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Psoriatic arthritis

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ABSTRACT: Psoriatic arthritis (PSA) is an entity of inflammatory joint disease associated with psoriasis. PSA belongs to the heterogeneous group of seronegative spondylarthropathies. Both peripheral joints and axial skeleton can be affected in a characteristic pattern. In addition to that, enthesitis and dactylitis are important extracutaneous manifestations. Uveitis anterior is temporarily seen in about one quarter of PSA patients. There is a closer relationship of nail and joint disease. This review provides data on drug and physical treatment options. In particular DMARDS and inhibitors of tumor necrosis factor α are established therapies with importance for quality of life and long term outcome. New drugs are tested in various trials.

KEYWORDS: biologics, dactylitis, DMARDS, enthesitis, psoriatic arthritis, treatment, uveitis

History, definition, and classification of psoriatic arthritis

The possible relationship between psoriasis and inflammatory joint disease was recognized first by French medicine since early 19th century (1,2). In 1973, Moll and Wright defined psoriatic arthritis (PSA) as: inflammatory arthritis (peripheral) and/or sacroiliitis or spondylitis, with psoriasis but rheumatoid factor negative (3). Current understanding sees PSA as a seronegative inflammatory disease of joints, entheses and periarticular connective tissue in association with any clinical type of psoriasis (4). There is no particular laboratory parameter for diagnosis. Rheumatoid factors or anti-cyclic citrullinated antibodies are seen in 4.7% and 7.6%, respectively (5). PSA can be classified according to the CASPAR criteria (Table 1) with a specificity of 98.7% and a sensitivity of 91.4% (5). A lower sensitivity of 77.3% was noted in early disease (6).

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Table 1. Classification criteria for psoriatic arthritis (CASPAR)

1. Criterion – inflammatory disease of joints, spine or tendons/enthesis (2 points)
   and
2. At least one of the following criteria (1 point each)
   1. Psoriasis (skin, scalp) – now
   2. Psoriasis in patient's history
   3. Psoriasis in family history
   4. Psoriatic nail involvement (now)
   5. Rheumatoid factor negative (ELISA)
   6. Dactylitis (now)
   7. Dactylitis in patient's history
   8. Radiological signs of new bone formation adjacent to the joints (except osteophytes)

PSA can be considered to be definite when at least 4 criteria are fulfilled.

Epidemiology

Most PSA patients show skin manifestations first but 15% develop extracutaneous manifestations before onset of psoriasis (4,7). In a recent analysis of 2009 psoriasis patients 19% had PSA. Another 7.7%

had intermittent but clinically unspecific joint symptoms, which could not be clearly attributed to PSA (8). Figures are lower from Asian countries (1–9%) (9). There is reason to believe that PSA incidence is increasing. In Olmsted County, Minnesota in the United States, age- and sex-adjusted incidence of PSA per 100,000 increased from 3.6 (1970 to 1979) to 9.8 (1990 to 2000). Reasons for the increase are unknown, but greater physician awareness of the diagnosis seems to be a possible factor (10).

In general, there is no relationship between severity and extension of cutaneous manifestations and articular manifestations but PSA patients in dermatological care tend to have a higher psoriasis area and severity score (PASI) than rheumatologic PSA patients (11).

Pathogenesis

The etiology of PSA although not completely understood genetic, environmental and immunologic-factors. Genetic analyses suggest two genetic pathways in PSA, one is through human leukocyte antigens (HLA) alleles B*27 and B*39, another is through the function of haplotypes containing the HLA-allele Cw*0602 (12). PSA has a well-recognized propensity for aggressive bone erosions. In some individuals, however, periarticular bone mineralization is maintained, and there is often associated new bone formation with periostitis and frank ankylosis suggesting a disorder of bone remodeling also far from the inflamed joints (13). T-cell driven immunopathology, pro-inflammatory cytokines in synovial tissue and the ability of peripheral mononuclear blood cells to produce osteoclasts in vitro are hallmarks of the interaction of inflammation and bone remodeling (14). Among the mechanisms of abnormal bone remodeling mediators of osteoclastogenesis such as RANK ligand and molecular signaling pathways including Dickkop-1 and bone morphogenetic proteins seem to be involved (15,16).

Neuropeptides, nerve growth factor (NGF) and its receptors (NGF-R) contribute to the inflammatory joint disease of PSA (4). Human synovial cells produce and release NGF and express high-affinity NGF-tyrosine kinase receptor TrkA/NGF. NGF enhances the expression of TrkA and down-regulates IL-1 beta-induced TNF-alpha and iNOS production by synovial fibroblasts (17). NGF may lead to synovial cell proliferation, and thus could influence the inflammatory and proliferative cascades of inflammatory arthritis (18).

Who is at risk for PSA?

A prevalence study in Reykjavik (Iceland) demonstrated that the relative risk for PSA in first degree relatives is 39, reflecting a strong genetic component (19). Psoriasis features associated with higher risk of PSA are scalp lesions (hazard ratio [HR] 3.89, 95% CI 2.18–6.94), nail dystrophy (HR 2.93, 95% CI 1.68–5.12), and intergluteal/perianal lesions (HR 2.35, 95% CI 1.32–4.19) (20). Psoriasis patients with asymptomatic enthesopathy seem to be at risk to develop PSA later (21).

