Review article

Management of psoriatic arthritis: Early diagnosis, monitoring of disease severity and cutting edge therapies

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Abstract
Psoriatic arthritis (PsA) is a heterogeneous disease that can involve a variety of distinct anatomical sites including a patient’s peripheral and axial joints, entheses, skin and nails. Appropriate management of PsA requires early diagnosis, monitoring of disease activity, and utilization of cutting edge therapies. To accomplish the former there are a variety of PsA-specific tools available to screen, diagnose, and assess patients. This review will outline the recently developed PsA screening tools, including the Toronto Psoriatic Arthritis Screening Questionnaire (TOPAS), the Psoriasis Epidemiology Screening Tool (PEST), the Psoriatic Arthritis Screening and Evaluation (PASE), and the Psoriasis and Arthritis Screening Questionnaire (PASQ). We will also review the Classification Criteria for Psoriatic Arthritis (CASPAR) and current PsA disease severity measures, such as the Disease Activity index for Psoriatic Arthritis (DAPSA), the Psoriatic Arthritis Joint Activity Index (PsAJAI) and the Composite Psoriatic Disease Activity Index (CPDAI).

As is the case for PsA screening and assessment tools, there are also a variety of new therapies available for PsA. Historically, patients with PsA were treated with NSAIDS and traditional disease-modifying anti-rheumatic drugs (DMARDs). However, the ability of these medications to slow down the radiographic progression of joint disease has not been demonstrated. In contrast, anti-TNF agents, such as etanercept, infliximab, adalimumab, golimumab and certolizumab, are effective in this regard. Emerging PsA treatments include an oral phosphodiesterase 4 inhibitor, apremilast; a Janus kinase (JAK) inhibitor, tofacitinib; and several new biologics that target the IL-23/IL-17 pathway including secukinumab, brodalumab, ixekizumab, and ustekinumab. Herein we will review the mechanisms of action of these drugs, their results in clinical trials, and guidelines for administration. Lastly, treatment recommendations from the European League Against Rheumatism (EULAR) and The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) will be discussed.

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1. Introduction

Psoriatic arthritis (PsA) is a heterogeneous disease characterized by involvement of skin, nails, peripheral and axial joints, and entheses [1,2]. The variety of affected organ systems makes the clinical diagnosis and management of PsA challenging. Optimal patient management centers around making the diagnosis early, accurately assessing disease severity, and initiating appropriate treatment for inflammatory arthritis and other PsA-associated comorbidities. A sensitive screening tool can aid the non-specialist in making a diagnosis of PsA, ideally at the earliest stage of disease prior to the development of the otherwise erosive arthropathies [3]. After a patient has been successfully screened for PsA, standard diagnostic criteria can then be applied to validate the diagnosis and to determine if the patient is eligible for enrollment in a clinical trial. The concept of screening tools, diagnostic criteria, and disease assessment tools for PsA are evolving concepts. Currently there are no widely accepted diagnostic criteria for PsA and PsA-specific outcome measures are still being developed and modified [4]. Herein, we will review the available tools to aid in the screening, diagnosis and monitoring of PsA, as well as provide a detailed review of currently available therapies, including the emerging categories of phosphodiesterase-4 inhibitors and biologics targeting the IL-23/IL-17 pathway. Over the last decade targeted therapies have revolutionized the treatment of PsA and the future looks even brighter [5–7].

1.1. Early diagnosis of psoriatic arthritis

In the vast majority of PsA patients, cutaneous lesions indicative of psoriasis precede development of arthritic signs and symptoms [8]. Although currently in development, there are no serum biomarkers to accurately predict which psoriasis patients will go on to develop PsA [9–11]. In fact, it may take many years for a patient with psoriasis to develop inflammatory arthritis [12]. Thus, dermatology and primary care providers should be keenly poised to diagnose PsA in their at-risk patients with cutaneous psoriasis. For these patients, achieving a good long-term clinical outcome depends in part on the physician’s ability to make an early diagnosis of PsA and to initiate treatment prior to the onset of significant and permanent joint damage [3,13]. Making an early diagnosis is also critical for testing new PsA therapies while the disease is still evolving and the capacity to prevent or slow joint damage may be assessed. An ideal diagnostic test for PsA will be both highly sensitive and highly specific. Although this is also true for screening tools, high sensitivity is particularly important to ensure that patients with PsA are not missed during screening. Recently, several screening questionnaires for PsA have been developed for use in dermatology and primary care offices (Table 1). These include the Toronto Psoriatic Arthritis Screening Questionnaire (TOPAS), Psoriasis Epidemiology Screening Tool (PEST), Psoriatic Arthritis Screening and Evaluation (PASE), and the Psoriasis and Arthritis Screening Questionnaire (PASQ) [14–16]. These screening questionnaires are now used internationally; sensitivity and specificity of these questionnaires are mentioned in the (Table 1). With proper use of these tools it is expected that PsA can be identified at the

<table>
<thead>
<tr>
<th>Screening tools</th>
<th>Description</th>
<th>Sensitivity/Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASQ</td>
<td>10 items + joint diagram</td>
<td>Sensitivity 82%</td>
</tr>
<tr>
<td>PASE</td>
<td>Self-administered</td>
<td>15 items</td>
</tr>
<tr>
<td>PEST</td>
<td>Self-administered</td>
<td>5 items + joint diagram</td>
</tr>
<tr>
<td>ToPAS</td>
<td>Self-administered</td>
<td>11 items + pictures/diagrams</td>
</tr>
</tbody>
</table>

Table 1: Screening tools for early diagnosis of Psoriatic arthritis.

TOPAS, Toronto Psoriatic Arthritis Screening; PEST, Psoriasis Epidemiology Screening Tool; PASE, Psoriatic Arthritis Screening and Evaluation; PASQ, Psoriasis and Arthritis Screening Questionnaire; NA, not applicable. (Table adapted from the article by Machado and Raychaudhuri [3]).
onset of the disease process and thus by treating at its early stage joint deformities and comorbidities of PsA may be minimized.

The Classification Criteria for Psoriatic Arthritis (CASPAR) was developed using data collected from patients with long-standing PsA and is based on an established diagnostic criteria for inflammatory arthritic disease that was modified to include additional clinical findings specific to PsA, such as the presence of psoriatic nail dystrophy, a negative RF test, dactylitis, and radiographic evidence of juxta-articular bone formation [17] (Table 2). These were identified as PsA-specific disease features by comparing 588 patients with PsA and 536 controls that were comprised mainly of patients with RA or ankylosing spondylitis. Signs specific to PsA were determined by multivariate statistical analysis of more than 50 variables. Importantly, classification criteria such as CASPAR are designed for use mainly in the research settings to identify subjects for inclusion in clinical studies. Thus, specificity is of the utmost importance. This will increase the homogeneity of the studied patient population and ensure that individuals enrolled in a trial actually have PsA. The CASPAR is regarded as being highly specific (99.1%) for the diagnosis of PsA, however the sensitivity for detecting early PsA was found to be much lower, 87.4% [18,19]. Also, in patients with early stage PsA, the sensitivity of the CASPAR may be further limited in patients in which the inflammatory arthritic component of PsA has not yet declared itself. In summary, while CASPAR has exceptional specificity for PsA, it is not ideally suited to be used as a sensitive screening tool, i.e. it is not as useful to identify psoriasis patients who are just developing PsA.

1.2. Outcome measures to assess PsA disease severity

As patients with PsA may have significant peripheral arthritis, clinical trials of PsA therapies often incorporate outcome measures developed and validated for rheumatoid arthritis (RA) [20]. These include the American College of Rheumatology (ACR) Responder Index (ACR-20) and the Disease Activity Score for 28 joints (DAS28) [21,22]. However, differences between the clinical presentation of PsA and RA raised concerns about the ability of ACR-20 and DAS28 to capture all of the manifestations contributing to PsA disease activity. For example, PsA has a greater tendency for asymmetric and oligoarticular joint involvement than RA. In addition, the distal interphalangeal (DIP) joints are commonly involved in PsA but not in RA—a potential issue because the 28 joint count comprising the DAS28 excludes the (DIP) joints of the fingers, as well as the ankles and feet [21]. Thus, in cases of oligoarthritis, use of the DAS28 can misclassify 20% of PsA cases and miss a significant number of patients with active disease [23]. As a result of this discrepancy, a 68 tender and 66 swollen joint count, including the DIP joints of the hands has been recommended for use in PsA clinical trials [24].

