

Psoriatic Arthritis: Pathogenesis, Clinical Features and Treatment

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ABSTRACT

Psoriatic Arthritis (**PsA**) is a chronic, progressive inflammatory arthritis that occurs in about 30% of patients with psoriasis and often results in permanent joint damage and disability. Its prevalence ranges between 0.02- 0.3% with significant geographic variation. The pathophysiology of PsA is multifactorial and encompasses a variety of genetic, environmental, and immunologic factors. In the 1970s, Moll and Wright formulated the initial diagnostic criteria for PsA and described five main clinical patterns or subtypes of the disease: asymmetric oligoarthritis (≤ 4 joints involved), symmetric polyarthritis (≥ 5 joints involved), predominant Distal Intraprophalangeal (**DIP**) involvement, predominant spondyloarthritis (axial involvement), and destructive (mutilans) arthritis. Since then, our knowledge about the disease has significantly expanded and new diagnostic criteria have been established. Equally important, treatment options have advanced from medications that merely improve symptoms to advanced therapies that slow disease progression and alter the natural history of the disease.

EPIDEMIOLOGY

Psoriatic Arthritis (**PsA**) is a chronic, progressive inflammatory arthritis that is common in patients with psoriasis and often results in permanent joint damage and disability. Research over the past 20 years has significantly changed the initial perception of PsA as a relatively benign disease. It is currently regarded as a systemic inflammatory disorder with significant health consequences not just limited to joint function including the occurrence of erosions and joint destruction, but also increased risk for cardiovascular disease [1,2].

There is data suggestive of wide variation in the incidence and prevalence of PsA among various countries and geographic areas around the world. The studies investigating the epidemiology of PsA still differ considerably in their methods and the criteria used to diagnose PsA. The methodological differences involve primarily the methods of case identification and case recording, as well as the type of incidence and prevalence rates [3]. There are relatively few studies that examine the incidence of PsA in the general population. The reported incidence of PsA in recent publications ranges from 3.6 to 7.2/100,000/year [4-7]. Prevalence estimates of PsA in the United States range from 0.06% to 0.25% with the lowest estimate derived from a paper where International Classification of Disease, ninth edition (ICD-9), codes were used to identify cases and the highest estimate derived from articles where patient self-report of diagnosis of PsA was used [8-10]. Prevalence estimates in Europe range from 0.05% in Turkey [11] and the Czech Republic [6] to 0.21% in Sweden [12]. There are only a few reports of the prevalence of PsA in South America and Asia and these suggest that the prevalence is lower in these regions; 0.07% in Buenos Aires[7] and 0.02% in China[13]. The low prevalence of PsA in China may be due to under-diagnosis of the disease, as suggested in one study [14].

The age and sex distribution of PsA cases vary significantly as well, suggesting a different epidemiologic profile among various countries. It is difficult to interpret the different epidemiologic profiles of PsA observed among European and American populations. Genetic, ethnic, environmental, and therapy-related factors have been considered as being potentially associated with disease occurrence and clinical manifestations, although the specific role of these factors remains uncertain [6,15-17]. The lack of studies in Africa, large parts of Asia, South America, and Eastern Europe represents another important limiting factor in fully understanding the geographical variations of PsA and the potential role of genetic and environmental factors in the occurrence of the disease. A number of reports suggest differences in the manifestations of PsA in different ethnic groups, but there are very few studies comparing the occurrence and the profile of the disease among different ethnic or racial groups [18,19]. In general, examining case series of patients with PsA, the average age of onset is around 40 years of age and the male: female ratio is approximately 1:1 (Table 1A and 1B) [20,21].

Table 1A: Reported prevalence of each clinical pattern of PsA reported in several case series of patients with PsA [20].

Feature	Roberts 1976	Kammer 1979	Scarpa 1984	Gladman 1987	Helliwell 1991	Torre- Alonso 1991	Veale 1994	Jones 1994	Trabace 1994	Marsal 1999
No. of patients	168	100	62	220	50	180	100	100	58	73
Male/Female	67/101	47/53	29/33	104/116	32/18	99/81	59/41	43/57	35/33	37/36
Age of onset (yrs)	36-45	33-45	40-60	37	39	39	34	37.6	42	42
Oligoarthritis (%)	53%	54%	16%	14%	14%	37%	43%	26%	50%	7%
Polyarthritis (%)	54%	25%	39%	40%	78%	35%	33%	63%	40%	88%
DIP (%)	17%	?	7.5%	12%	0%	0%	16%	1%	?	4%
Mutilans (%)	5%	?	2.3%	16%	2%	4%	2%	4%	?	14%
Spine (%)	5%	21%	21%	2%	6%	7%	4%	6%	?	1%
Sacroiliitis (%)	?	?	16%	27%	36%	20%	15%	6%	43%	14%
Joints before skin (%)	16%	30%	?	17%	?	15%	?	18%	?	?

Table 1B: Demographic and general features of PsA reported in several case series of patients with PsA [21].

Reference	Age of onset (years)	M:F ratio	Duration of PsO (years)	Onset of Arthritis in relation to PsO		
				After PsO	Simultaneous	Before PsO
Gladman, 1987	37	0.9:1	12.8	68%	15%	17%
Jones, 1994	38	0.8:1	8.7	63%	19%	18%
Rajendran, 2003	41	2.1:1	NA	51%	37%	12%
Torre-Alonso (1991)	40	1.2:1	8.0	73%	12%	15%
Madland (2005)	NA	1.1:1	NA	NA	NA	NA
Michet (2005)	39	NA	7.0	49%	35%	6%
Noosent (2009)	34	1.4:1	8.0	NA	NA	14%
Zisman (2010)	49	0.8:1	9.0	60%	30%	10%

Although PsA has a low prevalence in the general population, it is common among patients with psoriasis. Psoriasis has a prevalence of 2-3% of the general population. Prevalence estimates of PsA vary considerably (range 6%–42% [20]) depending on the definitions used such as diagnostic codes, rheumatologist diagnosis, classification criteria, and the target population studied [13,14,22-25].

In studies examining the cumulative incidence of PsA over time in patients with psoriasis, it was reported that 1.7%, 3.1%, 5.1%, and 20.5% developed PsA at 5, 10, 20, and 30 years, respectively, after the diagnosis of psoriasis [5,26]. In a prospective cohort of 313 patients with psoriasis, an annual incidence of 2.7 cases of PsA per 100 psoriasis patients was reported [27]. A severe psoriatic phenotype, nail pitting, uveitis, and low level of education are predictive of the development of PsA [27].

PATHOGENESIS OF PSA

The exact pathogenic mechanisms resulting in PsA are not fully understood, however, they involve a complex interaction of genetic, environmental, and immunologic factors. Approximately one third to one half of patients with PsA have at least one first degree relative with PsA [28]. The magnitude of familial predisposition in PsA is second only to Ankylosing Spondylitis (**AS**). In patients with PsA, the prevalence of PsA and psoriasis in first degree relatives was 7.6% and 15.2%, respectively. The familial aggregation as assessed by the recurrence risk ratio (λ) of PsA and psoriasis in first degree relatives for PsA was 30.4 and 7.6, respectively [29].

Genes associated with PsA include genes in the MHC (HLA) region which are involved in antigen presentation and non-MHC genes which are involved in other aspects of the immune response such as intracellular signaling, cytokine expression and signaling, and T cell effector function. Some genes are associated with both PsA and psoriasis while other genes are associated with only one disease entity. MHC (HLA) antigens are prominent in PsA and psoriasis. A study examining patients with PsA (n=158), psoriasis (n=101), and controls (n=243) showed genetic associations with PsA, different patterns of arthritis, and psoriasis. HLA-B16, HLA-B17, HLA-B27, HLA-B38, HLA-B39, and HLA-Cw6 were associated with PsA. No association with HLA-DR antigens and PsA were demonstrated. However, the subset of patients with symmetric polyarthritis demonstrated an association with HLA-DR4. Uncomplicated psoriasis patients had higher frequencies of HLA-B17, HLA-Cw6, and HLA-DR7 than patients with PsA, while HLA-B7 and HLA-B27 correlated with the development of arthritis. HLA-B27, HLA-Cw2, and HLA-DRw52 were associated with axial involvement and HLA-B38 and HLA-B39 were associated with polyarthritis [30].

Directed genetic studies have long shown a strong association between genes in the major histocompatibility complex (MHC) on chromosome 6p21.3 and PsA. In patients with psoriasis, the major effect in the MHC region is located within the ~300-kb segment HLA-Cw6 (*0602), known as psoriasis susceptibility region 1 (PSORS1) [31]. Interestingly, in patients with PsA, the magnitude of the association with PSORS1 is much lower [32]. HLA genes associated with PsA include HLA-B27 which is associated only with the spondylitis of PsA, not peripheral arthritis. Other HLA genes including HLA-B07, HLA-B08, HLA-B13, HLA-B38, HLA-B39, HLA-B57, and HLA-C06 [32,33]. The HLA-C06 and HLA-B27 had a strong association while the HLA-B07, HLA-B38, and HLA-B39 showed a moderate association with PsA [32]. The RA shared epitope, HLA-DRB1*04, was found to be associated with radiographic erosions in patients with PsA [34]. HLA-B39 alone, HLA-B27 only in the presence of HLA-DR7, and HLA-DQ3 only in the absence of HLA-DR7, and HLA-Cw*0602 are associated with a higher rate of disease progression in PsA [35].

Genes associated with PsA located outside of the MHC locus are often related to the immune response such as intracellular signaling, cytokine expression and signaling, and T cell effector function. Two genes locate in the MHC region but not MHC genes are the MICA and TNF- α which have a moderate association with PsA [32]. Other genes associated with PsA involved in the

immune response include those involved in 1) intracellular signaling: *REL*, *TNIP1*, *FBXL19*, *TYK2*, 2) Th1 signaling: *IL-12 β* , *TYK2*, 3) Th17 signaling: *IL-23R*, *IL12 β* , *TRAF3IP2*, *IL-23A*, *TYK2* [33].

More recently, Genome Wide Associations Studies (**GWAS**) have shown association between PsA and *HLA-B/C*, *HLA-B*, *IL-12B*, *IL-23R*, *TNIP1*, *TRAF3IP2*, *FBXL19* and *REL* in Caucasian populations [16]. In Chinese patients, gene associations includes *HLA-C*, *IL12B*, *LCE3D*, *ERAP1*, *TNIP1*, *PTTG1*, *CSMD1*, *GJB2*, *SERPINB8* and *ZNF816A* [15].