Clinical findings and course

PSA is seen mostly in adults but other age groups can also be affected. The natural course is characterized by flares and remissions (4). Primary diagnosis is clinical. Joint affection can be monoarthritic, oligoarthritic, or polyarthritic (Table 2) (22). Polyarthritis (58.7%) is the most common manifestation pattern, followed by oligoarthritis (31.6%) and arthritis mutilans (4.9%). Distal interphalangeal involvement is present in 41.0% and dactylitis in 23.7% of patients (23). PSA specific is the distal arthritis of finger or toe (FIG. 1) whereas the knee is most commonly affected in PSA monoarthritis (FIG. 2) (22). The spine can be involved in any part, but most often at lumbosacral transition and the neck. Sacroiliacal joints are typically affected asymmetrical with back pain and stiffness in the morning (FIG. 3).

Table 2. Clinical types of psoriatic arthritis

Asymmetric mono- or oligoarthritis	most common type, most affected are digits, knees, and ankle
Symmetric arthritis	rheumatoid arthritis-like
Mutilating arthritis	rare type (<5% of patients) with marked deformities and functional impairment
Spondylarthritis	mostly HLA B27-positive, with spondylitis and sacroiliitis, spondylitis ankylosans-like, in later stages roentgenologic differences like the formation of para-syndesmophytes
Other types	
SAPHO syndrome	sternoclavicular hyperostosis and osteitis, palmoplantar pustular psoriasis
Psoriatic pachydermo-periostosis	thickening of nail plates and/or onycholysis, dactylitis, thickening of the bone

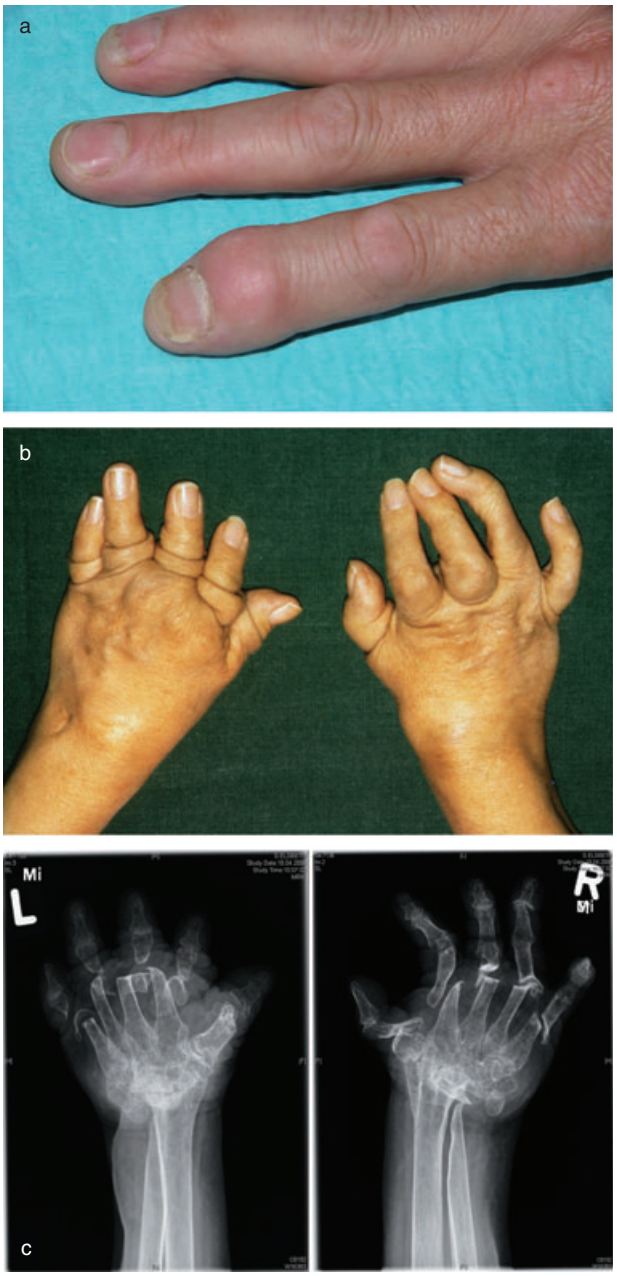

FIG. 1. Peripheral arthritis of small joints in PSA. (a) Distal joint affection and nail involvement. (b) Arthritis mutilans with telescope joints. (c) X-ray findings of the same patient as in (b) demonstrating severe joint destructions and dislocations.

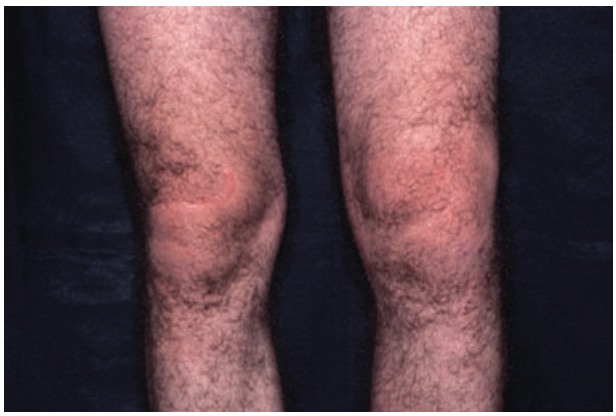

FIG. 2. Goanarthritis – one of the more common sites for oligioarthritic PSA.