Compared to RA where the major focus is peripheral arthritis, PsA disease extent is also determined by the severity of extra-articular manifestations including psoriatic skin lesions and dactylitis [25]. The development of valid, feasible, and reliable outcome measures that can ideally be employed in longitudinal cohorts and clinical trials remains a topic of research. Various validated disease scoring instruments are listed in Table 3. The degree of involvement of the different domains of PsA (such as joints, skin and nails and entheses) can vary significantly between patients as well as over time within the same patient but all of the domains may have a significant impact on the patient’s quality of life (QOL). Thus, to assess the disease activity in a heterogeneous condition such as PsA, a composite measure may be most accurate. For PsA this is a relatively new concept and The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has been actively pursuing this task. The goal is to integrate the different signs and symptoms of PsA at a specific point in time [26,27]. Through the efforts by GRAPPA and other investigators, PsA-specific composite disease measures are emerging. Among these, the following measures have been validated and are currently being evaluated in clinical trials: the Disease Activity index for Psoriatic Arthritis (DAPSA), the Psoriatic Arthritis Joint Activity Index (PsAJAI) and the Composite Psoriatic Disease Activity Index (CPDAI) [28–31]. In Table 4 a summary of various domains of these indices is provided.

The CPDAI categorizes PsA disease severity as mild, moderate and severe. This is a validated outcome measure that has been shown to demonstrate a significant correlation with patient (r = 0.777) and physician global (r = 0.809) assessments; CPDAI can discriminate between ineffectively and effectively treated patients [31]. In the CPDAI, disease involvement is assessed in five domains: peripheral joints (swollen joint count (SJC) of 66 and tender joint count (TJC) of 68), skin (PASI), dactylitis (by counting the number of digits involved), enthesitis (number of tendons/fascia insertion sites showing enthesitis), and spinal manifestations [Ankylosing Spondylitis Quality of Life (ASQoL) and Bath Ankylosing Spondylitis Disease Index (BASDAI)]. Each domain is scored from 0 to 3, resulting in a CPDAI score range of 0–15. A modified CPDAI (mCPDAI) [32], including only four domains (without the axial domain), has also been proposed. Table 5 summarizes the five domains of the CPDAI.

Additional composite measures for assessment of total disease activity in PsA are also being developed. GRAPPA has devised a composite measure for defining “minimal disease activity” (MDA) which has been validated. MDA requires assessments of joints, entheses, skin and assessment of physical function [33]. The GRAPPA MDA criteria indicates a low disease state and this can be used as a responder index (Table 6). To determine the severity of musculoskeletal and cutaneous involvement in psoriatic arthritis GRAPPA has been working on multiple projects including the GRAPPA Composite Exercise (GRACE) Project [34,35]. The GRACE project has helped to develop two new composite measures: the Arithmetic Mean of Desirability Functions (AMDF) and the Psoriatic Arthritis Disease Activity Score (PASDAS) [34].

1.3. Treatment guidance

Both the European League Against Rheumatism (EULAR) and GRAPPA have made official PsA treatment recommendations [36–39]. Published in 2012, the EULAR algorithm serves as a guide for physicians in outlining suitable treatment options for psoriatic

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**Table 2**

The Classification Criteria for Psoriatic Arthritis (CASPAR) consist of established inflammatory arthritic disease with at least 3 points from the following features.

- Current psoriasis (assigned a score of 2)
- A history of psoriasis (in the absence of current psoriasis; assigned a score of 1)
- A family history of psoriasis (in the absence of current psoriasis and history of psoriasis; assigned a score of 1)
- Dactylitis (assigned a score of 1)
- Juxta-articular new-bone formation (assigned a score of 1)
- RF negativity (assigned a score of 1)
- Nail dystrophy (assigned a score of 1)
Table 3
Assessment tools for disease measures of psoriatic arthritis.

<table>
<thead>
<tr>
<th>Disease assessment</th>
<th>Specific tools for disease measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral joint assessment</td>
<td>6/66 tender/swollen joint count, DAS, PSARC and ACR response criteria</td>
</tr>
<tr>
<td>Axial joint assessment</td>
<td>ASDAS, BASDAI, BASFI, BASMI</td>
</tr>
<tr>
<td>PsA Composite Measures</td>
<td>CPDAI, DAPSA, PsAJAI</td>
</tr>
<tr>
<td>Skin assessment</td>
<td>PASI, BSA, Target lesion, Global</td>
</tr>
<tr>
<td>Enthesitis assessment</td>
<td>Mander, MASES, Leeds, Berlin, SPARCC</td>
</tr>
<tr>
<td>Dactylitis assessment</td>
<td>Leeds, present/absent, acute/chronic</td>
</tr>
<tr>
<td>Patient global</td>
<td>VAS (global, skin + joints)</td>
</tr>
<tr>
<td>Physician global</td>
<td>VAS (global, skin + joints)</td>
</tr>
<tr>
<td>Function/QOL</td>
<td>HAQ, SF-36, PsAQoL, DLQI</td>
</tr>
</tbody>
</table>

Table 4
Composite measures for psoriatic arthritis and their clinical domains.

<table>
<thead>
<tr>
<th>Periphera arthritis</th>
<th>Pain</th>
<th>Patient global assessment</th>
<th>Physician global assessment</th>
<th>Skin</th>
<th>Enthesitis</th>
<th>Dactylitis</th>
<th>Spine disease</th>
<th>HAQ</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPSA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>PsAJAI</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CPDAI</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

DAPSA, Disease Activity for Psoriatic Arthritis; PsAJAI, Psoriatic Arthritis Joint Activity Index; CPDAI, Composite Psoriatic Disease Activity Index; HAQ, Health Assessment Questionnaire; CRP, C-reactive protein. [Table adapted from the article by Machado and Raychaudhuri [3]].

Table 5
The Composite Psoriatic Disease Activity Index (CPDAI) (CPDAI score total 0–15) [31].

<table>
<thead>
<tr>
<th>Not involved (0)</th>
<th>Mild (1)</th>
<th>Moderate (2)</th>
<th>Severe (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral arthritis</td>
<td>≤4 joints (swollen or tender); normal function (HAQ &lt;0.5)*</td>
<td>≤4 joints but function impaired; or &gt;4 joints, normal function</td>
<td>&gt;4 joints and function impaired</td>
</tr>
<tr>
<td>Skin disease</td>
<td>PASI &lt;10 and DLQI &lt;10</td>
<td>PASI &lt;10 but DLQI &gt;10; or PASI &gt;10 but DLQI &lt;10</td>
<td>PASI &gt;10 and DLQI &gt;10</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>≤3 Sites; normal function (HAQ &lt;0.5)*</td>
<td>≤3 Sites but function impaired; or &gt;3 Sites but normal function</td>
<td>&gt;3 Sites and function impaired</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>≤3 Digits; normal function (HAQ &lt;0.5)*</td>
<td>≤3 Digits but function impaired; or &gt;3 Digits but normal function</td>
<td>&gt;3 Digits and has function impaired</td>
</tr>
<tr>
<td>Spinal disease</td>
<td>BASDAI &lt;4; normal function (ASQoL &lt;6)</td>
<td>BASDAI &gt;4 but normal function; BASDAI &lt;4 but function impaired</td>
<td>BASDAI &gt;4 and function impaired</td>
</tr>
</tbody>
</table>

ASQoL, ankylosing spondylitis quality of life; BASDAI, Bath ankylosing spondylitis disease activity index; CPDAI, composite psoriatic disease activity index; DLQI, dermatology life quality index; PASI, psoriasis area severity index. * Health assessment questionnaire (HAQ) only counted if clinical involvement of domain (joint/enthesis/dactylitis) present.