From an immunologic standpoint, PsA has been traditionally regarded as a T-cell mediated disorder with CD8+ T-cells playing a major role in the pathogenesis of the disease [17]. Synovial fluid analysis has shown elevated concentrations of CD8+ T-cells [36], as well high levels of pro-inflammatory cytokines including interleukin (IL)-1, IL-2, IL-6, IL-8 and tumor necrosis factor-alpha (TNF- α) and Interferon-Gamma (INF- γ) [37,38]. In addition, monocytes have lately been implicated in the pathogenesis of PsA [39].

The role of environmental factors is less clear. Epidemiologic studies have shown an association between recent streptococcal infection [40] recent antibiotic exposure, or trauma and exacerbation of psoriatic arthritis [41,42]. On the other hand, smoking appears to have a protective effect in relationship with PsA [42].

CLINICAL FEATURES OF PSA

The first association of psoriasis with an inflammatory arthropathy is attributed to Alibert in 1818. It was later coined as “Psoriasis Arthritique” by Bazin in 1860. However, in the 1950s PsA was classified as a subtype of rheumatoid arthritis, known as “Rheumatoid Spondylitis” or “Rheumatoid Variant”[43]. In the early 1970s, Wright emphasized again that PsA is a distinct disease entity separate from rheumatoid arthritis (RA). In 1973, Moll and Wright formulated the initial diagnostic criteria for PsA. The diagnosis of PsA required 1) an inflammatory arthritis (peripheral arthritis and/or sacroiliitis or spondylitis), 2) the presence of psoriasis c) the absence of serologic tests for rheumatoid factor. Depending on the clinical features of articular involvement at presentation, five clinical patterns or subtypes of PsA were described; 1) Asymmetrical oligoarthritis (≤ 4 joints involved), 2) Symmetrical polyarthritis (≥ 5 joints involved), 3) Predominant distal interphalangeal (DIP) joint involvement, 4) Predominant spondyloarthritis, 5) Destructive (mutilans) arthritis [28]. Examples of the different clinical patterns of peripheral PsA can be seen in Figure 1.

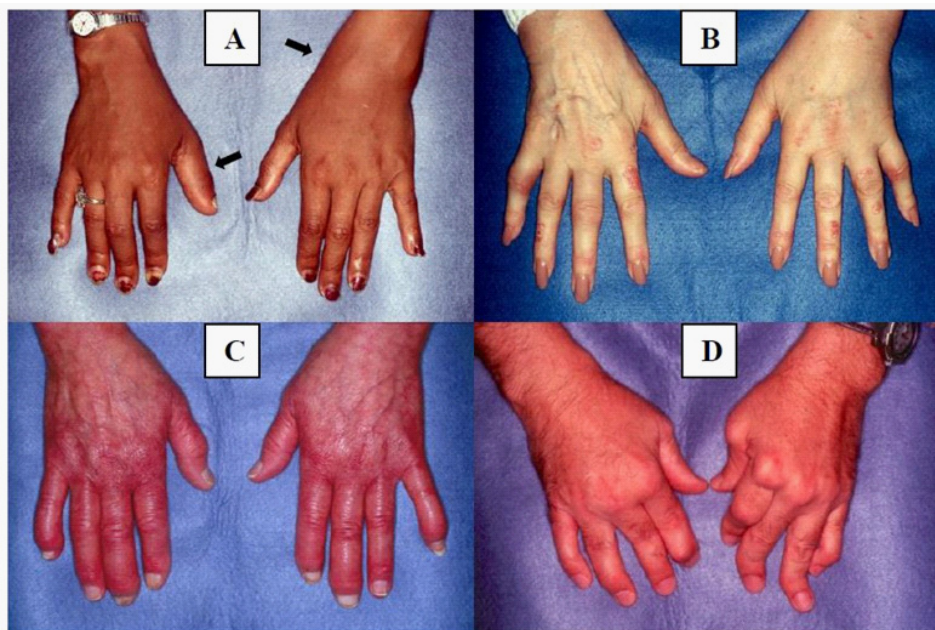


Figure 1: Clinical patterns of peripheral PsA, A) Asymmetric oligoarthritis, B) Symmetric polyarthritis, C) Predominant DIP joint involvement, D) Destructive (mutilans) arthritis.

It is not uncommon, however, for a patient to progress from one pattern of PsA to another. Asymmetric oligoarthritis is considered to be the most common pattern of PsA at initial diagnosis. It has been shown to account for up to 60% of PsA cases at initial presentation [44]. About 15-35% of patients have monoarticular arthritis as the initial presentation of disease. Predominant distal interphalangeal joint involvement, spondyloarthritis, and arthritis mutilans each account for about 5% of patients [44]. As patients are followed over time, they tend to develop the symmetric polyarthritis and it becomes the predominant pattern. In one study, approximately 2/3 of patients with oligoarthritis subsequently developed a symmetric polyarthritis [44]. In another study that followed patients with PsA for more than 10 years, more than half of the patients developed a polyarthritis involving >5 joints [45]. The reported prevalence of each clinical pattern of PsA in several reported case series of patients with PsA is shown in Table 1A [20]. These differences are attributed to the change of disease pattern with time. Therefore, the clinical pattern is more relevant at the time of initial presentation of PsA; patients who present with symmetric polyarthritis have more aggressive disease [20]. The arthritis of PsA can also present before the onset of skin disease making the diagnosis more difficult in these patients. In general, the arthritis presents about 9 years after the onset of psoriasis, 60% of patient have arthritis occurring after psoriasis, 25% of patients have simultaneous (within the same year) presentation of arthritis and psoriasis, and 15% of patient have arthritis occurring before the onset of psoriasis (Table 1B) [21]. After skin and nail involvement, the most common extra-articular manifestation is uveitis which occurs in 7-18% of patients, is more often bilateral and chronic, and usually associated with axial disease [46,47].

Laboratory Features

PsA is a chronic inflammatory condition. As such, inflammatory markers are useful in the diagnostic workup. Unfortunately, no specific biomarkers for PsA have yet been validated. The ESR and CRP, the most commonly used laboratory indices of inflammation, are elevated in approximately half of PsA patients [48]. This may partly account for the delay in diagnosis of PsA; in patients with normal ESR and CRP, physicians may be misled towards the diagnosis of a non-inflammatory condition. Interestingly, in one study, both ESR and CRP were found to be more commonly elevated in elderly individuals with newly diagnosed PsA compared to younger patients [49]. Among the PsA patients who have elevated ESR or CRP at disease diagnosis, their utility for monitoring disease activity and prognosis is well established [50]. Low ESR and CRP levels are associated with a better prognosis, while ESR levels > 15 mm/hr are associated with increased mortality [51,52]. Anemia is also common in patients with PsA. It may represent a marker of chronic disease or result from occult blood loss due to use of Non-Steroidal Anti-Inflammatory Drugs (**NSAIDs**) [46].

Laboratory markers classically associated with Rheumatoid Arthritis (**RA**) can also be positive in PsA patients. The Rheumatoid Factor (**RF**) and the more specific antibodies to cyclic citrullinated peptide (anti-CCP) are positive in 5-15% of patients with PsA [48,53]. In patients with symmetric polyarticular involvement, the presence of RF or anti-CCP antibodies, found in up to 15% of patients, may make the differential diagnosis between PsA and RA very difficult. Interestingly, RF and anti-CCP antibodies can be encountered in 7-10% of patients with the mono- or oligoarticular pattern of PsA. Therefore, their use as the sole parameter for differentiating between RA and PsA is unreliable. However, in patients with known PsA, the presence of RF or anti-CCP antibodies is a marker of a more aggressive disease course associated with bone erosions [53]. In one case series from Canada, approximately 50% of patients had positive ANA titers ($\geq 1:40$). However, clinically significant titers ($\geq 1:80$) were only seen only in 15% of patients and the more specific antinuclear antibodies for Systemic Lupus Erythematosus (**SLE**) such as anti-dsDNA antibodies were found in only 2% of PsA patients [54].

Synovial fluid analysis may also yield important diagnostic information. PsA is characterized by a high degree of synovial membrane neovascularization, significantly more than found in RA synovial tissue. As a result, synovial fluid overexpression of angiogenic factors such as transforming growth factor- β (TGF- β) and Vascular Endothelial Growth Factor (**VEGF**) is commonly encountered among PsA patients [55,56].

Imaging

Multiple imaging modalities are useful in the diagnosis and follow up of patients with PsA. In addition to the conventional radiography, newer modalities such as Computed Tomography (**CT**), Magnetic Resonance Imaging (**MRI**), and more recently Ultrasonography (**US**) have shed

new light in the disease. A characteristic feature of PsA is the presence of bone destruction seen as erosions and bone production (proliferation) seen as periostitis in the same joint or the same digit with plain radiography [57]. This is best seen in the radiographs of the hands and feet. Figure 2, 3, and 4 show these changes at various stages of PsA. The radiologic features seen in patients with PsA depends on the clinical pattern and include an asymmetric distribution in patients with asymmetric oligoarthritis, symmetric distribution in patients with symmetric polyarthritis, distal interphalangeal joint involvement in any form of peripheral arthritis but characteristically in predominant DIP joint involvement, and severe destructive disease in destructive (mutilans) arthritis (Figure 5A). Several features are very characteristic of peripheral disease in PsA including preservation of bony mineralization, the presence of bone destruction (erosions) and bone production (periostitis) in the same joint or digit (Figures 2, 3, 4), bony ankylosis, distal tuft resorption (Figure 4 and 5B), and pencil-in-cup deformity (Figure 5B) [58]. Axial involvement in PsA may occur alone or in association with other clinical patterns of peripheral arthritis. Axial involvement in PsA is characterized by asymmetric sacroiliitis and paravertebral new bone formation called syndesmophytes (Figure 6) [59]. The spondylitis is often discontinuous and the syndesmophytes are typically non marginal and bulky. Involvement of the cervical spine may manifest with atlanto-axial instability as seen in patients with RA. However, the mechanism in PsA is different and mostly characterized by new bone formation [59]. Involvement of entheses in PsA can result in radiographic changes including bone destruction seen as erosions and bone production seen as periostitis with new bone formation [60]. These changes are most commonly seen in the heel (Figure 7).