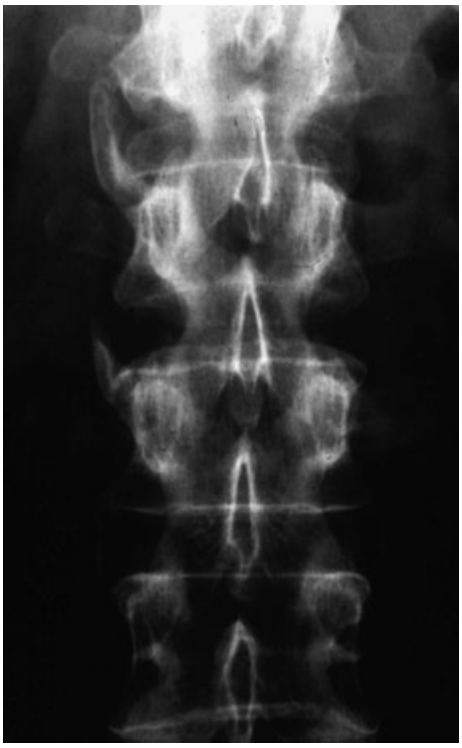

FIG. 3. Axial involvement with characteristic parasyndesmophytes of the spine.

The PSA characteristic "sausage" fingers or toes are caused by dactylitis (FIG. 4). By palpation both dactylitis and peripheral arthritis in PSA cause a more tender sensation than in RA. Dactylitis appears to be a severity marker for the disease (24).

A very characteristic and often painful manifestation of PSA is enthesitis (FIG. 5). Collectively, the fibrocartilages, bursa, fat pad, and the enthesis itself constitute the enthesis organ. It also includes both the immediately adjacent trabecular bone networks and in some cases deep fascia (25). Enthesitis remains an elusive clinical feature: recent data confirmed the poor association between clinical and ultrasonographic enthesitis in PSA (26).

The nail is functionally integrated with entheses associated with the distal phalanx that provides anchorage to the skin and joint (27). When the nail organ is involved in nail psoriasis, a secondary affection of the joint may develop as vice versa (28)

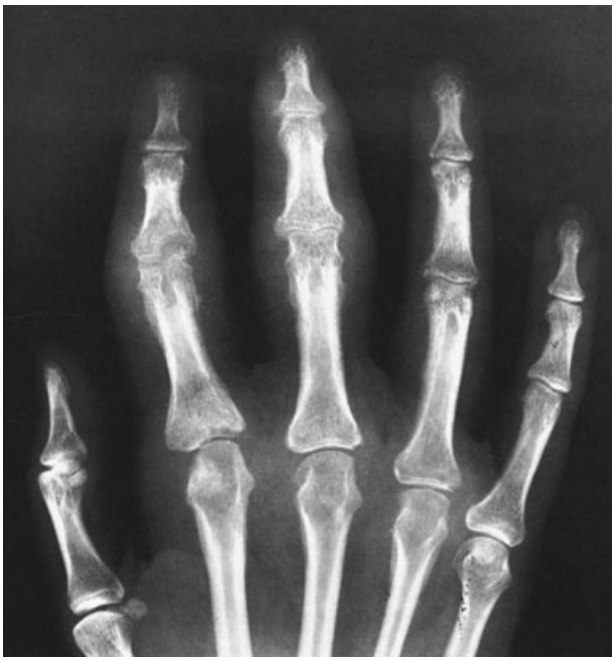

FIG. 4. Dactylitis digit II and II in combination with articular involvement of distal and proximal interphalangeal joints.

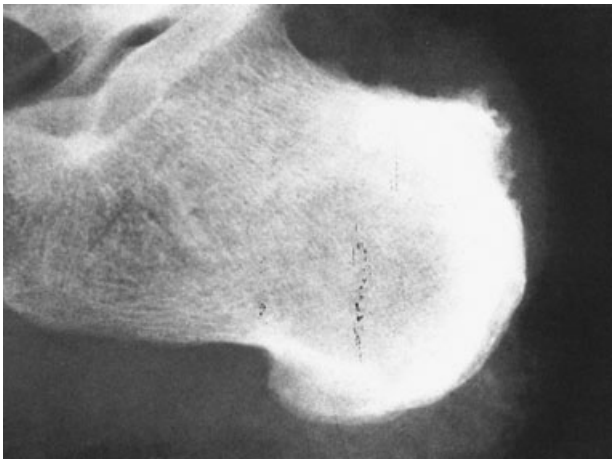

FIG. 5. Enthesistis at the insertion of the Achilles tendon.

(FIG. 6). Therefore, nail involvement may be an indicator for PSA (29). The 20 MHz sonography is a useful tool for follow-up of nail disease (30). Like other spondylarthopathies, PSA has an increased risk for acute anterior uveitis with a prevalence of 25.1% (31).

Radiologic findings

Several radiological imaging techniques can be used to diagnose PSA. The typical initial examination consists of plain-film X-rays of the peripheral skeleton focused on small joints of feet and hands. High resolution sonography is a useful tool to evaluate of joint disease (32).