Table 6
GRAPPA measures for minimal disease activity of psoriatic arthritis [adapted from original article by Coates et al. [33]].

A patient is classified as having ‘minimal disease activity’ when achieving 5 of 7 following criteria:
- Tender joint count ≤1
- Swollen joint count ≤1
- Psoriasis Activity and Severity Index ≤1 or body surface area ≤3
- Patient pain visual analogue score ≤15
- Patient global disease activity visual analogue score ≤20
- Health assessment questionnaire ≤0.5
- Tender entheseal points ≤1

Fig. 1 provides a schematic of the EULAR treatment algorithm for PsA.
**EULAR 2015 Recommendations for the Management of Psoriatic Arthritis**

**Phase 1**
Clinical diagnosis of active**
psoriatic arthritis

- Start NSAIDs +/- local glucocorticoid injections

  - Achieve target*** in 3-6 months or toxicity

**Phase 2**
Predominantly axial disease or enthesitis

- Start methotrexate. If methotrexate is contraindicated, start leflunomide or sulfasalazine (or cyclosporin A)

  - Achieve target*** in 3-6 months or toxicity

**Phase 3**
Adverse prognostic factors**

- Start biologic agent, usually anti-TNF agent. If contraindicated, start IL12/23 or IL17 inhibitors§.
  - Achieve target*** in 3-6 months or toxicity

- Start a second synthetic DMARD: Leflunomide, sulfasalazine, MTX or cyclosporin A

  - Achieve target*** in 3-6 months or toxicity

**Phase 4**
Change treatment. Switch to another TNF inhibitor or another mode of action or a tsDMARD.

- Achieve target*** in 3-6 months

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*Refer to Gossec et al. (2015) for situations from covered in this figure.
**Per EULAR, active disease is defined as 1 or more tender and swollen joints; tender enthesis point, dactylytic digit and/or inflammatory back pain.

Adverse prognostic factors are defined as 5 or more active joints, radiographic damage, elevated acute phase reactants, extraarticular manifestations (dactylitis).

***Treatment target is clinical remission (the absence of signs or symptoms), or low disease activity if remission is unlikely.

§ For patients with peripheral arthritis and an inadequate response to at least one csDMARD, in whom TNF inhibitors are not appropriate. With predominant spinal involvement, active enthesitis and/or dactylitis no csDMARD is needed—use bDMARD with preference for a TNF inhibitor.

§§ For peripheral arthritis and an inadequate response to at least one csDMARD, in whom bDMARDS are not appropriate.

**Fig. 1.** EULAR 2015 algorithm for treatment of PsA (figure and legend adapted from the official publication by Gossec et al. [38]). bDMARD, biological DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; IL, interleukin; MTX, methotrexate; PSA, psoriatic arthritis; TNFI, tumor necrosis factor inhibitor; tsDMARD, targeted synthetic DMARD.
The GRAPPA treatment recommendations are the result of an evidence-based literature review and address the six key clinical domains of PsA (arthritis, enthesitis, dactylitis, spondylitis, nail and skin disease), encouraging the clinician to use a “grid” approach when evaluating a PsA patient. GRAPPA developed a grading system to assess the disease severity (mild/moderate/severe) of each clinically involved domain in PsA and the impact of these domains on physical function and QOL (Table 7), and disease severity was incorporated into the previous GRAPPA treatment recommendations released in 2009 [37]. In 2015, the GRAPPA treatment grid was modified and the distinctions between mild/moderate/severe disease were removed due to lack of evidence supporting cut-off points between severity grades. Instead, the revised 2015 treatment grid provides evidence-based (GRADE) treatment recommendations for each of the six clinical domains, stratified according to the strength of supporting evidence (Table 8) [40]. In addition, in 2015 GRAPPA released treatment recommendations for the key manifestations of the disease in the form of flowcharts for each clinical domain affected and organized into a larger treatment grid (Fig. 2) [40]. The authors of this review believe that GRAPPA’s “expedited” treatment recommendations are most appropriate, given the evidence supporting the use of anti-TNF agents for prevention of joint destruction in PsA as described below.

1.4. Management of comorbidities in psoriatic arthritis

As is the case with psoriasis, PsA is strongly associated with a number of comorbid conditions including metabolic syndrome (central obesity, insulin resistance, dyslipidemia and hypertension), atherosclerotic cardiovascular disease (CVD), valvular heart disease, inflammatory bowel disease, osteoporosis, uveitis, fatigue and various comorbidities secondary to chronic pain, disability and reduced quality of life (Table 9) [41–47]. Thus, many experts have recognized the need for a PsA treatment plan that addresses these comorbidities [41] and the therapeutic paradigm for PsA has shifted to a multisystem, multidisciplinary approach involving consultation with various subspecialists (including internal medicine, psychiatry, endocrinology, cardiology and dietary/lifestyle modification programs) who may best identify and treat the numerous conditions that may occur in concert with PsA [48]. Failing to address the multiple comorbidities associated with PsA is incomplete management of the disease, and it is important for the rheumatologists and dermatologists managing PsA patients to work closely with the patient’s primary care providers to identify these potential comorbidities and provide appropriate referrals to subspecialists for further care.

2. Conventional therapies

2.1. Non-steroidal anti-inflammatory drugs (NSAIDs)

Treatment of PsA requires consideration of both skin and joint manifestations, thus the ideal therapeutic agents should be effective for both the psoriatic and arthritic components of the disease [37]. Patients with minor joint involvement can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs) [49]. There are two randomized controlled trials (RCTs) evaluating the efficacy of NSAIDs for treatment of PsA. A 4 week trial comparing the COX-2 selective NSAID, nimesulide and placebo in 76 patients showed that there was a significant decrease in the tender and swollen joint count with 200 mg and 400 mg daily dosing of nimesulide (not observed with 100 mg daily compared to placebo [50]. A 12 week RCT compared the safety and efficacy of celecoxib (also a selective COX-2 inhibitor) at doses of 200 mg and 400 mg daily to placebo for relief of PsA symptoms. At the conclusion of the study (Week 12), there was no statistically significant difference in ACR20 response criteria between the celecoxib and placebo groups [51]. Though NSAIDs may relieve symptoms of PsA such as joint pain and swelling, it should be noted that NSAIDs do not modify the disease course in PsA. Specifically, they do not prevent development or slow the progression of joint erosions.

2.2. Glucocorticoids

Oral steroids, a classical therapy for inflammatory arthritis, are generally not used to treat PsA due to the fear of exacerbating the skin manifestations of psoriasis when tapering. In addition to increasing the risk of a disease flare, glucocorticoids pose a risk for induction of pustular psoriasis which can be extremely debilitating [37]. There is no clinical trial data to support the use of glucocorticoids for the treatment of PsA [52].

Table 7
Disease severity of psoriatic Arthritis-GRAPPA GRID.

<table>
<thead>
<tr>
<th>Clinical domains</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral arthritis</td>
<td>≤5</td>
<td>≥5 (swollen or tender)</td>
<td>≥5 (swollen or tender)</td>
</tr>
<tr>
<td>No. of joints</td>
<td>No damage</td>
<td>Moderate damage</td>
<td>Severe damage</td>
</tr>
<tr>
<td>Damage on X-ray</td>
<td>No</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Loss of function</td>
<td>Minimal impact</td>
<td>Moderate impact</td>
<td>Severe impact</td>
</tr>
<tr>
<td>QOL</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Patient evaluation</td>
<td>BSA &lt;5</td>
<td>Inadequate response to mild Rx</td>
<td>Inadequate response to mild-moderate Rx</td>
</tr>
<tr>
<td>Skin involvement</td>
<td>PASI &lt;5</td>
<td>Non-response to topicals</td>
<td>BSA &gt;10</td>
</tr>
<tr>
<td>Spinal disease</td>
<td>Asymptomatic</td>
<td>DLQI</td>
<td>DLQI &gt;10</td>
</tr>
<tr>
<td>Mild pain</td>
<td>Mild</td>
<td>PASI &gt;10</td>
<td>PASI &gt;10</td>
</tr>
<tr>
<td>No loss of function</td>
<td>Loss of function or</td>
<td>Loss of function</td>
<td>Failure of response</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>&gt;2 sites or loss of function</td>
<td>Erosive disease or</td>
<td>Loss of function or</td>
</tr>
<tr>
<td>1-2 sites</td>
<td>Erosive disease or</td>
<td>≥2 sites or failure of response</td>
<td>≥2 sites or failure of response</td>
</tr>
<tr>
<td>No loss of function</td>
<td>Loss of function</td>
<td>Failure of response</td>
<td>Failure of response</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>Pain: About to mild</td>
<td>Erosive disease or</td>
<td>Loss of function</td>
</tr>
<tr>
<td>Normal function</td>
<td>Loss of function</td>
<td>Failure of response</td>
<td></td>
</tr>
</tbody>
</table>