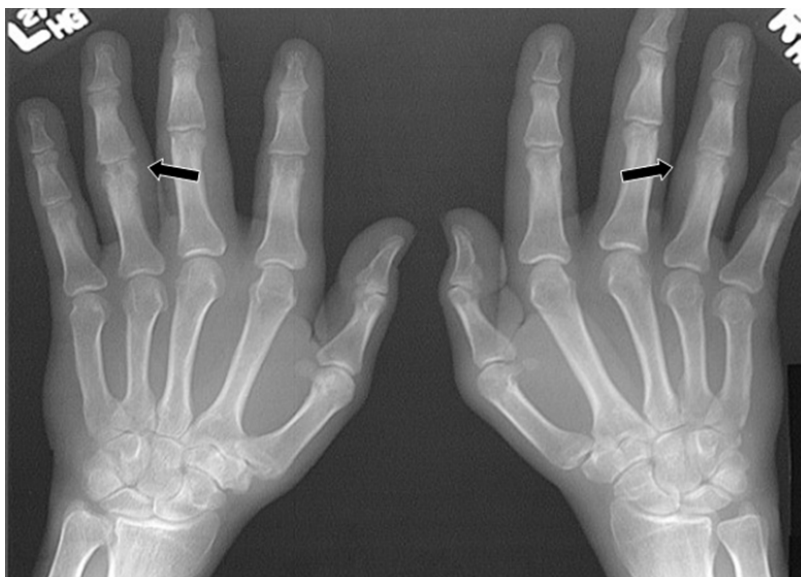


Figure 2: Plain radiographs of the hands in a patient with early PsA showing some PIP joints with bone destruction (marginal erosions) and bone formation (periostitis with new bone formation) (arrows).

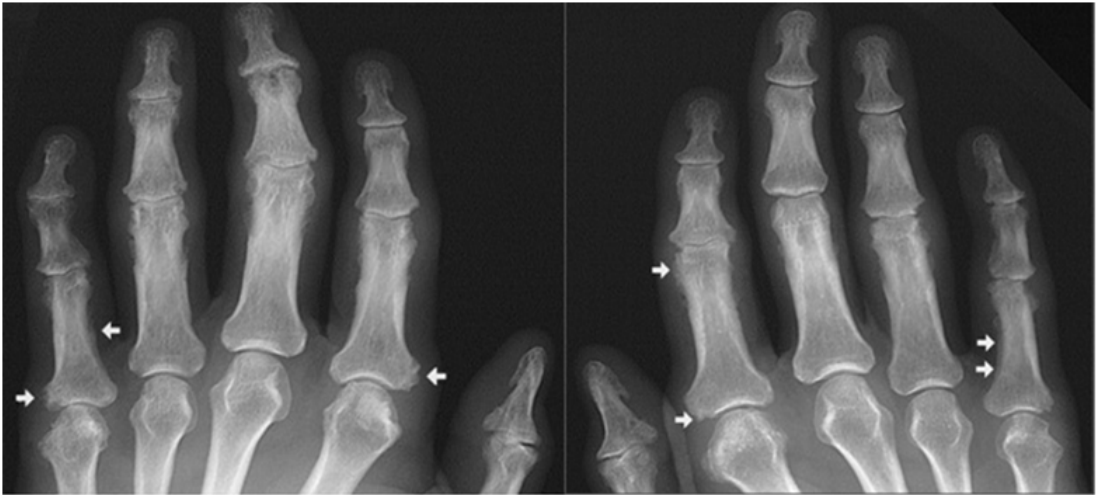


Figure 3: Plain radiographs of the hands in a patient with more advanced PsA showing PIP and DIP joints with bone destruction (marginal erosions) and bone formation (periostitis with new bone formation) (arrows).

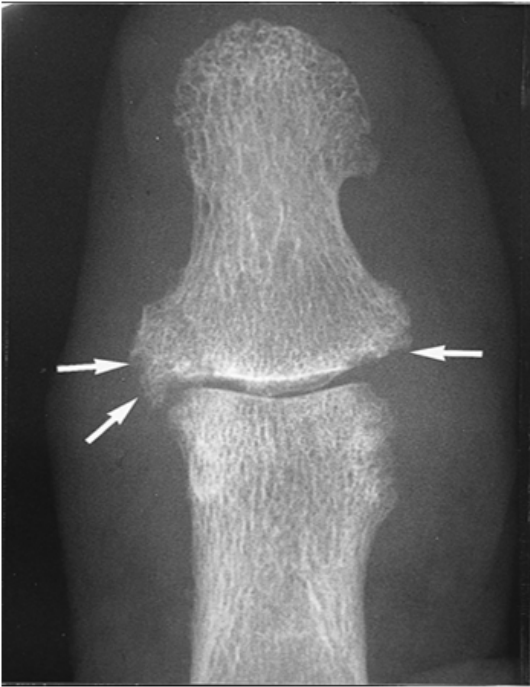


Figure 4: DIP joint involvement in a patient with PsA showing erosions and periosteal new bone formation as well as early distal tuft resorption.

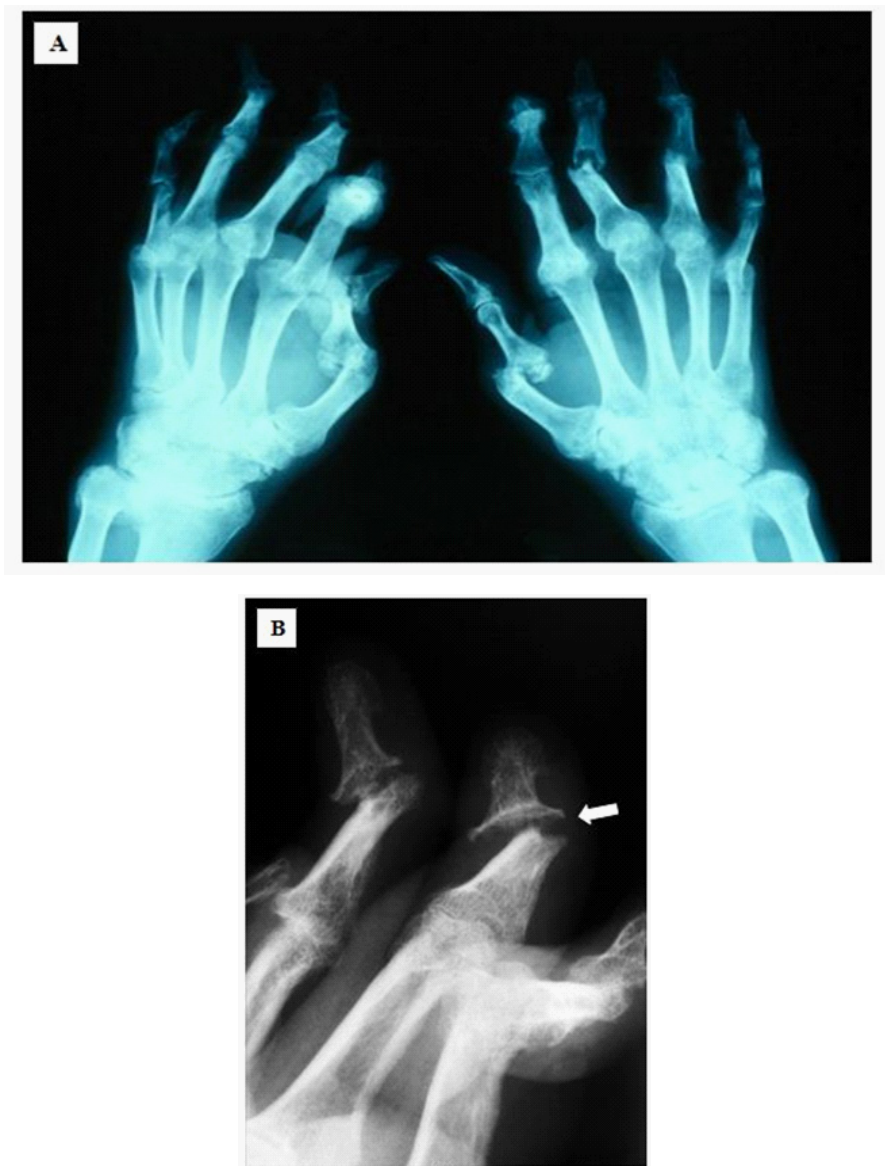


Figure 5: A. Severe PsA, “Arthritis Mutilans” of the hands. B. “Pencil in Cup” deformity of a DIP joint (arrow).



Figure 6: Axial involvement of PsA showing asymmetric sacroiliitis (black arrow) and spondylitis with non marginal syndesmosphytes (white arrow) with discontinuous spinal involvement.



Figure 7: Radiographic findings of peripheral enthesitis of the heel with erosions (white arrow) and periostitis with new bone formation (black arrow).

Magnetic Resonance Imaging (**MRI**) is an important imaging modality for the assessment of both peripheral and axial disease as it is more sensitive than conventional radiography for the detection of joint, periarticular and soft tissue inflammation [61]. STIR (Short Tau Inversion Recovery) imaging or use of gadolinium is useful for identifying inflammatory activity in peripheral joints, entheses and the axial skeleton. In peripheral PsA, key MRI findings include synovitis, enthesitis, tenosynovitis, periarticular inflammation, bone marrow edema, bone erosions and bone proliferation [62-64]. MRI of the sacroiliac joints and spinemay show evidence of inflammation seen as bone marrow edema on STIR imaging (Figure 8), post-inflammatory changes seen as fat infiltration, or bony proliferation seen as syndesmophytes [57]. Whole-body MRI can be used to identify active inflammatory lesions in patients with PsA in the axial skeleton, peripheral joints and entheses [65,66].