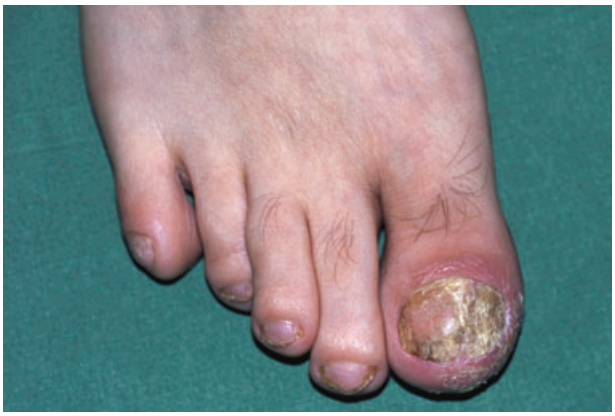

FIG. 6. Pachydermoperiostitis of the great toe in PSA.

X-ray computed tomography (CT), today modified as multi-detector-/multi-row-CT (MD) provides excellent spatial resolution down to tiny submillimeter structures based on isotropic volume elements (Voxel's) for multiplanar image reformation. Because it is associated with a high radiation exposure, it should be avoided in younger patients with childbearing potential. Magnetic resonance imaging (MRI) provides an excellent soft tissue contrast. MRI can give clinically relevant additional information by spine and sacroiliacal joint examinations (33). MRI-based scoring systems are under investigation (34). MRI sensitivity can be further increased by the use of intraveneous contrast (e.g., gadolinium-chelates) for early stages of PSA (35). One should be aware that a negative X-ray and other imaging techniques do not exclude PSA.

Typical PSA findings on X-ray images are bony erosions (lytic subchondral cysts, mutilations) combined with proliferations (i.e. protuberances, periostal ossifications along diaphysial parts) (FIG. 7). Calcifications of joint capsules, periarticular connective tissue and the insertion of tendons may occur in an irregular order. In approximately 30%, the distal interphalangeal (DIPs) joints of fingers and toes are involved (transversal type) (4).

The axial type with involvement of at all joints of a digit can be seen in 10% of all cases. In the majority of PSA cases asymmetric joint involvement combining DIPs, proximal IPs, and the metacarpophalangeal joints built the radiological picture. Arthritis of smaller joints is more frequent (50%) than those of the larger ones (10%). The sacro-iliac

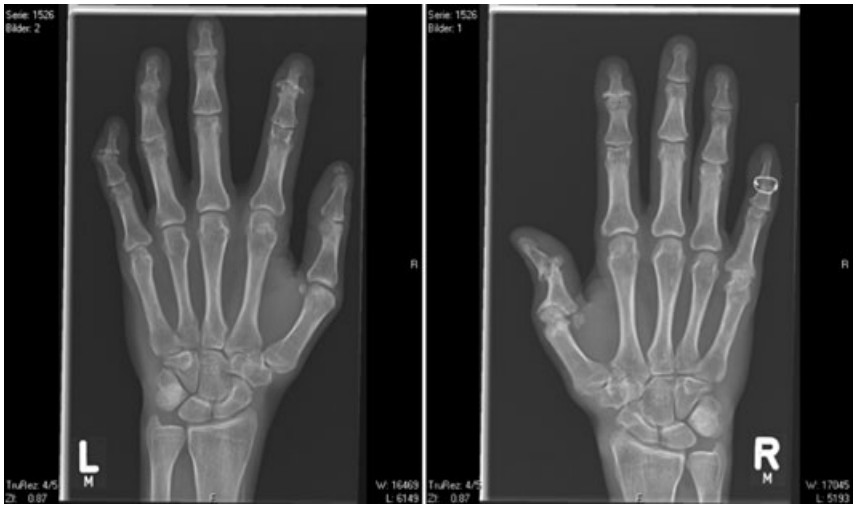

FIG. 7. Typical erosions and mutlitation with "pencil-in-cup" formation of distal interphalangeal joints.

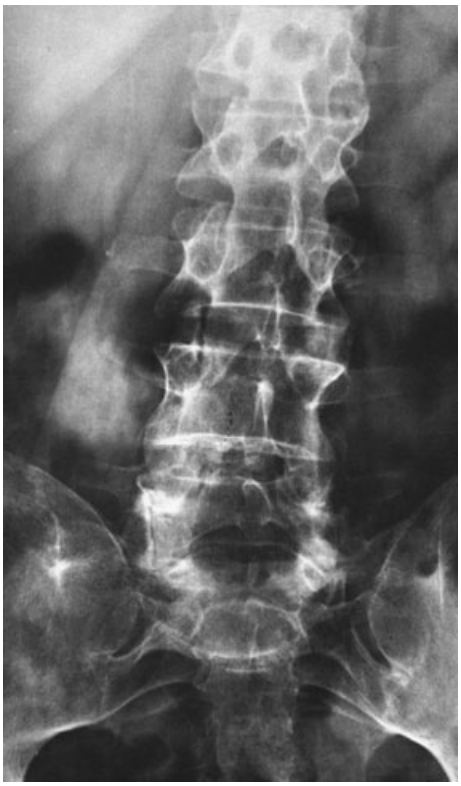

FIG. 8. Bilateral ankylosis of the sacro-iliacal joint.

joints are affected in more the 50% of cases, usually bilaterally but asymmetric (FIG. 8). Unilateral involvement occurs in 20%. Isolated sacroiliitis without peripheral symptoms is rare. The combination with spinal affection can be found more frequently (20% lumbar spine). The affected sacroiliacal joint shows blurred contours, subchondral erosions / sclerotic formations, widening of the joint space, and bony ankylosation. Erosive changes are localized predominantly in the iliacal part, not the sacral (4,34).