(Adapted from original article by Ritchlin et al., 2009 [37]).
2.3. Methotrexate

Methotrexate is competitive inhibitor of dihydrofolate reductase (DHFR), an enzyme that is required for tetrahydrofolate synthesis. Through this mechanism methotrexate will eventually inhibit the synthesis of DNA, RNA, thymidylates, and proteins. It is currently FDA approved for severe, refractory and incapacitating psoriasis [53]. The MIPA (Methotrexate In Psoriatic Arthritis) study was a large RCT comparing methotrexate (target dose 15 mg weekly) to placebo with the primary outcome measure being improvement in the Psoriatic Arthritis Response Criteria (PsARC) and secondary endpoints included ACR and Disease Activity Scores (DAS28). Though 221 patients were enrolled, a total of 151 patients completed the trial (74 in MTX and 77 in placebo groups respectively). Though there was improvement in the PsARC in both groups, no statistically significant difference in the PsARC, ACR, DAS28, ESR levels and tender or swollen joint counts was observed between the MTX and placebo groups [54].

Although proper clinical evidence is lacking on the effectiveness of methotrexate in PsA, it is usually used first-line as a monotherapy or in combination with biologics [55]. The Norwegian DMARD registry compared the efficacy and retention rate of methotrexate in 430 PsA patients with 1280 rheumatoid arthritis (RA) patients, both with similar disease duration (mean 4.4 years) [56]. PsA and RA patients both improved in most disease activity measures and patient-reported outcomes after 6 months; however, this improvement was less pronounced in PsA patients compared to RA patients. Although two randomized, placebo-controlled studies confirmed significant improvement in global assessment ratings with the use of methotrexate, neither of them showed encouraging results with objective measures such as tender and swollen joint counts [54,57]. Moreover, a comparison of PsA patients treated with or without methotrexate over a period of 24 months failed to show a statistically significant difference in the radiographic progression of their joint disease [58].

Assessment of the retention rate of a drug provides an indirect

| Table 8 |
| 2015 GRAPPA Treatment Recommendations (Adapted from original article by Coates et al. [40]). |
| Indication | Recommended strong | Recommended conditionally | Not recommended | No Recommendations |
| Peripheral arthritis, DMARD naive | DMARDs: Methotrexate, Sulfasalazine, Leflunomide, TNF inhibitors | NSAIDs | IL-12/23 inhibitors, IL-17 inhibitors |
| Peripheral arthritis, DMARD inadequately responsive | TNF inhibitors, IL-12/23 inhibitors (ustekinumab), PDE4 inhibitors | NSAIDs | IL-17 inhibitors |
| Axial PsA, biologic naive (based on AS literature) | NSAIDs, Physiotherapy, Simple analgesia | IL-17 inhibitors | DMARDs |
| Axial PsA, Biologic inadequately responsive (based on AS literature) | TNF inhibitors, Physiotherapy, Simple analgesia | NSAIDs | IL-6 inhibitors, CD20 inhibitors |
| Enthesitis | TNF inhibitors, IL-12/23 inhibitors | NSAIDs, Physiotherapy | IL-17 inhibitors |
| Dactylitis | TNF inhibitors, (Infliximab, Adalimumab, Golimumab, Certolizumab) | Intra-articular corticosteroids, DMARDs (Methotrexate, Leflunomide, Sulfasalazine), TNF inhibitors (Etanercept) | IL-12/23 inhibitors, IL-17 inhibitors, Secukinumab | PDE4 inhibitors |
| Psoriasis (Skin) | Topical therapies, Phototherapy, DMARDs (Methotrexate, Leflunomide, Cyclosporine), TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, PDE4 inhibitors | | |
| Nail psoriasis | TNF inhibitors, IL-12/23 inhibitors | Topical therapies, Procedural therapies, DMARDs (Methotrexate, Leflunomide, Cyclosporine, Acitretin) | IL-17 inhibitors | PDE4 inhibitors |
method of evaluating its efficacy and toxicity, and in the above study the two-year retention rate for methotrexate therapy was 65% in PsA and 66% in RA [56]. Methotrexate carries the risk of dose-limiting toxicity. Possible adverse effects associated with this therapy include myelosuppression, pneumonitis, nephrotoxicity and hepatotoxicity [59]. Furthermore, in patients with risk factors for hepatic disease such as obesity and alcoholism the potential for transaminitis and worsening liver pathology may prohibit the long-term use of methotrexate.

2.4. Leflunomide

Leflunomide is a pyrimidine synthesis inhibitor that prevents T cell activation and proliferation [60]. Although approved by the European Medicines Agency (EMA) for PsA, it is currently only approved by the U.S. Food and Drug Administration (FDA) for the treatment of RA. In a 24-week randomized placebo-controlled trial in 186 patients, leflunomide showed significant improvement in the PsA response criteria (PsARC) (59% vs 30%, respectively) as well as in tender and swollen joint scores, Health Associated Questionnaire (HAQ), and the Dermatology Quality of Life Index (DLQI) when compared to placebo [61]. In a recent randomized, double-blind, placebo-controlled clinical trial in 190 patients with concomitant psoriasis and PsA, leflunomide was found to produce significant clinical responses in both skin and joint symptoms when compared to placebo [39, 62, 63]. The main side effects of leflunomide are gastrointestinal toxicity (e.g. diarrhea and nausea), elevated liver enzymes and leukopenia [64].

2.5. Sulfasalazine

Sulfasalazine is a sulfa drug that is synthesized by combining sulfapyridine and salicylate through an azo bond. Sulfasalazine is believed to act by inhibiting the 5-lipoxxygenase pathway [65]. It has been evaluated in six randomized controlled clinical trials (RCT) in PsA [66–70]. A large sulfasalazine study by Clegg and colleagues included 221 patients randomized to 2 g/day of sulfasalazine versus placebo [71]. The analysis revealed that 55% of patients from the treatment arm and 45% of patients from the placebo arm attained response based on PsARC. The other sulfasalazine RCTs involved fewer patients, and responses were noted only in pain scores, with no effect on radiologic progression [69–71]. The major adverse

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**Table 9**

Comorbidities in psoriatic arthritis.

- Metabolic syndrome
- Coronary artery disease
- Valvular heart disease
- Uveitis
- Inflammatory bowel disease
- Fatigue
- Depression
- Osteoporosis
- Comorbidities sequel to therapy with NSAID, DMARD, Biologic DMARD
- Comorbidities secondary to chronic pain, disability, anxiety, economic and psychosexual problems
effects associated with sulfasalazine include gastrointestinal intolerance, arthralgia, reversible oligospermia, leukopenia and agranulocytosis [72].

2.6. Cyclosporine A, azathioprine and antimalarials

Cyclosporine A is approved by the FDA for treatment of severe refractory psoriasis [72]. Three RCTs have also confirmed the safety of cyclosporine A in PsA; however, its efficacy is only modest and the potential for severe adverse events limits enthusiasm for its use [73–75]. Due to cyclosporine-associated nephrotoxicity and hypertension it is generally not used long-term, which also limits its feasibility for use in PsA [72].