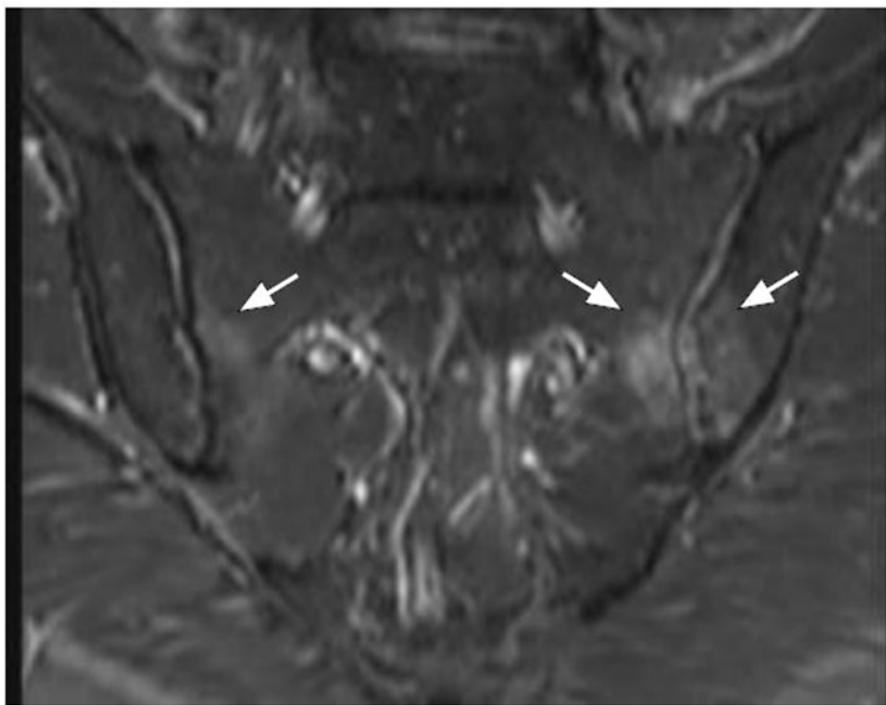


Figure 8: Coronal oblique STIR image of the sacrum demonstrates periarticular bone marrow edema (arrows) consistent with active sacroiliitis, note bilateral but asymmetric distribution.

Ultrasonography can be a useful imaging technique for the diagnosis of peripheral involvement of PsA; its use in axial disease is very limited. Ultrasonography has been shown to be more sensitive than clinical exam for the detection of peripheral joint involvement (synovitis and erosions) (Figure 9) and periarticular involvement (enthesitis) [67]. Ultrasonography of affected entheses may show inflammatory changes (increased thickness of tendon, hypoechogenicity of the entheses and tendons, bursitis, Power Doppler signal in the enthesis) and/or chronic changes (enthesophytes, calcifications, and erosions at the insertion site) [57,64].

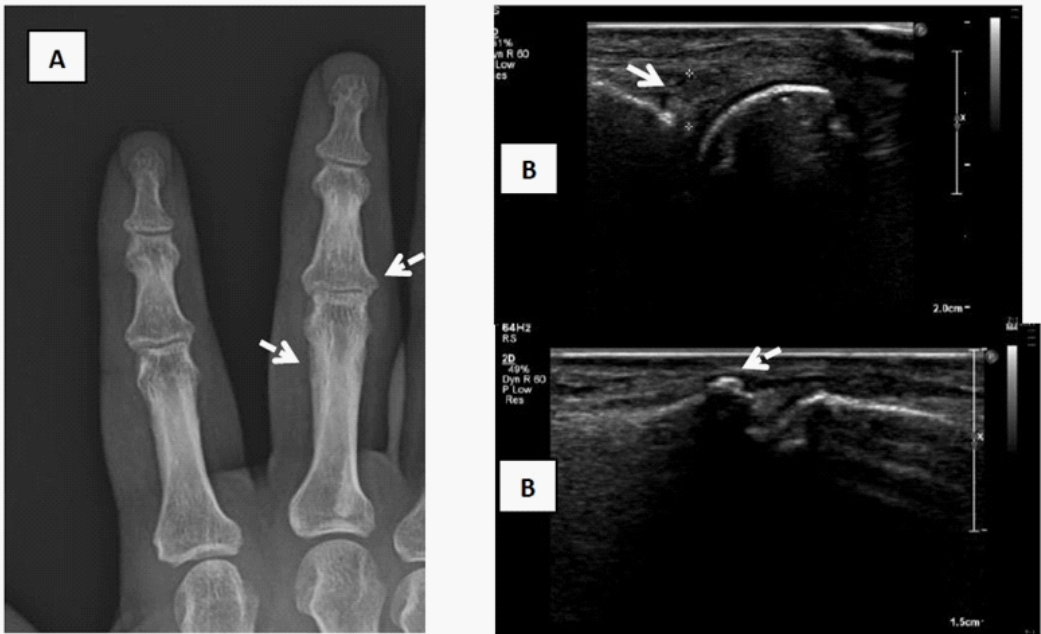


Figure 9: Radiographs (A) show chronic bone proliferation at the base of the 3rd middle phalanx as well as chronic shaft periostitis with thickened appearance of the 3rd proximal phalanx (dashed arrows). Ultrasound images demonstrate synovial thickening without hypervascularity of the 2nd MCP (B) and productive bone changes at 2 and 3rd PIP joints (dashed arrows) (C) Ultrasound images courtesy Cheryl Kirby, MD.

Computed Tomography (CT) has also been used in the diagnosis of axial PsA. It is useful for detecting bony erosions and bony sclerosis in the peripheral and axial skeleton. CT is unable to detect active inflammatory lesions and its use involves ionizing radiation. MRI has greater sensitivity for active inflammatory lesions and erosions and is generally more useful in the assessment of patients with PsA [57].

Classification Criteria for Psoriatic Arthritis and Diagnosis

After Moll and Wright proposed the initial diagnostic criteria in 1973, several other diagnostic criteria have been proposed (Table 2) [12,68-70]. However, the criteria most frequently used today for clinical study of PsA are the ones proposed by the CLASSification criteria for Psoriatic Arthritis (CASPAR) Study Group which have a sensitivity of 91% and specificity of 99% [69]. For the diagnosis of PsA, a patient must have inflammatory articular disease (joint, spine, enthesal) and score at least 3 points from the following criteria including 1) Evidence of psoriasis, 2) Psoriatic nail dystrophy, 3) Negative test for rheumatoid factor, 4) Dactylitis, 5) Radiographic evidence of juxta-articular new bone formation (criterion 1 is 2 points, all other criteria are 1 point)(Table 3)[69]. The sensitivity and specificity of the various classification criteria for PsA are shown in Table 4 [69].

Table 2: Classification criteria for PsA.

<u>Moll and Wright (1973)</u> [28] • Inflammatory arthritis (peripheral arthritis and/or sacroiliitis or spondylitis) • The presence of psoriasis • The absence of serologic tests for rheumatoid factor
<u>Bennett (1979)</u> [71] <u>Mandatory</u> • Clinically apparent psoriasis (skin or nails) Pain and soft tissue swelling and/or limitation of motion in at least one joint observe by a physician for ≥ 6 weeks <u>Supportive</u> • Pain and soft tissue swelling and/or limitation of motion in one or more other joints observed by a physician • Presence of an inflammatory arthritis in a distal interphalangeal joint (not OA) • Presence of sausage digits in hands or feet • An asymmetrical distribution of arthritis in the hands and feet • Absence of subcutaneous nodules • A negative test for rheumatoid factor • An inflammatory synovial fluid with a normal or increased C3 or C4, absence of infection, negative crystal exam • A synovial biopsy showing hypertrophy of synovial lining with a predominantly mononuclear cell infiltrate without granuloma or tumor • Peripheral radiographs showing erosive arthritis of small joints without osteopenia; exclusion: erosive OA • Axial radiographs showing sacroiliitis, syndesmophytes, or paravertebral ossification Definite PsA: mandatory plus 6 supportive criteria Probable PsA: mandatory plus 4 supportive criteria Possible PsA: mandatory plus 2 supportive criteria
<u>Vasey and Espinoza Criteria (1984)</u> [72] <u>PsA defined as criterion I + criterion II or III</u> <u>Criterion I:</u> • Psoriatic skin or nail involvement <u>Criterion II: peripheral pattern</u> • Pain and soft tissue swelling with or without limitation of motion of the distal interphalangeal joint for over 4 weeks • Pain and soft tissue swelling with or without limitation of motion of the peripheral joints involved in an asymmetrical peripheral pattern for over 4 weeks. Includes a sausage digit. • Symmetrical peripheral arthritis for over 4 weeks, in the absence of rheumatoid factor or subcutaneous nodules • Pencil in cup deformity, whittling of terminal phalanges, fluffy periostitis, and bony ankylosis <u>Criterion III: central pattern</u> • Spinal pain and stiffness with the restriction of motion present for over 4 weeks • Sacroiliitis: grade 2 symmetric or grade 3 or 4 unilateral sacroiliitis (New York criteria)
<u>Modified ESSG criteria for PsA (1991)</u> [73] <u>Inflammatory spinal pain or Synovitis (either asymmetrical or predominantly lower limb) plus ≥ 1 of the following</u> • Positive family history of psoriasis • Psoriasis

Modified McGonagle criteria for PsA (1999) [124]

Psoriasis or family history of psoriasis plus any one of the following

- Clinical inflammatory enthesitis
- Radiographic enthesitis
- Distal interphalangeal joint disease
- Sacroiliitis/spinal inflammation
- Uncommon arthropathies (SAPHO, spondylodiscitis, arthritis mutilans, onycho-pachydermo-periostitis, chronic multifocal recurrent osteomyelitis)
- Dactylitis
- Monoarthritis
- Oligoarthritis (≤4 swollen joints)

Psoriatic Arthritis Criteria of Fournié (1999) [125]

<u>Diagnosis of PsA ≥ 11 points</u>	<u>Points</u>
• Psoriasis antedating of concomitant with joint symptom onset	6
• Family history of psoriasis (if criterion 1 negative) or psoriasis post dating joint symptom onset	3
• Arthritis of a distal interphalangeal joint	3
• Asymmetric monoarthritis or oligoarthritis	1
• Buttock pain, heel pain, spontaneous anterior chest wall pain, enthesitis	2
• Radiological criteria (any 1 criterion) Erosions of distal interphalangeal joint Osteolysis Ankylosis Juxt-articular periostitis Phalangeal tuft resorption	5
• HLA-B16 (38, 39) or B17	6
• Negative rheumatoid factor	4

Table 3: CASPAR classification criteria for PsA [69].

CASPAR Criteria (2006)		
Inflammatory articular disease (joint, spine, enthesal) with ≥ 3 points from the following:		
		Points
1. Evidence of psoriasis	Current psoriasis	2
	Personal history of psoriasis	1
	Family history of psoriasis	1
2. Psoriatic nail dystrophy	Onycholysis, pitting, hyperkeratosis	1
3. Negative test result for RF	By any method except latex: ELISA or nephelometry preferable	1
4. Dactylitis	Current swelling of an entire digit	1
	History of dactylitis by Rheumatologist	1
5. Radiological evidence of juxta-articular new bone formation	Ill-defined ossification near joint margins excluding osteophyte formation on conventional radiographs of hand or foot	1

Table 4: Sensitivity and specificity of various classification criteria for PsA[69].