In case of spine affection, typical paravertebral ossifications are found (parasyndesmophytes) (FIG. 3). They may occur isolated adjacent to the intervertebral space or can develop in a short distance to the roof and basal plate of the vertebral bodies starting in a horizontal direction followed by a perpendicular growth. Syndesmophytes are rare in PSA (FIG. 9). Non-articular inflammatory changes (periostitis, tendinitis, enthesitis) may be seen in several regions (34).

Differential diagnosis

Because RA is the most common differential diagnosis of PSA, major findings of both disorders are summarized in Table 3. Indeed, rheumatoid arthritis can occur in a patient with psoriasis. Gonarthritis, although a typical manifestation of PSA, can also be found in gonorrhea and gout. Activated osteoarthritis is another differential diagnosis. Distal joint affection of fingers and toes is often seen in PSA. The most common differential diagnosis in particular in females is Heberden's arthrosis. For axial skeleton involvement other spondylarthropathies including spondylitis ankylosans have to be considered. Radiological differential diagnosis has to include disorders like erosive osteoarthrosis (more elderly patients, more symmetric order), ankylosing spondylitis (parasyndesmophytes are pathognomonic for PSA) and atypical manifestations of rheumatoid arthritis as well (22,34).

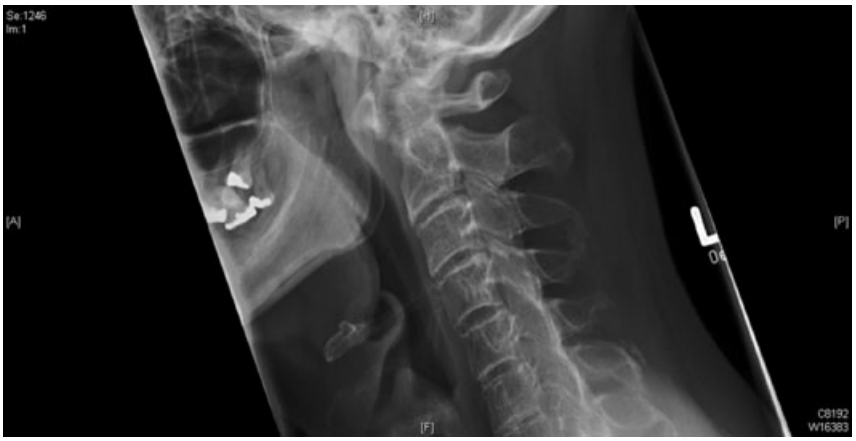

FIG. 9. Cervical spine involvement of PSA, in this case with syndesmophytes.

Table 3. Clinical findings and differential diagnosis of rheumatoid arthritis (RA) and psoriatic arthritis (PSA)

Finding	RA	PSA
Morning stiffness > 1 h	+++	+
Arthritis > 3 joints	+++	–
Arthritis of the hand	+++	+
Symmetrical arthritis	+++	+/–
Rheumatoid nodules	+++	–
Rheumatoid factor	++	+/–
Erosions and demineralization (wrist)	++ (later)	+/–
Dactylitis	–	+++
New bone formation (near joints)	–	+++ (later)
Affection of distal finger/toe joints	–	+++

Enthesiopathy is seen in reactive arthritides like *Yersinia*-associated arthritis, in SAPHO syndrome, ochronosis, acromegaly, diffuse idiopathic hyperostosis, and fibromyalgia (4).

Treatment

1. Drug therapy (Tables 5 & 6)

Symptomatic therapy. Peripheral mild mono- or oligoarticular and axial PSA, dactylitis and enthesitis benefit from nonsteroidal anti-inflammatory drugs (NSAID) (36). Monoarthritis of small joints can be treated by periarticular corticosteroid injections (4). Periodic intra-articular injection of corticosteroid are of particular value in the management of patients with oligoarticular disease or those with controlled polyarticular disease but one or two persistently actively inflamed joints (37).

Disease modifying drugs (DMARDS). DMARDS remain the first choice for the treatment of peripheral arthritis despite scarce evidence of their efficacy or ability to halt radiographic progression. Effective DMARDS in PSA are methotrexate (MTX), sulfasalazine, ciclosporin A, and leflunomide (38). MTX is used once a week (15–50 mg) with a good efficacy on skin disease, some effects on joints, low costs, and mostly mild adverse effects on liver and blood. Bioavailability is better with subcutaneous injections than oral application (39,40). Folic acid (5 mg) given 24 h later reduces potential adverse effects (4). Some studies are in favor of an earlier treatment with higher dosages than previously used. Response rates up to 68% could be achieved (41,42) associated with an improvement of health related quality of life (43). MTX increases drug survival and reduces drop-outs during treatment with biologics (44,45).