A purine antimetabolite, azathioprine is an immunosuppressant currently approved for post-transplant immunosuppression and rheumatoid arthritis. There is only one randomized trial evaluating azathioprine for PsA in the literature, a double-blind crossover study conducted over 12 months that randomized patients to azathioprine or placebo for each six month period [76]. This trial showed a significant improvement in both skin and joint manifestations during azathioprine treatment. A more recent case series in 28 patients demonstrated azathioprine to be well-tolerated over the course of 12 weeks with similar efficacy to DMARDs, suggesting that it may be of benefit in methotrexate-refractory PsA or in patients in which methotrexate is contraindicated [77]. Adverse effects of azathioprine include myelosuppression, gastrointestinal upset, and hepatic toxicity [72].

Antimalarials such as hydroxychloroquine are approved for rheumatoid arthritis but are not often used to treat PsA due to their potential to worsen psoriasis or trigger an outbreak in susceptible individuals [78]. However, a case control series of 32 patients treated with hydroxychloroquine failed to show an increased risk of a psoriasis flare in the hydroxychloroquine group compared to placebo. In addition, a significant decrease in the number of actively inflamed joints was observed in the hydroxychloroquine group [79].

3. Beyond traditional DMARDs: biologics in the treatment of psoriatic arthritis

3.1. Anti-TNF agents

Tumor Necrosis Factor (TNF) plays a central role in chronic inflammatory conditions such as psoriasis and PsA. Currently there are multiple TNF inhibitors that a clinician can choose from. Although a variety of oral inhibitors have the ability to inhibit TNF, biologic therapies have emerged as elegant agents to selectively target TNF. The three most commonly used biologic anti-TNF agents for psoriasis are etanercept, infliximab, and adalimumab, and newer anti-TNF agents include golimumab and certolizumab [80]. Etanercept is a genetically engineered protein composed of a dimer of the human TNFR2, fused to the Fc portion of human IgG1. It binds to only a single trimer of TNF, resulting in complexes of etanercept and TNF in a 1:1 ratio. Etanercept is also unique in that it binds to and inhibits other TNF receptor ligands such as the lymphotixin (LT) family members, which are thought to also play a role in chronic inflammatory arthritis [81].

Infliximab is a mouse–human IgG1 chimeric anti-TNF monoclonal antibody. Adalimumab and golimumab are also anti-TNF monoclonal antibodies but they are fully humanized IgG1 [80]. In contrast to etanercept, the anti-TNF monoclonal antibodies can bind to both the monomer and trimer forms of TNF. As bivalent antibodies, they can also bind to two different TNF trimers, allowing for the formation of large multimeric complexes of TNF molecules linked together by anti-TNF monoclonal antibodies. In addition to its soluble form, TNF exists as a transmembrane protein (tmTNF). Infliximab and adalimumab can also be directly cytotoxic to tmTNF-bearing cells by inducing antibody-dependent cellular cytotoxicity (ADCC) and complement-mediated cytotoxicity (CDC). Studies have also shown that once bound to TNF, both adalimumab and infliximab, but not etanercept, are able to bind strongly to FcγRI and FcγRII receptors [80]. Furthermore, etanercept is unable to bind to the complement protein C1q. For these reasons, adalimumab and infliximab are able to induce ADCC much more potently than etanercept. Thus, differences in Fc receptor and complement C1q binding may contribute to the differences in efficacy of the TNF antagonists [80].

As a whole, TNF antagonists have revolutionized management of PsA and their effectiveness in treating psoriasis and PsA has been validated by their ability to inhibit radiographic progression of arthritis [82–92]. To date they have shown the highest efficacy of any treatment, a finding that has held true across the different clinical aspects of PsA. Among the TNF-antagonists studied, the efficacy in treating joint disease activity, inhibiting structural damage, and improving function and quality of life are quite similar depending on the dose employed. Safety concerns are present such as risk for infection, but there are no additional concerns in the PsA population compared to the more broadly studied RA patient population. Currently five specific anti-TNF agents are approved for PsA, which are described in Table 10. A summary of the clinical evidence supporting the use of each in PsA is provided below.

3.1.1. Etanercept

Etanercept received FDA approval for psoriatic arthritis in 2002. A randomized controlled trial (RCT) of etanercept 25 mg twice weekly in 205 patients with PsA showed significant improvement in the ACR20 criteria for joint response compared to placebo (59% vs 15%) [87]. A total of 141 patients (70 originally randomized to etanercept and 71 to placebo) subsequently completed the 48 week open label study of etanercept 25 mg twice weekly, and radiographic joint progression was evaluated for all participants at baseline, 1 and 2 years [93]. The etanercept group demonstrated significant inhibition of radiographic progression (mean adjusted change in total Sharp score of −0.38 from baseline to 2 years) compared to the placebo group that began etanercept during the open-label extension (mean adjusted change of −0.22 from 1 year to 2 years) [93].

The large, multicenter Psoriasis Randomized Etanercept Study in Subjects with Psoriatic Arthritis (PRESTA) trial compared the efficacy of two different etanercept regimens, 50 mg once weekly (QW) and 50 mg twice weekly (BIW) in a total of 752 patients with moderate to severe psoriasis as well as PsA over the course of 12 weeks. The study found that the efficacy of 50 mg BIW was superior to 50 mg QW in terms of clearing the cutaneous psoriasis, with 46% of the BIW group achieving a score of clear or almost clear on the physician’s global assessment as compared to the QW group at Week 12. For the joint manifestations of PsA however, there were no significant differences between the QW and BIW dosing schedules as assessed by the psoriatic arthritis response criteria at Week 12. The PRESTA trial also enrolled patents into a 12 week open label extension of etanercept 50 mg QW versus 60 mg BIW, which demonstrated similar responses for the cutaneous psoriasis and joint manifestations in both dosage groups [94].

3.1.2. Infliximab

Infliximab was approved for the treatment of PsA in 2005. There were two large RCTs that preceded this approval, the IMPACT (Infliximab Multinational Psoriatic Arthritis Controlled Trial) and IMPACT 2 studies [83,95]. The 16-week IMPACT trial evaluated infliximab 5 mg/kg at weeks 0,2,6 and 14 compared to placebo in
104 patients, with the primary endpoint being achievement of ACR20 at Week 16 and additional endpoints of achievement of ACR 50 and ACR70 responses. A significantly higher proportion of the infliximab group (65%) achieved ACR20 compared to the placebo cohort (10%), as well as ACR 50 (46% vs none of placebo patients) and ACR70 (29% vs none of placebo patients) [83].

The 24-week IMPACT2 study randomized 200 patients to infliximab 5 mg/kg or placebo at weeks 0, 2, 6, and 14 with the primary endpoint being achievement of ACR20 and secondary endpoints including the Psoriatic Arthritis Response Criteria (PsARC), Psoriasis Area and Severity Index (PASI) and dactylitis/enthesitis assessments [97]. Significantly more patients in the infliximab group (18% and 20% respectively) had active enthesopathy compared to the placebo group (30% and 37%) [95]. Hand and foot radiographs from patients one year following completion of both the IMPACT and IMPACT2 trials were analyzed and assigned a PsA modified van der Heijde-Sharp (vdH-S) score to determine the effect of infliximab on radiographic progression. Both the analyses from the IMPACT and IMPACT2 trials demonstrated a significant effect of infliximab in retarding progression of joint disease [84,96]. For the IMPACT trial, mean change in the modified vdH-S scores from baseline to Week 50 were −1.95 and −1.52 for the infliximab and placebo groups respectively (p < 0.001) [84]. Follow up from IMPACT2 trial also demonstrated a significant effect, with vdH-S scores of −0.70 and 0.82 at Week 24 and −0.94 and 0.53 at Week 54 in the infliximab and placebo groups respectively (p < 0.001) [96].

