL-17 inhibition