There are five randomized controlled trials (RCT) for sulfasalazine available that suggest some effect in milder forms of peripheral but not axial arthritis (38). Ciclosporin A is used at a dosage of 2.5–5 mg/kg body weight. RCTs have not been performed in PSA. Available data suggest some effect on arthritis, good response of skin disease and improvement of arthritis-related pain (46).

Leflunomide treatment is started with a "loading dose" of 100 mg/d for three days, followed by 20 mg/d. The anti-inflammatory effect is in the range of MTX but without any beneficial effect on skin disease. The TOPAS study involved 190 PSA patients treated with leflunomide for 6 months. The American College of Rheumatology 20% crite-

Table 4. Pharmacokinetics of tumor necrosis factor-α inhibitors infliximab, etanercept, and adalimumab

Drug	Half-life (days)	Maximum concentr. (mg/L)	Minimum concentr. (mg/L)	Average concentr. (mg/L)	AUC0-T (mg h/L) steady state
Infliximab i.v.	7.6 (5 mg/kg)	165 ± 42 (5 mg/kg)	8.3 ± 11.9 (5 mg/kg)	37.1 (5 mg/kg)	120,000 ± 37,000 (5 mg/kg)
	10 (10 mg/kg)	299 (10 mg/kg)	7.11 (10 mg/kg)	58.2 (10 mg/kg)	
Etanercept s.c.	2.8 ± 0.8 (25 mg)	2.5 ± 0.5 at 53 ± 35 h (25 mg BIW)	1.5 ± 0.6 (25 mg BIW)	1.9 ± 0.5 (25 mg BIW)	321 ± 83 (25 mg BIW)
		4.9 ± 2.5 at 69 ± 48 h (50 mg BIW)	3.1 ± 1.6 (50 mg BIW)	3.7 ± 2 (50 mg BIW)	600 ± 291 (50 mg BIW)
Adalimumab s.c.	10–20 (40 mg)	7.7 ± 3.4 at 90 ± 48 h steady state	3.8 ± 2.1 steady state	5.5 ± 2.5 steady state	1830 ± 850

Table 5. Overview about randomized controlled trials in PSA with documented ACR response

Drug	No.	Pts. Rx	ACR20 (verum versus placebo/control)	Reference
Leflunomide	190	20 m/d, orally	36.6 vs. 20% (week 12)	(47)
Infliximab	104	5 mg/kg bw[a], iv	65% vs. 10% (week 16)	(53)
Infliximab	200	5 mg/kg bw[a], iv	54% vs. 16% (week 98)	(55)
Etanercept	60	25 mg taw[c], sc	25% vs. 13% (week 12)	(57)
Etanercept	752	50 mg weekly versus eaw[b], sc	66% or 77% (week 12)	(61)
Adalimumab	313	40 mg eaw, sc	58% vs. 14% (week 24)	(63)
Golimumab	405	50/100 mg sc 1× mo, sc	48% vs. 9% (week 12)	(74)
Alefacept	185	15 mg weekly + MTX, im versus MTX alone	54% vs. 23% (MTX alone)	(57)
Ustekinumab	146	90/63 mg sc	42% vs. 19% (week 12)	(74)

[a]bw, body weight; [b]eaw, every other week; [c]taw, twice weekly.
iv, intravenous; im, intramuscular; mo, month.

ria for improvement in rheumatoid arthritis (ACR 20) response was 36.6% in the leflunomide group and 20% in the placebo group ($p = 0.0138$) (47). Leflunomide is approved for PSA in Europe.

Combinations of DMARDS have not systematically been studied. In a single 12 months RCT comparing MTX with MTX plus ciclosporin A ($n = 72$) both the tender joint score and the PASI score were significantly lower with the combined treatment (48).

Tumor necrosis factor-α inhibitors (TNFαI). The proof of concept of use of TNFαI in PSA was done in an open MRI-controlled study with 10 PSA patients with polyarticular affection and infliximab for 10 weeks (49). The first symptom that responds to intravenous infliximab is arthritis-related pain (50). There is now a range of TNFαI available for PSA patients. Pharmacokinetics of the infliximab etanercept and adalimumab are summarized in Table 4. Available data for a patient of standard weight (70 kg) with golimumab are: apparent clearance = 1.38 ± 0.04 L/d, apparent volume of distribution = 24.9 ± 1.04 L, and absorption rate constant = 0.908 ± 0.121 per day (51). Association and dissociation rates of binding to soluble TNF were found to be similar for adalimumab, infliximab, and etanercept, as were their calculated binding affinities. Avidity of binding to soluble TNF was 10- to 20-fold greater for soluble etanercept (K(D) = 0.4 picomolars [pM]) than for soluble adalimumab or infliximab (K(D) = 8.6 and 4.2 pM, respectively) (52).