More recently, the Remicade Study in Psoriatic Arthritis Patients of Methotrexate-Naïve Disease (RESPOND) trial compared efficacy and safety of infliximab plus methotrexate with methotrexate alone in 115 methotrexate-naïve patients with PsA. Patients were assigned to receive infliximab (5 mg/kg) at weeks 0, 2, 6 and 14 plus methotrexate (15 mg weekly) or methotrexate (15 mg/week) alone with the primary outcome measure of achieving ACR20 at Week 16 and secondary endpoints being PASI, DAS28 and dactylitis/enthesitis assessments [97]. Significantly more patients in the infliximab-methotrexate group achieved ACR20 at Week 16 (86.3%) compared to methotrexate alone (66.7%, p < 0.0001). A total of 97.1% of the combination therapy group achieved PASI-75 at Week 16, compared to 54.3% of patients receiving methotrexate alone (p < 0.0001). A total of 46% of patients in the infliximab-methotrexate combination group experienced treatment-related adverse events (AEs) during the study period compared to 24% in the methotrexate monotherapy group [97].

### 3.1.3. Adalimumab

The Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT) was a 24 week RCT in 313 patients comparing the efficacy of adalimumab 40 mg versus placebo every other week for the treatment of NSAID-refractory PsA [85]. The primary endpoints of the ADEPT trial were achievement of ACR20 response at Week 12 as well as change in modified Sharp score for assessing structural joint damage at Week 24. Achievement of ACR20 at Week 12 was accomplished in 58% of the adalimumab-treated patients compared to 14% of the placebo group (p < 0.001). ACR20 response rates were maintained at Week 24, and mean change in the modified Sharp score was −0.2 in patients receiving adalimumab and 1.0 in the placebo group (p < 0.001) [85]. Interim analysis of an open-label extension of the ADEPT study consisting of adalimumab 40 mg every other week for up to 120 weeks demonstrated maintenance of similar ACR20 responses and improvements in joint disease at 2 years of treatment [98].

Another multicenter RCT evaluated adalimumab in a subset of 100 PsA patients with a history of inadequate response to disease modifying anti-rheumatic drugs (DMARDs) over the course of 24 weeks [99]. Patients were randomized to receive adalimumab 40 mg or placebo every other week for 12 weeks followed by an open label period in which all patients received adalimumab 40 mg every other week up to Week 24. A total of 39% of adalimumab-treated patients achieved the primary endpoint of ACR20 at week 12, compared to 16% of patients in the placebo group (p < 0.012). In the open label phase, continued improvement was seen in the adalimumab group with 65% achieving ACR20 at Week 24, and initiation of improvement was observed in the group previously randomized to placebo with 57% achieving ACR20 at Week 24 (p < 0.007) [99].

The efficacy of adalimumab was also compared to that of cyclosporine in a prospective 12-month nonrandomized open-label clinical trial in which patients received cyclosporine (2.5–3.75 mg/kg/day), adalimumab (40 mg every other week) or combination of both therapies [100]. At one year, ACR20 was achieved by 65% of patients in the cyclosporine group (p = 0.0003 vs combination), 85% in the adalimumab group (p = 0.15 vs combination) and 95% of patients receiving both therapies. The ACR50 rates were 36% for cyclosporine, 69% for adalimumab and 87% for combination therapy (p < 0.0001 and p = 0.03 vs combination) [100]. Importantly, this trial did not indicate any significant increase in the incidence of treatment-related adverse events in the group on dual therapy.

#### 3.1.4. Golimumab

A once-monthly anti-TNF agent, golimumab received FDA approval for PsA in 2009 following completion of the large Golimumab-A Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody (mAb) (GO-REVEAL) study in 405 patients [101]. In this 24 week trial, patients were randomized to receive subcutaneous golimumab (50 mg or 100 mg) or placebo every 4 weeks through Week 20. At Week 14, ACR20 was achieved by 51% of the patients in the 50 mg golimumab group, 45% in the 100 mg golimumab group and 9% in the placebo group (p < 0.001). Improvement in PASI (for patients with at least 3% body surface area (BSA)
affected by psoriasis) was an additional endpoint of the study, and PASI-75 was achieved in 40% of patients in the 50 mg golimumab arm, 58% in the golimumab 100 mg arm and 3% in the placebo cohort (p < 0.001) [101]. In addition, efficacy for both of these clinical endpoints was maintained at Week 24. A blinded extension of the trial in which placebo patients were switched to golimumab 50 mg monthly, and all other patients who had previously been on either 50 mg or 100 mg golimumab monthly were maintained on the same regimen, demonstrated maintenance of the clinical improvement in ACR20 and PASI score that had been achieved by Week 24 of the GO-REVEAL study [102]. In addition, one year follow up of the GO-REVEAL trial demonstrated significant radiologic benefit in the golimumab group compared to placebo with respect to PASA-modified Sharp/van der Heijde scores (SHSs). Mean change in score from baseline to Week 24 for both golimumab (50 mg and 100 mg) groups was −0.09 compared to 0.27 for the placebo group, and this radiologic improvement was maintained through one year of follow up [102].

A five-year open-label extension of the GO-REVEAL trial was completed by 279 patients from the original trial, and after Week 24 all patients were maintained on golimumab 50 mg or 100 mg every four weeks [103]. Concomitant therapy with methotrexate was allowed but not required and was taken by approximately half of the patients in the trial. A review of the 5 year efficacy data revealed that golimumab was effective at maintaining clinical improvement in the ACR20 (62.8–69.9% for randomized patients) and PASI75 (60.8–72.2% for randomized patients with >3% BSA involved by psoriasis). In addition, golimumab was also effective in inhibiting radiographic progression (based on review of 267 patients with radiographic data to this timepoint), demonstrating a mean change in SHSs of 0.1–0.3 at Week 256. The administration of methotrexate did not significantly affect the ACR20 and PASI75 outcome measures, but did appear to reduce radiographic progression [103].

3.1.5. Certolizumab

Certolizumab is the newest anti-TNF agent approved for PsA, receiving approval for this indication in 2013 [104]. Certolizumab differs from the other TNF antagonists because it is a pegylated, humanized Fab’ fragment of an anti-TNF monoclonal antibody. The RAPID-PsA multicenter RCT randomized a total of 409 patients to receive certolizumab pegol (CZP) 200 mg every two weeks, CZP 400 mg every four weeks or placebo [105]. Primary endpoints of the study included achievement of ACR20 at Week 12 and modified Total Sharp Score (mTSS) from baseline to Week 24. The ACR20 response at Week 12 was significantly greater in the patients receiving CZP 200 mg every two weeks (58%) and CZP 400 mg every four weeks (51.9%) compared to 24.3% in the placebo group (p < 0.001).

During the analysis of mTSS scores to determine radiographic progression, it was noted that the majority of patients (both CZP and placebo) experienced no change in mTSS over the course of 24 weeks in the study [106]. In addition, the radiographic progression data analysis was limited by absence of two or more mTSS values for comparison in 21 of the 368 patients that completed the 24 week double blind phase of the trial, which was addressed by prespecified imputation methodologies in order to reconstruct missing Week 24 mTSS values. Thus, though post-hoc analyses showed a higher rate of mTSS non-progression in the CZP groups (83.3% in the CZP 200 mg group and 76.3% in the CZP 400 mg group) as compared to placebo (34.6%), the authors cautioned that inappropriate prespecified imputation methodologies for the mTSS scores were a significant limiting factor in this data analysis as it considered all patients who withdrew or escaped to active treatment as mTSS progressors, thus overestimating the mTSS progression in all arms of the study and severely limiting the interpretation of radiologic data for the trial [106].

3.2. IL-12/23 inhibition: ustekinumab

Among other cytokines and immune modulators, psoriasis plaques over-express IL-12, IL-17, and IL-23 [107]. IL-23 is required for the maintenance of IL-17-secreting Th17 cells. Th17 T cells play an active role in a variety of inflammatory diseases, including psoriasis, PsA, and ankylosing spondylitis (AS) [108]. As evidence in favor of IL-23’s importance in psoriasis, it has been demonstrated that repeat subcutaneous injections of IL-23 can induce a psoriasis phenotype in mice [109].