Criteria	Sensitivity	Specificity
Moll and Wright	91%	98%
Bennett	44%	100%
Vasey and Espinoza	97%	96%
Modified ESSG	74%	91%
Modified McGonagle	98%	91%
Fournié	94%	95%
CASPAR	99%	91%

A good clinical history and physical examination are essential in the evaluation of patients with suspected PsA. Laboratory tests and imaging studies also have an important role as described above. Physicians should obtain a thorough history including inquiring about current or past diagnosis of psoriasis; psoriasis is typically diagnosed about 10 years prior to the onset of articular disease in patients with PsA. Other key historical elements are a history of peripheral joint pain or swelling, Achilles's tendinitis or plantar fasciitis, dactylitis, inflammatory back pain (worse in the morning and better with exercise), and a family history of psoriasis or PsA.

Physical examination can help in differentiating PsA from other inflammatory arthropathies including RA. While RA is seen more commonly in female patients, PsA is seen equally in male and female patients. Detailed examination needs to be performed for the detection of psoriatic skin lesions, nail changes (onycholysis, pitting, hyperkeratosis), involvement of the distal interphalangeal joints, enthesitis, and dactylitis. Examination may reveal asymmetric joint involvement, enthesitis, and absence of rheumatoid nodules. Particular attention to the presence of axial involvement is also of significant importance. Eye examination may reveal conjunctivitis or uveitis[21]. Peripheral joint involvement of the hands and feet, especially with an asymmetric pattern, along with psoriatic skin lesion and nail changes is highly suggestive of PsA [21].

Treatment of PsA

The goals of treatment of PsA include pain control, prevention of joint destruction, improvement in quality of life, and decrease in mortality. For patients with active skin disease, it would also include reduction in activity of psoriasis. Several response criteria have been developed to monitor response to treatment in PsA most useful in clinical treatment trials. The American College of Rheumatology (**ACR**) Response Criteria (ACR20, 50, 70) were initially developed for assessment of response to treatment in patients with RA; they have also been used in clinical trials of patients with PsA (Table 5) [76,77]. The Disease Activity Score (**DAS**) using a 78 tender joint count and 76 swollen joint count has been used for the assessment of response to treatment in PsA. Compared to the ACR20 Response Criteria which measures disease activity relative to a previous visit, the DAS measures disease activity at a single point in time (visit) [76,77]. The PsA Response Criteria (**PsARC**) were specifically developed for PsA in a trial of sulfasalazine for the treatment of PsA (Table 6) [76,77]. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (**GRAPPA**) have proposed an algorithm for assessment of disease severity with categories of disease activity of mild, moderate, severe to be used as a tool in clinical decision making (Table 7) [78]. Another method of assessing response to treatment is the concept of Minimal Disease Activity (**MDA**). Disease activity is assessed by evaluating 7 parameters including tender joint count, swollen joint count, psoriasis skin disease activity, patient assessment of pain, patient assessment of global disease activity, Health Assessment Questionnaire (**HAQ**), and assessment of enthesitis. A patient is considered to have achieved MDA if 5 out of the 7 criteria have very low scores (Table 8) [79].

Table 5: American College of Rheumatology 20 Response Criteria – ACR20.

ACR20 Response Criteria (ACR50, ACR70)
1. ³ 20% reduction in the tender joint count
2. ³ 20% reduction in the swollen joint count
3. ³ 20% reduction in 3 of 5 additional measures including
a. Patient assessment of pain
b. Patient global assessment of disease activity
c. Physician global assessment of disease activity
d. Disability index of the Health Assessment Questionnaire
e. Acute phase reactants (ESR or CRP)

Table 6: Psoriatic Arthritis Response Criteria (PsARC).

PsA Response Criteria	
At least 2 of the following (Must include improvement in tender and swollen joint counts)	None of the following
20% improvement in physician global assessment of disease activity	Worsening in tender or swollen joint count Worsening in any PsARC component
20% improvement in patient global assessment of disease activity	
30% improvement in tender joint count	
30% improvement in swollen joint count	

Table 7: Severity assessment in PsA; stratification of patients with PsA by disease severity for clinical decision making [78].

	Mild	Moderate	Severe
Peripheral arthritis	< 5 joints (tender/swollen) No damage on x-ray No LOF QoL, minimal impact Patient evaluation, mild	≥ 5 joints (tender/swollen) Damage on x-ray IR to mild treatment Moderate LOF Moderate impact of QoL Patient evaluation, moderate	≥ 5 joints (tender/swollen) Severe damage on x-ray IR to mild-mod treatment Severe LOF Severe impact on QoL Patient evaluation, severe
Skin disease	BSA < 5 PASI, 5 Asymptomatic	Non-response to topicals DLQI, PASI <10	BSA > 10 PASI > 10 DLQI > 10
Spinal disease	Mild pain No LOF	LOF or BASDAI >4	Failure to respond
Enthesitis	1-2 sites No LOF	>2 sites or LOF	LOF or > 2 sites and failure to respond
Dactylitis	Pain, absent to mild Normal function	Erosive disease or LOF	Failure of response

QoL: Quality Of Life; **BSA:** Body Surface Area; **PASI:** Psoriasis Activity Severity Score; **LOF:** Loss of Function; **IR:** Inadequate Response; **DLQI:** Dermatology Quality of Life; **BASDAI:** Bath Ankylosing Spondylitis Disability Activity Index.

Table 8: Minimal disease activity (MDA) in PsA [79].

Minimal Disease Activity (MDA) in Psoriatic Arthritis (5 of 7 of the following)
• Tender joint count 1 • Swollen joint count 1 • Psoriasis Activity and Severity Index 1 or Body Surface Area 3 • Patient pain by Visual Analogue Score (VAS) 15 • Patient global disease activity Visual Analogue Scale(VAS)20 • Health Assessment Questionnaire (HHAQ) 0.5 • Tender entheses points 1

Treatment of PsA includes both non-pharmacologic and pharmacologic measures. Both ACR and EULAR guidelines emphasize that non-pharmacologic measures are an integral aspect of the treatment strategy [76,80,81]. Patient education about the pathophysiology and natural course of the disease is essential as it promotes compliance with treatment and long term follow up. Physical therapy is also of paramount importance, as it promotes regular exercise and a sense of well-being.

Pharmacologic treatment of PsA includes non-steroid anti-inflammatory drugs (NSAIDs), corticosteroids, and disease modifying anti-rheumatic drugs (DMARDs). DMARDs can be further classified in three categories: conventional synthetic DMARDs (csDMARDs) (methotrexate, sulfasalazine, and leflunomide), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) such as phosphodiesterase 4 (PDE4) inhibitors (apremilast), and Janus kinase (JAK) inhibitors (tofacitinib). Table 9 shows the EULAR recommendations for pharmacological therapy in PsA [80].

Table 9: EULAR recommendations for the pharmacological therapy of psoriatic arthritis [80].

EULAR Recommendations for the Management of psoriatic arthritis with Pharmacological Therapies: 2015 Update	
1	Treatment should be aimed at reaching the target of remission or, alternatively, minimal/ low disease activity, by regular monitoring and appropriate adjustment of therapy
2	In patients with PsA, NSAIDs may be used to relieve musculoskeletal signs and symptoms
3	In patients with peripheral arthritis, particularly in those with many swollen joints, structural damage in the presence of inflammation, high ESR/CRP and/or clinically relevant extra-articular manifestations, csDMARDs should be considered at an early stage, with methotrexate preferred in those with relevant skin involvement
4	Local injections of glucocorticoids should be considered as adjunctive therapy in PsA; systemic glucocorticoids may be used with caution at the lowest effective dose
5	In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD, usually a TNF inhibitor, should be commenced
6	In patients with peripheral arthritis and an inadequate response to at least one csDMARD, in whom TNF inhibitors are not appropriate, bDMARDs targeting IL12/23 or IL17 pathways may be considered
7	In patients with peripheral arthritis and an inadequate response to at least one csDMARD, in whom bDMARDs are not appropriate, a targeted synthetic DMARD such as a PDE4 inhibitor may be considered
8	In patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a bDMARD should be considered, which according to current practice is a TNF inhibitor
9	In patients with predominantly axial disease that is active and has insufficient response to NSAIDs, therapy with a bDMARD should be considered, which according to current practice is a TNF inhibitor
10	In patients who fail to respond adequately to a bDMARD, switching to another bDMARD should be considered, including switching between TNF inhibitors

NSAIDs were previously the mainstay of treatment in PsA [82,83]. They are commonly prescribed as the initial agent in mild peripheral or axial disease for the relief of joint pain and stiffness and in small studies they have been shown to be more effective than placebo. However, they have no effect on the psoriatic rash; actually some studies have shown a detrimental effect of NSAIDs on the rash, perhaps due to shunting of arachidonic acid metabolites into the leukotriene pathway [84,85]. No significant difference in effectiveness has been demonstrated among the different categories of NSAIDs [83]. When treating patients with PsA who have known or suspected coronary artery disease, special consideration must be given to using NSAIDs and COX-2 inhibitors as they increase the risk for cardiovascular events [83,86,87].

Among the csDMARDs, methotrexate (MTX) is the most commonly prescribed medication for the treatment of PsA. The most robust data for the efficacy of MTX comes from NOR-DMARD, a large registry study from Norway [88]. In this study, 430 MTX-naïve patients with PsA were followed over a period of two years, while 1218 MTX-naïve patients with rheumatoid arthritis (RA) from the same study served as a reference population. At 6 months, treatment with MTX was associated with improvement in disease activity and health-related quality of life in patients with PsA (although to a lesser degree when compared to RA patients). A recently published randomized placebo-controlled trial, however, by Kingsley et al. casts doubt about the efficacy of MTX in PsA treatment [89]. In this study 221 patients with PsA were randomized to receive MTX (at a dose of 15 mg/week) or placebo. Interestingly, at 6 months, no significant difference was seen in PsARC, ACR20, or DAS-28. Also, MTX had no statistically significant effect on the number of tender and swollen joints, ESR, CRP, HAQ, and pain when compared to placebo [89].