Infliximab. More than 300 patients with PSA were recruited into the IMPACT and IMPACT 2 trials. Patients received infusions of infliximab (5 mg/kg) or placebo at weeks 0, 2, 6, and 14. After week 16, patients initially assigned to receive placebo crossed over to receive infliximab 5 mg/kg every 8 weeks through week 50, while patients initially randomized to infliximab continued to receive active treatment at the same dose through week 50. Sixty-five percent of infliximab-treated patients achieved an ACR20 response at week 16 (65%), but only 10% with placebo (53). Infliximab significantly inhibited radiographic progression in patients with PSA as early as 6 months after starting treatment,

Table 6. Treatment algorithm for PSA modified according to Ritchlin et al. (99)

Therapeutic target	Initial therapy	Second line therapy
Peripheral arthritis	NSAIDs, intraarticular corticosteroids, DMARDs, in severe cases: TNFαIs	Combined treatment
Axial arthritis	NSAIDs, physiotherapy, pain management, in moderate to severe cases: TNFαIs	TNFαIs alone or in combination with MTX
Enthesitis	NSAIDs, physiotherapy, corticosteroids, in severe cases: TNFαIs	TNFαIs (infliximab, etanercept)
Dactylitis	NSAIDs, corticosteroids, DMARDs	TNFαIs (infliximab)

and the beneficial effect continues through one year of infliximab therapy (54).

In the 2-year follow-up of IMPACT, 62% (48/78) of infliximab-treated patients achieved an ACR20 response, while 45% and 35% of patients achieved ACR50 and ACR70 responses, respectively. The average estimated annual radiographic progression with infliximab treatment was significantly reduced versus the estimated baseline rate of progression. No new safety issues were observed during the second year of the study (55).

Safety considerations: Screening for latent TB (through a PPD and/or chest x-ray) should be done at baseline. Other optional tests conducted at baseline include: BUN, creatinine, SGOT, SGPT, hepatitis C serology, and β-HCG (to exclude gravity). Consider periodic CBC and clinical follow up every three months (56).

Etanercept. In an RCT with 60 patients with either PSA or psoriasis over 12 weeks, efficacy and safety of etanercept (25 mg twice-weekly subcutaneous injections) or placebo was assessed. The ARC20 was achieved by 22 (73%) of etanercept-treated patients compared with four (13%) of placebo-treated patients. Etanercept was well tolerated (57). A total of 1122 patients who had active PSA were enrolled in a Phase 4, non-randomized, open-label, single-arm, 24-week study. They received etanercept therapy 50 mg subcutaneously once weekly for 24 weeks. After 24 weeks of treatment, 865 patients (77.1%) achieved a "mild or better" score on the physician global assessment of psoriasis and were improved from baseline. Patient global assessment of joint pain and joint disease scores were improved by means of 2.7 and 1.5, respectively (58). A sustained benefit of treatment, including inhibition of radiographic progression, was observed during 3 years of treatment (59,60).

The PRESTA trial for adult PSA patients ($n = 752$) compared 50 mg etanecerpt biweekly with 50-mg etanercept every week in a 12-week double-blinded period followed by another 12-week open label period with 50-mg etanercept every week. The ACR20 and PSARC at week 12 were 66% and 77% (biweekly etanercept), and 61% and 76% (weekly etanercept), respectively. ACR50 and ACR70 were 45% and 41%, and 35% and 37%, respectively (61). At week 24 ACR20 was 69% and 72%, PSARC was 82% and 80%, respectively. Both treatment modalities obtained comparable results for improvement of enthesitis, DLQI and C-reactive protein (62).

Safety considerations: The US FDA does not require any monitoring but this might be different in other states. It is recommended that the following tests be undertaken at baseline: PPD and or/chest x-ray, BUN, creatinine, SGOT, SGPT, hepatitis C serology, and β-HCG. Consider three periodic CBC, ESR, and clinical follow up every 3 months (56).

Adalimumab. In the ADEPT trial patients with moderately to severely active PSA and a history of inadequate response to NSAIDs were randomized to receive 40 mg adalimumab or placebo subcutaneously every other week for 24 weeks. At week 12, 58% of the adalimumab-treated patients (87 of 151) achieved an ACR20 response, compared with 14% of the placebo-treated patients (23 of 162) ($p < 0.001$). At week 24, similar ACR20 response rates were maintained and the mean change in the modified total Sharp score was –0.2 in patients receiving adalimumab and 1.0 in those receiving placebo ($p < 0.001$). Disability and quality of life measures were significantly improved with adalimumab treatment compared with placebo. Adalimumab was generally safe and well tolerated (63). Patients who completed ADEPT could elect to receive open-label adalimumab, 40 mg subcutaneously every other week after week 24. At week 48, patients from the adalimumab arm of ADEPT ($n = 151$) had achieved ACR20, ACR50, and ACR70 response rates of 56%, 44%, and 30%, respectively. Improvements in disability were sustained from week 24 to week 48. Adalimumab demonstrated

clinical and radiographic efficacy regardless of whether patients were receiving methotrexate (MTX) at baseline (64). The clinical and radiographic efficacy of adalimumab demonstrated during short-term treatment was sustained during long-term treatment (120 weeks) with a favorable risk-benefit profile (65).

Safety considerations: The FDA requires that patients be screened for latent TB (PPD and/or chest x-ray), routine CBC/chemistries at baseline, and anti-dsDNA antibodies if lupus-like symptoms are present. In addition β-HCG, liver function tests, and RFT, can be considered at baseline (56).