Ustekinumab is an anti-IL-12/23 monoclonal antibody that has shown effectiveness in treating moderate-to-severe psoriasis. Ustekinumab was found to be superior to etanercept for treatment of psoriasis although this trial lacked a quality of life questionnaire and the timing of the assessment favored the faster acting ustekinumab [110,111]. With regards to PsA, a randomized, double-blind, placebo-controlled, crossover trial of ustekinumab in PsA, showed improvement in ACR response rates and significant improvement in skin disease, enthesitis, dactylitis and physical functioning but required a higher dose than that used for treating psoriasis [112]. Analogous results were again reported with ustekinumab in a randomized, placebo-controlled, phase III clinical trial in PsA patients who had received anti-TNF and DMARD treatment [113]. PSUMMIT 1 was a randomized control trial (n = 615) where PsA patients received either ustekinumab 45 mg/ustekinumab 90 mg or placebo at weeks 0 and 4 and then every 12 weeks. At week 24, ACR20 responses were achieved by 42.4%, 49.5%, and 22.8% of patients, respectively. At 24 weeks, a significant number of ustekinumab-treated patients achieved ACR 50/70 responses [113]. Improvements were also seen in dactylitis, enthesitis and HAQ [114]. Skin disease also improved; 42.5% of the ustekinumab treated patients achieved PASI 75, compared to only 2.7% in the placebo arm [113]. A similar ACR20 response for ustekinumab was seen in the PSUMMIT 2 trial in 312 patients with PsA [115]. Fig. 3 provides an overview of the mechanisms of action and dosing schedules of biologic agents used for the treatment of psoriatic arthropitis.

3.3. Anti-IL-17 antagonists

IL-17 is a pro-inflammatory cytokine that has a crucial role in the pathogenesis of psoriasis and PsA [116]. Interestingly, using an IL-17A gene transfer model investigators were able to demonstrate that IL-17 alone induces the expansion of IL-17RA+CD11b+Gr1low osteoclast precursors and a concomitant elevation of biomarkers indicative of bone resorption [117]. This occurred at a time preceding noticeable joint inflammation, suggesting that IL-17A is critical for the induction of pathological bone resorption seen in PsA through direct activation of osteoclast precursors. Moreover, in the same study IL-17 gene transfer was able to induce cutaneous pathology including epidermal hyperplasia, parakeratosis and formation of Munro’s microabcesses.

Targeting the IL-17 pathway has been the object of immense drug development research. The major biologics targeting either IL-17 or its receptors that are being investigated for psoriatic disease are secukinumab, brodalumab and ixekizumab. Each agent has slightly different specificity with respect to targeting the IL-17 pathway, as listed below:

i) Secukinumab: a fully human anti-IL-17A monoclonal antibody that is FDA approved for the treatment of psoriasis and PsA.
ii) Brodalumab: a fully human IL-17 receptor (IL-17RA) monoclonal antibody

iii) Ixekizumab: a humanized anti-IL-17A monoclonal antibody

Secukinumab, brodalumab and ixekizumab have been reported to be highly effective for psoriasis, and secukinumab is the first anti-IL-17 agent to receive FDA approval for treatment of psoriasis in January 2015, followed by approval for PsA in January 2016 [118-120]. Until recently, all three of these biologic agents were being evaluated in Phase III trials for PsA [121-123]. However, all United States clinical trials of brodalumab have been halted following termination of the marketing agreement with AstraZeneca and halted all ongoing clinical trials of brodalumab in axial spondyloarthritis, psoriasis (AMAGINE-2) and psoriatic arthritis (AMVISION-2) secondary to safety concerns over increased rates of suicidal ideation seen in clinical trial patients taking the drug [124-126].

Below is a summary of past and ongoing clinical trials in PsA for all of the anti-IL17 monoclonal antibody therapies:

### 3.3.1. Secukinumab

The recent FDA approval of secukinumab for treatment of PsA was based on the results of several Phase II and Phase III trials. A 24-week, Phase II proof of concept trial compared secukinumab (two doses of 10 mg, spaced 3 weeks apart) to placebo in 42 patients with PsA with the endpoint of achieving ACR20 at Week 6 [121]. Though the primary endpoint was not met, with 39% of secukinumab patients achieving ACR20 versus 23% for placebo (p = 0.27), significant reductions in C-reactive protein (CRP, p = 0.039), erythrocyte sedimentation rate (ESR, p = 0.038), Health Assessment Questionnaire Disability Index (HAQDI, p = 0.002) and the Short Form Health Survey (SF-36, p = 0.030). A 48-week, Phase III RCT in 798 patients with PsA examined regimens of placebo versus secukinumab 150 mg and 300 mg at weeks 1, 2 and 3 followed by every 4 weeks thereafter, and demonstrated a significant improvement in both the PASI75 and HAQ-DI responses for the secukinumab cohort compared to placebo [127]. Most recently, the FUTURE2 trial was a multi-center RCT compared three different dosing regimens of secukinumab (300 mg, 150 mg or 75 mg once...
weekly for 4 weeks then every 4 weeks from Week 4) to placebo in 397 patients with PsA, with the primary endpoint of achieving ACR20 at Week 24 [128]. The proportion of patients achieving this endpoint was significantly higher than that seen in the placebo group (15%) and appeared to be dose-dependant with the 300 mg secukinumab group being the highest at 54% (p < 0.0001) followed by the 150 mg dosage group (51%, p < 0.0001) and the 75 mg dosage group (29%, p < 0.0001) [128].

3.3.2. Brodalumab

As noted above, the development of brodalumab for axial spondyloarthritis, psoriasis and psoriatic arthritis in the United States has been halted as of May 2015 due to safety concerns over potentially increased risk of depression and suicidal ideation. However, prior to this announcement brodalumab was in Phase III trials for all the above indications. A recent 52 week Phase II RCT in 168 patients with PsA randomized participants to receive brodalumab (140 mg or 280 mg) or placebo on Day 1 and at weeks 1, 2, 4, 6, 8 and 10. At Week 12, patients continuing in the trial were transitioned to open-label brodalumab 280 mg every two weeks. The primary endpoint was achievement of ACR20 at Week 12. Results of the study showed that the brodalumab groups had higher rates of ACR20 (37% in the 140 mg group and 39% in the 280 mg group) compared to placebo (18%), and that these findings were significant (p = 0.03, p = 0.02 respectively) [122]. At Week 24 (following transition of all continuing patients to brodalumab 280 mg every two weeks at Week 12), rates of ACR20 were 51% and 64% in the patients originally enrolled in 140 mg and 280 mg brodalumab arms compared to 44% of patients who switched from placebo to open label brodalumab at Week 12 [122].

3.3.3. Ixekizumab

Currently, ixekizumab is being studied in both psoriasis (UNCOVER-2 and UNCOVER-3 Phase III trials) as well as PsA (SPIRIT-P1, Phase II) [123,129]. Recently published data from the UNCOVER trials comparing ixekizumab (160 mg loading followed by 80 mg every 2 or 4 weeks) to etanercept (50 mg twice weekly) and placebo in psoriasis showed promising results [129]. In both the UNCOVER-2 and UNCOVER-3 studies, ixekizumab displayed a favorable efficacy profile compared to etanercept and placebo in terms of proportion of patients achieving PASI75 at Week 12 [129].

For the indication of PsA, the ongoing Phase III SPIRIT-P1 trial is comparing ixekizumab 100 mg adalimumab as well as placebo in patients with PsA who are naïve to biologic DMARDs [123]. In the 24 week study, patients are randomized to receive ixekizumab (160 mg loading dose followed by 80 mg every two or four weeks), adalimumab (40 mg every other week) or placebo. Following completion of the RCT, patients will also be monitored for up to 3 years to evaluate the long-term efficacy and safety of brodalumab. In April 2015, the corporate sponsor of ixekizumab (Eli Lilly) announced that the ixekizumab-treated patients had a statistically significant improvement in ACR20 (the primary endpoint) compared to placebo.

3.4. Phosphodiesterase (PDE) 4 inhibition

Apremilast is an orally administered inhibitor of PDE4 that was approved by the FDA in early 2014 for the treatment of PsA. PDE4 is a PDE isozyme found mostly in immune cells such as monocytes, T cells and neutrophils [130]. Enzymatic degradation of cyclic AMP (cAMP) occurs by the phosphodiesterase (PDE) family of enzymes. cAMP is a crucial second messenger in all cells that controls a wide variety of cellular functions [130]. Apremilast inhibits the PDE4-mediated breakdown of cAMP within immune cells, which ultimately attenuates the inflammatory mediators responsible for the pathogenesis of psoriasis and PsA [131,132].

The Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) program evaluated the effectiveness of apremilast on the signs and symptoms of PsA in patients with active PsA despite prior treatment with DMARDs and/or biologic agents. The PALACE program consisted of four randomized, placebo-controlled trials with long-term, open-label extensions [133–139]. The approval of apremilast for PsA was based on the results from PALACE1, PALACE2 and PALACE3 trials.

PALACE1 was a 24 week trial in which 504 patients were randomized to apremilast 20 mg twice daily (APR20), apremilast 30 mg twice daily (APR30) and placebo and the primary endpoint was achievement of ACR20 at Week 16 [139]. Significantly more patients in the apremilast 20 mg BID (31%) and 30 mg BID (40%) achieved ACR20 than in the placebo group (19%, p < 0.0001) [139]. The PALACE2 trial was a long-term (52 week) study in which 484 patients were randomized to apremilast 20 mg twice daily (BID), apremilast 30 mg BID and placebo [138]. At Week 16, the proportion of patients achieving ACR20 was 38.4% in the APR20 group, 34.4% in the APR30 group and 19.5% in the placebo cohort. Importantly, the improvements in ACR20 were increased at 52 weeks (52.3% in the APR20 group, 52.6% in the APR30 group) [138]. PALACE3 was a long-term (52 week) trial in 505 patients with active PsA as well as at least one psoriasis lesion [135]. At Week 16, the proportion of patients achieving ACR-20 was 29.4% in the APR20 group (p = 0.0235), 42.8% in the APR30 group (p < 0.0001) and 18.9% in the placebo group [135]. The PALACE 4 trial examined DMARD-naïve patients with PsA, and week 16 ACR20 response rates were 29% in the APR20 group (p < 0.0235), 32% in the APR30 group (p < 0.0001) and 17% in the placebo cohort [136].

4. Emerging treatment options

4.1. Janus kinase (JAK) inhibitors

JAK is a family of intracellular, non-receptor tyrosine kinases that transduce cell surface cytokine-mediated signals to the cell’s interior via the JAK-STAT signal transduction pathway [140]. A variety of pro-inflammatory cytokine receptors utilize the JAK-STAT signal transduction pathway, including IL-21, which is essential for T cell activation and functioning. JAK inhibition interrupts these key components of the immune response that underlie both psoriasis and PsA. Tofacitinib (an orally administered small-molecule inhibitor of JAK1 and JAK3 with some effect on JAK2) is approved in USA for RA in patients who are unresponsive to DMARDs [141]. It is administered orally in a dose of 5 mg twice daily. A phase I, randomized double-blind, placebo-controlled, dose-escalation study, reported efficacy of tofacitinib in patients with psoriasis [142]. Similarly, in a 12-week, phase II, double-blind, placebo-controlled dose-ranging study, tofacitinib (2, 5 and 15 mg twice daily) demonstrated effectiveness in patients with moderate to severe plaque psoriasis [143]. Although well-tolerated, tofacitinib was associated with a decrease in mean neutrophil counts and haemoglobin values and an increase in lipoprotein levels [143]. Currently Phase III studies with tofacitinib 5 and 10 mg twice daily are ongoing in patients with moderate to severe plaque psoriasis. To date, no clinical efficacy and safety data is available for PsA, however, initial results in RA and psoriasis, warrant further evaluation of tofacitinib in PsA.

4.2. Co-stimulatory blockade

Abatacept (CTLA4-Ig), is a recombinant human fusion protein in which the inhibitory molecule, CTLA4, is fused to the IgFc region. When administered, abatacept binds to the CD80/86 on the surface...
of antigen presenting cells (APCs). APCs normally function to process and present antigen to T cells [144]. Binding of abatacept to CD80/86 prevents CD28 from binding to CD80/86 on the surface of the APC [145]. Acting as a co-stimulatory signal, CD28 usually helps to induce T cell activation; therefore, abatacept inhibits T cell activation by blocking this critically important co-stimulatory signal. It is administered as monthly intravenous injections. Abatacept has proven efficacy in psoriasis [146,147]. In a phase II trial in PsA, 48% of patients receiving abatacept, 10 mg/kg IV monthly, achieved ACR20 response at day 169 (n = 40) as compared to 19% in the placebo arm (p = 0.006) [147]. However, the cutaneous manifestations of PsA were only modestly improved in this trial, with only 14% of patients in the 10 mg/kg arm achieving a PASI 75 versus 5% in the placebo arm. Abatacept is generally well tolerated with the chief safety concern being the risk of infection.

5. Drugs in preclinical development for psoriatic arthritis

Preclinical studies have shown that levels of nerve growth factor (NGF) are higher in synovial fluid samples from PsA and RA patients as compared to samples from OA patients [148]. Although traditionally characterized as a small protein important for the growth maintenance and survival of target neurons, it is now clear that NGF is also a prosurvival factor for activated T cells. As evidence of its role in the pathogenesis of inflammatory arthritis, activated T cells freshly isolated from the joints of patients with PsA and RA over express the NGF high affinity receptor, TrkA [148]. Thus targeting NGF or its receptor may have benefit in treating psoriasis and PsA. An in vivo study using the severe combined immunodeficient mouse-human skin model of psoriasis showed that treatment with K252a, a high-affinity NGF receptor blocker led to improvement in psoriasis [149]. Currently NGF and TrkA targeted therapies are in development for psoriasis and psoriatic arthritis [150].

The mTOR signaling pathway is constitutively activated in various malignant disorders and the efficacy of PI3K/Akt/mTOR inhibitors in preclinical models of malignant diseases demonstrate its role in ‘uncontrolled cell proliferation’ [151]. The key pathologic effects in psoriasis and PsA are also the ‘uncontrolled proliferation’ of keratinocytes, synovial fibroblasts, endothelial cells and T cells. We have reported that mTOR signaling proteins were significantly upregulated in psoriatic disease and have observed that a dual kinase PI3K/mTORC1 inhibitor, NVP-BEZ235, has potent antiproliferative effects on keratinocyte and synovial cells [152]. This finding supports the further development of mTOR inhibitors to treat PsA.

Numerous mTOR kinase inhibitors are currently in clinical development as anti-cancer agents and we expect that they soon will be evaluated in psoriatic disease. Kv1.3, is one of the two major K+ channels that are expressed in lymphocytes. These channels not only play a regulatory role during signal transduction in immunocytes but also induce proliferation and activation of immunocytes [153]. Our preclinical study reported an increased number of Kv1.3 positive cells in psoriatic skin as well as in the synovium of psoriatic arthritis [153]. Currently several Kv1.3 inhibitors are in preclinical development for psoriatic disease. Among these small molecule inhibitors, PAP-1 has shown promising effects in our preclinical studies of psoriasis [153].

Angiogenesis is known to be an important pathogenic feature of psoriasis [154]. Local and systemic elevation of VEGF-A have been demonstrated in the skin and plasma of patients with psoriasis and normalization of these elevations are noted following the successful treatment of psoriasis [154]. In addition there have been case reports demonstrating improvement in psoriasis and psoriatic arthritis following administration of VEGF inhibitors for cancer, bevacizumab, sunitinib and sorafenib [155,156]. Recently we have discovered that bevacizumab may be effective in PsA [157]. These results warrant further studies with VEGF inhibitors in psoriasis and PsA.

6. Conclusion

Psoriatic arthritis is a chronic and progressive inflammatory arthritis intimately associated with psoriasis that can lead to substantial morbidity. Dermatologists treating psoriasis patients are capable of routinely screening for early PsA by asking about possible joint pain, stiffness or tenderness. Early PsA can also be identified by rapid screening questionnaires. Ideal interventions for active PsA should target skin and joint involvement simultaneously. Although conventional DMARDS may possibly work for some patients, they have not been shown to arrest the PsA disease process. It is essential that patients with PsA are diagnosed early and treated more aggressively at the inception of the disease to control the inflammatory process and to stop joint destruction and disability.

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