Sulfasalazine (**SSZ**) is another csDMARD initially found to be helpful in the management of RA that has also been used for the treatment of PsA patients. In a large randomized placebo controlled trial performed by the Department of Veterans Affairs, 221 patients were randomized to receive SSZ or placebo. In those patients receiving SSZ, 58% of patients had clinical response compared to 47% of patients receiving placebo ($p=0.05$) [90].

Leflunomide is another csDMARD that inhibits denovo pyrimidine synthesis. Kaltwasser et al reported a randomized multinational randomized placebo-controlled trial of 190 patients. At 24 weeks, 59% of patients on leflunomide were classified as PsARC responders versus only 29% of patients given placebo ($p<0.001$). In addition, leflunomide was associated with better ACR20 response [91].

Cyclosporin A (**CSA**), an immunosuppressive agent use to prevent organ transplant rejection, has also been used for the treatment of PsA. In a small trial of 35 patients comparing CSA to MTX, the two agents appeared equally effective in reducing signs and symptoms. However, a higher percentage of CSA patients had to discontinue therapy due to adverse events [92]. In a larger, multicenter randomized trial, 99 patients were randomized to receive CSA or SSZ plus standard treatment or standard treatment alone (standard therapy consisted of NSAIDs $\pm$ low dose corticosteroids). At 24 weeks, CSA was found to be superior to SSZ and standard therapy or standard therapy alone for decreasing pain which was the primary endpoint, and reduction in the PASI. CSA was superior to standard therapy for several other variables including the tender and swollen joint count, patient and physician global assessment, and the spondylitis functional index [93].

Other csDMARDs that have been used in the management of PsA include azathioprine, retinoic acid derivatives, Psoralen and Ultraviolet Light (**PUVA**), antimalarial drugs, and gold salts, but data is limited [94]. In a Cochrane meta-analysis, only SSZ and parenteral MTX were found to be effective in PsA when compared to placebo [95].

A major advance in the treatment of PsA and psoriasis has been the use of biologic agents which have shown to be very effective in controlling the articular and cutaneous manifestations [96]. In most clinical trials of PsA, patients who were on MTX or other csDMARDs, NSAIDs, or prednisone (up to 10 mg daily) were allowed to continue these medication during the study period. Among the biologic DMARDs (bDMARDs), TNF- α inhibitors (TNFi) were the first to be used in the treatment of PsA. They were also found to be effective in psoriasis. There are 5 different agents available and all are FDA approved for the treatment of PsA and all but one are approved for the treatment of psoriasis. The TNFi are also effective in psoriasis, RA, and AS, and the monoclonal antibodies are effective in inflammatory bowel disease. Infliximab is a chimeric anti-TNF- α monoclonal antibody that is administered intravenously. The two major randomized placebo controlled trials evaluating infliximab in the treatment of PsA are IMPACT (Infliximab Multinational PsA Controlled Trial) and IMPACT 2. In these studies, patients who had failed treatment with at least one csDMARD were recruited [97,98]. In both trials, patients treated with infliximab were shown to have statistically significantly better responses as assessed by both ACR20 and PsARC ($p < 0.001$). In longer studies, infliximab therapy resulted in inhibition of radiographic progression in patients with PsA [99,100]. Etanercept is a recombinant human p75 TNF- α receptor:IgG Fc fusion protein that acts as a soluble TNF- α receptor and is administered subcutaneously. In a trial in which 205 patients were randomized to receive either etanercept or placebo, etanercept was associated with a significantly better ACR20 response rate at 12 weeks that was sustained at 24 and 48 weeks. It was also associated with a reduction in radiographic progression and improvement in the psoriatic skin lesions [101,102]. Adalimumab is a fully human monoclonal anti-TNF- α monoclonal antibody that is administered subcutaneously. In the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT), 315 patients were randomized to receive adalimumab or placebo. At 12 weeks, 58% of adalimumab treated patients achieved an ACR20 response compared to 14% of placebo treated patients ($p < 0.001$). This response was sustained at 24 weeks. Also, adalimumab treated patients had improvement in skin lesions and inhibition of radiographic progression [103-105]. Golimumab is a human anti-TNF- α monoclonal antibody that is administered subcutaneously or intravenously. In the placebo-controlled GO-REVEAL trial involving 405 patients, golimumab treated patients achieved an ACR20 response at a statistically significantly higher rate when compared to placebo (48% vs 9%, $p < 0.001$). As with other TNFi, there was improvement in psoriatic skin lesions and reduced radiographic progression [106-108]. The most recent TNFi to be FDA is certolizumab pegol which is a pegylated humanized Fab' fragment specific for TNF- α . This agent has also shown efficacy in controlling the signs and symptoms of PsA including joints, skin, enthesitis, dactylitis, and nail disease [109].

Several biologic agents which target the IL-23/IL-17 axis are approved or being investigated as therapies for PsA and psoriasis [110,111]. Ustekinumab is a fully human monoclonal antibody directed against the common p40 subunit shared by both IL-12 and IL-23 that is administered subcutaneously and approved for use in psoriasis and PsA. In multinational randomized clinical

trials including the PSUMMIT 1 and PSUMMIT 2 trials, ustekinumab was superior in reducing signs and symptoms of PsA and in diminishing psoriatic skin lesions when compared to placebo [112-114]. In addition, ustekinumab was shown to significantly inhibit radiographic progression [115]. Secukinumab is a fully human anti-interleukin-17A monoclonal antibody that is administered intravenously and approved for PsA, psoriasis, and AS. In two randomized controlled trials of patients with PsA including the FUTURE 2 trial, secukinumab was shown to be superior to placebo in achieving an ACR20 response [116,117]. These trials included some patients who had previously failed TNFi. Secukinumab was also effective in inhibiting radiographic progression [118]. Ixekizumab is a humanized anti-IL-17A monoclonal antibody that is approved for use in psoriasis [119,120] and is currently being evaluated as a treatment for PsA. Brodalumab is a human anti-IL17RA monoclonal antibody that has been shown to be efficacious in the treatment of active PsA and psoriasis but has not yet been approved for use [121]. Abatacept, a selective T cell costimulation modulator administered intravenously or subcutaneously, showed promising results in a phase II multicenter trial in patients with PsA [122].

Interest in the use of small molecules has increased recently in the treatment of PsA and psoriasis because of ease of delivery. Apremilast is a novel targeted synthetic DMARD (tsDMARD) which is a phosphodiesterase 4 inhibitor [123]. Apremilast has the advantage of oral delivery and no requirement for regular laboratory monitoring. It is approved for use in both PsA and psoriasis. Efficacy and safety in PsA was evaluated in 2 clinical trials and shown to be effective [124,125]. In the PALACE 1 trial, after 16 weeks of treatment, 40% of apremilast treated patients using a dose of 30 mg BID achieved an ACR20 response compared to 19% of placebo treated patients [125]. Tofacitinib, a novel oral JAK inhibitor approved for use in RA, that has been shown effective in psoriasis, is another tsDMARD that is currently being studied for use in PsA and psoriasis [126,127].

CONCLUSION

Over the past 15 years, many major advances have been made in regards to PsA and psoriasis. This includes epidemiology, genetics, and pathogenesis. Information regarding pathogenesis including dysregulation of inflammatory cytokines, in particular TNF- α and IL-17, has led to the development of targeted therapies which has greatly benefited patients with PsA and psoriasis. These agents have shown very good to excellent efficacy in reducing the signs and symptoms of PsA and also reducing the activity of the psoriatic skin rash with good safety profiles. In addition, many of these biologic agents also are effective in inhibiting radiographic progression. More recently, targeted small molecules have been used in the treatment of PsA and more are being developed and investigated. The advances in therapies available to patients with PsA have greatly increased hope for these patients.

References

1. Finzel S, Englbrecht M, Engelke K, Stach C, Schett G. A comparative study of periarticular bone lesions in rheumatoid arthritis and psoriatic arthritis. *Ann Rheum Dis*. 2011; 70: 122-127.
2. Ogdie A, Yu Y, Haynes K. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis*. 2015; 74: 326-332.
3. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of psoriatic arthritis: a systematic review. *J Rheumatol*. 2008; 35: 1354-1358.
4. Nossent JC, Gran JT. Epidemiological and clinical characteristics of psoriatic arthritis in northern Norway. *Scand J Rheumatol*. 2009; 38: 251-255.
5. Wilson FC, Icen M, Crowson CS, McEvoy MT, Gabriel SE. Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study. *Arthritis Rheum*. 2009; 61: 233-239.
6. Hanova P, Pavelka K, Holcatova I, Pikhart H. Incidence and prevalence of psoriatic arthritis, ankylosing spondylitis, and reactive arthritis in the first descriptive population-based study in the Czech Republic. *Scand J Rheumatol*. 2010; 39: 310-317.
7. Soriano ER, Rosa J, Velozo E. Incidence and prevalence of psoriatic arthritis in Buenos Aires, Argentina: a 6-year health management organization-based study. *Rheumatol*. 2011; 50: 729-734.
8. Asgari MM, Wu JJ, Gelfand JM, Salman C, Curtis JR, et al. Validity of diagnostic codes and prevalence of psoriasis and psoriatic arthritis in a managed care population, 1996-2009. *Pharmacoepidemiol Drug Saf*. 2013; 22: 842-849.
9. Shbeeb M, Uramoto KM, Gibson LE, O'Fallon WM, Gabriel SE. The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982-1991. *J Rheumatol*. 2000; 27: 1247-1250.
10. Gelfand JM, Gladman DD, Mease PJ, Smith N, Margolis DJ, et al. Epidemiology of psoriatic arthritis in the population of the United States. *J Am Acad Dermatol*. 2005; 53: 573.
11. Cakir N, Pamuk ÖN, Derviş E, İmeryüz N, Uslu H, et al. The prevalences of some rheumatic diseases in western Turkey: Havsıa study. *Rheumatol Int*. 2012; 32: 895-908.
12. Lofvendah S, Theander E, Svensson A, Carlsson KS, Englund M. Validity of diagnostic codes and prevalence of physician-diagnosed psoriasis and psoriatic arthritis in southern Sweden--a population-based register study. *PLoS ONE*. 2014; 9: e98024.
13. Li R, Sun J, Ren LM. Epidemiology of eight common rheumatic diseases in China: a large-scale cross-sectional survey in Beijing. *Rheumatol*. 2012; 51: 721-729.
14. Yang Q, Qu L, Tian H, Hu Y, Peng J, et al. Prevalence and characteristics of psoriatic arthritis in Chinese patients with psoriasis. *J Eur Acad Dermatol Venereol*. 2011; 25: 1409-1414.
15. Chandran V. The genetics of psoriasis and psoriatic arthritis. *Clin Rev Allergy Immunol*. 2013; 44: 149-156.
16. O'Rielly DD, Rahman P. Genetics of psoriatic arthritis. *Best Pract Res Clin Rheumatol*. 2014; 28: 673-685.
17. Panayi GS. Immunology of psoriasis and psoriatic arthritis. *Baillieres Clin Rheumatol*. 1994; 8: 419-427.
18. Marchesoni A, Helliwell P, Gallazzi M, Gibertini P, Rossetti A. Psoriatic arthritis in British and Italian patients: a comparative clinical, radiologic, and scintigraphic study. *J Rheumatol*. 1999; 26: 2619-2621.
19. Thumboo J, Tham SN, Tay YK, Chee T, Mow B, et al. Patterns of psoriatic arthritis in Orientals. *J Rheumatol*. 1997; 24: 1949-1953.
20. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis*. 2005; 64: 7-14.
21. Dhir V, Aggarwal A. Psoriatic arthritis: a critical review. *Clin Rev Allergy Immunol*. 2013; 44: 141-148.
22. Love TJ, Gudbjornsson B, Gudjonsson JE, Valdimarsson H. Psoriatic arthritis in Reykjavik, Iceland: prevalence, demographics, and disease course. *J Rheumatol*. 2007; 34: 2082-2088.
23. Carneiro JN, Paula AP, Martins GA. Psoriatic arthritis in patients with psoriasis: evaluation of clinical and epidemiological features in 133 patients followed at the University Hospital of Brasilia. *An Bras Dermatol*. 2012; 87: 539-544.
24. Ogdie A, Langan S, Love T, Haynes K, Shin D, et al. Prevalence and treatment patterns of psoriatic arthritis in the UK. *Rheumatology*. 2013; 52: 568-575.
25. Henes JC, Ziupa E, Eisfelder M. High prevalence of psoriatic arthritis in dermatological patients with psoriasis: a cross-sectional study. *Rheumatol Int*. 2014; 34: 227-234.
26. Christophers E, Barker JN, Griffiths CE. The risk of psoriatic arthritis remains constant following initial diagnosis of psoriasis among patients seen in European dermatology clinics. *J Euro Acad Dermatol Venereol*. 2010; 24: 548-554.

27. Eder L, Haddad A, Rosen CF, Lee KA, Chandran V. The Incidence and Risk Factors for Psoriatic Arthritis in Patients With Psoriasis: A Prospective Cohort Study. *Arthritis Rheumatol*. 2016; 68: 915-923.
28. Moll JM, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum*. 1973; 3: 55-78.
29. Chandran V, Schentag CT, Brockbank JE, Pellett FJ, Shanmugarajah S, et al. Familial aggregation of psoriatic arthritis. *Ann Rheum Dis*. 2009; 68: 664-667.
30. Gladman DD, Anhorn KA, Schachter RK, Mervart H. HLA antigens in psoriatic arthritis. *J Rheumatol*. 1986; 13: 586-592.
31. Nair RP, Stuart PE, Nistor I. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. *Am J Hum Genet*. 2006; 78: 827-851.
32. Chandran V, Rahman P. Update on the genetics of spondyloarthritis--ankylosing spondylitis and psoriatic arthritis. *Best Pract Res Clin Rheumatol*. 2010; 24: 579-588.
33. O'Rielly DD, Rahman P. Genetic, Epigenetic and Pharmacogenetic Aspects of Psoriasis and Psoriatic Arthritis. *Rheum Dis Clin North Am*. 2015; 41: 623-642.
34. Korendowych E, Dixey J, Cox B, Jones S, McHugh N. The Influence of the HLA-DRB1 rheumatoid arthritis shared epitope on the clinical characteristics and radiological outcome of psoriatic arthritis. *J Rheumatol*. 2003; 30: 96-101.
35. Ellinghaus D, Ellinghaus E, Nair RP. Combined analysis of genome-wide association studies for Crohn disease and psoriasis identifies seven shared susceptibility loci. *Am J Hum Genet*. 2012; 90: 636-647.
36. Costello P, Bresnihan B, O'Farrelly C, FitzGerald O. Predominance of CD8+ T lymphocytes in psoriatic arthritis. *J Rheumatol*. 1999; 26: 1117-1124.
37. Ritchlin C, Haas-Smith SA, Hicks D, Cappuccio J, Osterland CK. Patterns of cytokine production in psoriatic synovium. *J Rheumatol*. 1998; 25: 1544-1552.
38. Van Kuijk AW, Reinders-Blankert P, Smeets TJ, Dijkmans BA, Tak PP. Detailed analysis of the cell infiltrate and the expression of mediators of synovial inflammation and joint destruction in the synovium of patients with psoriatic arthritis: implications for treatment. *Ann Rheum Dis*. 2006; 65: 1551-1557.
39. Neumüller J, Dunky A, Burtscher H, Jilch R, Menzel JE. Interaction of monocytes from patients with psoriatic arthritis with cultured microvascular endothelial cells. *Clin Immunol*. 2001; 98: 143-152.
40. Thorleifsdottir RH, Sigurdardottir SL, Sigurgeirsson B. Improvement of psoriasis after tonsillectomy is associated with a decrease in the frequency of circulating T cells that recognize streptococcal determinants and homologous skin determinants. *J Immunol*. 2012; 188: 5160-5165.
41. Pattison E, Harrison BJ, Griffiths CE, Silman AJ, Bruce IN. Environmental risk factors for the development of psoriatic arthritis: results from a case-control study. *Ann Rheum Dis*. 2008; 67: 672-676.
42. Eder L, Law T, Chandran V, Shanmugarajah S, Shen H. Association between environmental factors and onset of psoriatic arthritis in patients with psoriasis. *Arthritis Care Res*. 2011; 1091-1097.
43. Gladman D, Chandran V. Psoriatic Arthritis. In: Goldsmith L, Katz S, Gilchrist B, Paller A, Leffell D, Wolff K, eds. *Fitzpatrick's Dermatology in General Medicine* 8th ed. New York City: McGraw Hill; 2012: 232-242.
44. Jones SM, Armas JB, Cohen MG, Lovell CR, Evison G. Psoriatic arthritis: outcome of disease subsets and relationship of joint disease to nail and skin disease. *Br J Rheumatol*. 1994; 33: 834-839.
45. Gladman DD. Natural history of psoriatic arthritis. *Baillieres Clin Rheumatol*. 1994; 8: 379-394.
46. Gladman DD, Shuckett R, Russell ML, Thorne JC, Schachter RK. Psoriatic arthritis (PSA)--an analysis of 220 patients. *Q J Med*. 1987; 62: 127-141.
47. Queiro R, Torre JC, Belzunegui J. Clinical features and predictive factors in psoriatic arthritis-related uveitis. *Semin Arthritis Rheum*. 2002; 31: 264-270.
48. Mease P, Goffe BS. Diagnosis and treatment of psoriatic arthritis. *J Am Acad Dermatol*. 2005; 52: 1-19.
49. Punzi L, Pianon M, Rossini P, Schiavon F, Gambari PF. Clinical and laboratory manifestations of elderly onset psoriatic arthritis: a comparison with younger onset disease. *Ann Rheum Dis*. 1999; 58: 226-229.
50. Punzi L, Podswiadek M, Oliviero F. Laboratory findings in psoriatic arthritis. *Reumatismo*. 2007; 59: 52-55.
51. Gladman DD, Farewell VT, Wong K, Husted J. Mortality studies in psoriatic arthritis: results from a single outpatient center. II. Prognostic indicators for death. *Arthritis Rheum*. 1998; 41: 1103-1110.
52. Gladman DD, Farewell VT. Progression in psoriatic arthritis: role of time varying clinical indicators. *J Rheumatol*. 1999; 26: 2409-2413.

53. Bogliolo L, Alpini C, Caporali R, Scirè CA, Moratti R, Montecucco C. Antibodies to cyclic citrullinated peptides in psoriatic arthritis. *J Rheumatol*. 2005; 32: 511-515.
54. Johnson SR, Schentag CT, Gladman DD. Autoantibodies in biological agent naive patients with psoriatic arthritis. *Ann Rheum Dis*. 2005; 64: 770-772.
55. Fiocco U, Cozzi L, Chieco-Bianchi F, Rigon C, Vezzù M. Vascular changes in psoriatic knee joint synovitis. *J Rheumatol*. 2001; 28: 2480-2486.
56. Fearon U, Reece R, Smith J, Emery P, Veale DJ. Synovial cytokine and growth factor regulation of MMPs/TIMPs: implications for erosions and angiogenesis in early rheumatoid and psoriatic arthritis patients. *Ann N Y Acad Sci*. 1999; 878: 619-621.
57. Poggendorf RP, Ostergaard M, Terslev L. Imaging in Psoriatic Arthritis. *Rheum Dis Clin North Am*. 2015; 41: 593-613.
58. Liu JT, Yeh HM, Liu SY, Chen KT. Psoriatic arthritis: Epidemiology, diagnosis, and treatment. *World J Orthop*. 2014; 5: 537-543.
59. Jurik AG. Imaging the spine in arthritis-a pictorial review. *Insights Imaging*. 2011; 2: 177-191.
60. McGonagle D. Imaging the joint and enthesis: insights into pathogenesis of psoriatic arthritis. *Ann Rheum Dis*. 2005; 64: ii58-ii60.
61. Offidani A, Cellini A, Valeri G, Giovagnoni A. Subclinical joint involvement in psoriasis: magnetic resonance imaging and X-ray findings. *Acta Derm Venereol*. 1998; 78: 463-465.
62. McQueen F, Lassere M, Østergaard M. Magnetic resonance imaging in psoriatic arthritis: a review of the literature. *Arthritis Res Ther*. 2006; 8: 207.
63. McQueen FM, Dalbeth N, Doyle A. MRI in psoriatic arthritis: insights into pathogenesis and treatment response. *Curr Rheumatol Rep*. 2008; 10: 303-310.
64. Coates LC, Hodgson R, Conaghan PG, Freeston JE. MRI and ultrasonography for diagnosis and monitoring of psoriatic arthritis. *Best Pract Res Clin Rheumatol*. 2012; 26: 805-822.
65. Poggendorf RP, Pedersen SJ, Eshed I. Head-to-toe whole-body MRI in psoriatic arthritis, axial spondyloarthritis and healthy subjects: first steps towards global inflammation and damage scores of peripheral and axial joints. *Rheumatol*. 2015; 54: 1039-1049.
66. Poggendorf RP, Eshed I, Ostergaard M. Enthesitis in patients with psoriatic arthritis, axial spondyloarthritis and healthy subjects assessed by 'head-to-toe' whole-body MRI and clinical examination. *Ann Rheum Dis*. 2015; 74: 823-829.
67. Milosavljevic J, Lindqvist U, Elvin A. Ultrasound and power Doppler evaluation of the hand and wrist in patients with psoriatic arthritis. *Acta Radiol*. 2005; 46: 374-385.
68. Helliwell PS, Taylor WJ. Classification and diagnostic criteria for psoriatic arthritis. *Ann Rheum Dis*. 2005; 64: ii3-ii8.
69. Taylor W, Gladman D, Helliwell P. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum*. 2006; 54: 2665-2673.
70. Coates LC, Conaghan PG, Emery P, Green MJ, Ibrahim G. Sensitivity and specificity of the classification of psoriatic arthritis criteria in early psoriatic arthritis. *Arthritis Rheum*. 2012; 64: 3150-3155.
71. Bennett RM. Psoriatic Arthropathy. In: McCarty DJ, ed. *Arthritis and Related Conditions*. 9th ed. Philadelphia: Lea & Febiger. 1979: 642-655.
72. Vasey FB, Espinoza LR. Psoriatic Arthritis. In: Calin A, ed. *Spondyloarthropathies*. Orlando: Grune and Stratton; 1984: 151-185.
73. Dougados M, van der Linden S, Juhlin R. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum*. 1991; 34: 1218-1227.
74. McGonagle D, Conaghan PG, Emery P. Psoriatic arthritis: a unified concept twenty years on. *Arthritis Rheum*. 1999; 42: 1080-1086.
75. Fournie B, Crognier L, Arnaud C. Proposed classification criteria of psoriatic arthritis. A preliminary study in 260 patients. *Revue du Rhumatisme*. 1999; 66: 446-456.
76. Gottlieb A, Korman NJ, Gordon KB, Feldman SR, Lebwohl M, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and guidelines of care for tre... *J Am Acad Dermatol*. 2008; 58: 851-864.
77. Gladman DD, Helliwell P, Mease PJ, Nash P, Ritchlin C. Assessment of patients with psoriatic arthritis: a review of currently available measures. *Arthritis Rheum*. 2004; 50: 24-35.
78. Ritchlin CT, Kavanaugh A, Gladman DD, Mease PJ, Helliwell P. Treatment recommendations for psoriatic arthritis. *Ann Rheum Dis*. 2009; 68: 1387-1394.
79. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. *Ann Rheum Dis*. 2010; 69: 48-53.

80. Gossec L, Smolen JS, Ramiro S. European League against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis.* 2016; 75: 499-510.
81. Coates LC, Kavanaugh A, Mease PJ. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. *Arthritis Rheum.* 2016; 68: 1060-1071.
82. Cuéllar ML, Citera G, Espinoza LR. Treatment of psoriatic arthritis. *Baillieres Clin Rheumatol.* 1994; 8: 483-498.
83. Nash P, Clegg DO. Psoriatic arthritis therapy: NSAIDs and traditional DMARDs. *Ann Rheum Dis.* 2005; 64: ii74-ii77.
84. Meyerhoff JO. Exacerbation of psoriasis with meclofenamate. *N Engl J Med.* 1983; 309: 496.
85. Clark DW, Coulter DM. Psoriasis associated with rofecoxib. *Arch Dermatol.* 2003; 139: 1223.
86. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA.* 2001; 286: 954-959.
87. Graham DJ. COX-2 inhibitors, other NSAIDs and cardiovascular risk: the seduction of common sense. *JAMA.* 2006; 296: 1653-1656.
88. Lie E, van der Heijde D, Uhlig T, Heiberg MS, Koldingsnes W, et al. Effectiveness and retention rates of methotrexate in psoriatic arthritis in comparison with methotrexate-treated patients with rheumatoid arthritis. *Ann Rheum Dis.* 2010; 69: 671-676.
89. Kingsley GH, Kowalczyk A, Taylor H. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. *Rheumatol.* 2012; 51: 1368-1377.
90. Clegg DO, Reda DJ, Mejias E. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. *Arthritis Rheum.* 1996; 39: 2013-2020.
91. Kaltwasser JP, Nash P, Gladman D. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. *Arthritis Rheum.* 2004; 50: 1939-1950.
92. Spadaro A, Riccieri V, Sili-Scavalli A, Sensi F, Taccari E. Comparison of cyclosporin A and methotrexate in the treatment of psoriatic arthritis: a one-year prospective study. *Clin Exp Rheumatol.* 1995; 13: 589-593.
93. Salvarani C, Macchioni P, Olivieri I, Marchesoni A, Cutolo M. A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. *J Rheumatol.* 2001; 28: 2274-2282.
94. Gladman DD. Psoriatic arthritis. *Dermatol Ther.* 2004; 17: 350-363.
95. Jones G, Crotty M, Brooks P. Interventions for psoriatic arthritis. *Cochrane Database Syst Rev:* CD000212. 2000.
96. Mease PJ. Biologic Therapy for Psoriatic Arthritis. *Rheum Dis Clin North Am.* 2015; 41: 723-738.
97. Antoni CE, Kavanaugh A, Kirkham B. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). *Arthritis Rheum.* 2005; 52: 1227-1236.
98. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis.* 2005; 64: 1150-1117.
99. Kavanaugh A, Antoni CE, Gladman D. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year. *Ann Rheum Dis.* 2006; 65: 1038-1043.
100. Van der Heijde D, Kavanaugh A, Gladman DD. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the induction and maintenance psoriatic arthritis clinical trial 2. *Arthritis Rheum.* 2007; 56: 2698-2707.
101. Mease PJ, Kivitz AJ, Burch FX. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum.* 2004; 50: 2264-2272.
102. Mease PJ, Kivitz AJ, Burch FX. Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. *J Rheumatol.* 2006; 33: 712-721.
103. Mease PJ, Gladman DD, Ritchlin CT. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum.* 2005; 52: 3279-3289.
104. Gladman DD, Mease PJ, Ritchlin CT. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. *Arthritis Rheum.* 2007; 56: 476-488.
105. Mease PJ, Ory P, Sharp JT, Ritchlin CT, Van den Bosch F, et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). *Ann Rheum Dis.* 2009; 68: 702-709.

106. Kavanaugh A, McInnes I, Mease P. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum.* 2009; 60: 976-986.
107. Kavanaugh A, Van der Heijde D, McInnes IB. Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo-controlled trial. *Arthritis Rheum.* 2012; 64: 2504-2517.
108. Kavanaugh A, McInnes IB, Mease PJ. Clinical efficacy, radiographic and safety findings through 2 years of golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of the randomised, placebo-controlled GO-REVEAL study. *Ann Rheum Dis.* 2013; 72: 1777-1785.
109. Mease PJ, Fleischmann R, Deodhar AA. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis.* 2014; 73: 48-55.
110. Yermenko N, Paramarta JE, Baeten D. The interleukin-23/interleukin-17 immune axis as a promising new target in the treatment of spondyloarthritis. *Curr Opin Rheumatol.* 2014; 26: 361-370.
111. Tausend W, Downing C, Tying S. Systematic review of interleukin-12, interleukin-17, and interleukin-23 pathway inhibitors for the treatment of moderate-to-severe chronic plaque psoriasis: ustekinumab, briakinumab, tildrakizumab, guselkumab, secukinumab, ixekizumab, and brodalumab. *J Cutaneous Med Surg.* 2014; 18: 156-169.
112. Gottlieb A, Menter A, Mendelsohn A. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. *Lancet.* 2009; 373: 633-640.
113. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-c... *Lancet.* 2013; 382: 780-789.
114. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non... *Ann Rheum Dis.* 2014; 73: 990-999.
115. Kavanaugh A, Ritchlin C, Rahman P. Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials. *Ann Rheum Dis.* 2014; 73: 1000-1006.
116. Mease PJ, McInnes IB, Kirkham B. Secukinumab Inhibition of Interleukin-17A in Patients with Psoriatic Arthritis. *N Engl J Med.* 2015; 373: 1329-1339.
117. McInnes IB, Sieper J, Braun J. Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. *Ann Rheum Dis.* 2014; 73: 349-356.
118. Van der Heijde D, Landewe RB, Mease PJ. Brief Report: Secukinumab Provides Significant and Sustained Inhibition of Joint Structural Damage in a Phase III Study of Active Psoriatic Arthritis. *Arthritis Rheum.* 2016; 68: 1914-1921.
119. Leonardi C, Matheson R, Zachariae C. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med.* 2012; 366: 1190-1199.
120. Gordon KB, Leonardi CL, Lebwohl M. A 52-week, open-label study of the efficacy and safety of ixekizumab, an anti-interleukin-17A monoclonal antibody, in patients with chronic plaque psoriasis. *J Am Acad Dermatol.* 2014; 71: 1176-1182.
121. Mease PJ, Genovese MC, Greenwald MW, Ritchlin CT, Beaulieu AD, et al. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. *N Engl J Med.* 2014; 370: 2295-306.
122. Mease PJ, Genovese MC, Gladstein G, Ritchlin CT, Beaulieu AD. Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. *Arthritis Rheum.* 2011; 63: 939-948.
123. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. *Biochem Pharmacol.* 2012; 83: 1583-1590.
124. Schett G, Wollenhaupt J, Papp K. Oral apremilast in the treatment of active psoriatic arthritis: results of a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum.* 2012; 64: 3156-3167.
125. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis.* 2014; 73: 1020-1026.
126. Hansen RB, Kavanaugh A. Novel treatments with small molecules in psoriatic arthritis. *Curr Rheumatol Rep.* 2014; 16: 443.
127. Papp KA, Menter A, Strober B. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a Phase 2b randomized placebo-controlled dose-ranging study. *Br J Dermatol.* 2012; 167: 668-677.