Golimumab. In the recent GOREVEAL trial adult patients with PSA who had at least three swollen and three tender joints and active psoriasis were randomly assigned to receive subcutaneous injections of placebo (n = 113), golimumab 50 mg (n = 146), or golimumab 100 mg (n = 146) every 4 weeks through week 20. At week 14, 48% of all patients receiving golimumab achieved an ACR20 response compared with 9% of patients receiving placebo (p < 0.001 for all comparisons). Significant improvement was observed for quality of life scores (SF-36; HAQ), the nail disease, and enthesitis. This efficacy was maintained through week 24. Golimumab was generally well tolerated (66).

Certozilumab pegol. Cetrozilumab pegol is the recombinant antibody Fab' fragment of a humanized TNFα inhibitory monoclonal antibody. A phase II trial in psoriasis demonstrated superiority of 200 mg and 400 mg s.c. injections given every other week over placebo (67). Adverse effects are comparable to other TNFαIs.

General safety considerations. All TNFαIs can induce psoriasis in PSA patients, mostly of the pustular palmoplantar type. Usually this side effect can be controlled by switching the treatment to another compound and topical therapy or PUVA therapy for palmoplantar lesions. The pathogenesis, however, is not fully understood (68). Other possible adverse effects are infusion reactions (only for infliximab), lupus-like disorders, vasculitis, granulomatous reactions, infections, neoplasia, and central nervous system-related adverse effects (69).

Comparative trials of TNFαIs. Atteno et al. (2010) investigated the effectiveness and safety of three in 100 consecutive PSA patients with inadequate response to DMARDs. After enrolment, all patients were randomly given infliximab 5 mg/kg every 6–8 weeks, etanercept 50 mg weekly, or adalimumab 40 mg every other week. ACR20 response rates after 12 weeks were 75%, 72%, and 70%, respectively. Two drug-related adverse reactions were seen in patients with infliximab, none with the other TNFαIs. Etanercept showed the greatest improvement of tender joints count, whereas infliximab and adalimumab achieved the greatest reduction in PASI score (70).

An observational study in the UK analyzed efficacy and safety of TNFαIs in 596 PSA patients. Disease activity was measured by the EULAR response. The study found that 75.8, 70.3 and 68.2% of the PSA cohort were EULAR responders at 6, 12 and 18 months, respectively. After 18 months a good EULAR response was achieved 52% (etanercept), 53% (infliximab), and 58% (adalimumab) of those remaining on initial therapy. The incidence rate of severe adverse reactions (0.9) was not increased compared with a control group of seronegative RA patients on DMARDs (71).

Other biologics

Alefacept. Alefacept is a bioengineered fusion protein of soluble lymphocyte function antigen (LFA-3) with Fc fragments of IgG1. A single course of alefacept intramuscularly in combination with methotrexate (MTX) was effective in treating both psoriasis and psoriatic arthritis (PSA). ACR20 was achieved in 54% of patients of the verum group compared to 23% with MTX alone (72).

In an open-label extension study, patients with PSA on stable doses of MTX were treated with an additional 12 weekly intramuscular injections of alefacept followed by 12 weeks of observation. At the end 86 of 160 (54%) patients achieved ACR20, of which 28 of 55 had received placebo plus MTX and 58 of 105 received alefacept plus MTX in the prior double-blind phase. Those patients achieving ACR50 and ACR70 increased from 17% and 7%, respectively, in the double-blind phase to 32% and 12%, respectively, in the open-label extension phase. No additional toxicity was observed (73). Alefacept has been approved in the United States.

Safety considerations: The FDA requires that a CD4 level be taken at baseline and then weekly. Alefacept should be held if the CD4 drops <250 cells/μL. Other possible tests to undertake include a PPD and chest x-ray, β-HCG, CBC with differential, liver function test, and RFTs at baseline (56).

Ustekinumab. Ustekinumab is a fully human monoclonal antibody that binds with high specificity and affinity to the cytokines interleukin (IL)-12

and IL-23, thereby suppressing IL-12- and IL-23-mediated inflammation associated with psoriasis (67).

In a phase II double-blind, randomized, placebo-controlled, crossover study patients with active PSA were randomly allocated either ustekinumab (90 mg or 63 mg) every week for 4 weeks (weeks 0–3) followed by placebo at weeks 12 and 16 (n = 76; Group 1) or placebo (weeks 0–3) and ustekinumab (63 mg) at weeks 12 and 16 (n = 70; Group 2). At week 12, 32 (42%) patients in Group 1 and ten (14%) in Group 2 achieved an ACR20 (difference 28% [95% CI 14.0–41.6]; p = 0.0002). Ustekinumab significantly reduced signs and symptoms of PSA and diminished skin lesions compared with placebo, and the drug was well tolerated (74).

Other new treatment options. Abatacept is a fusion protein of the cytotoxic T-lymphocyte antigen (CTLA) molecule and IgG1 that blocks CD80 and CD86 ligands on the surface of antigen-presenting cells that must interface with the T-cell CD28 receptor to activate T cells (75). Rituximab is a monoclonal anti-CD20 antibody leading to B-cell depletion (67). Sipiluzimab is a humanized monoclonal IgG1 antibody against CD2 selectively inhibiting activation and proliferation of T-memory cells. Antipsoriatic activity has been shown (76). Orthoclone is a humanized antihuman CD4 IgG4 antibody preventing T-cell activation via MHC receptor binding (77). Two anti-CD25 antibodies, i.e. basiliximab and daclizumab, have been shown anti-psoriatic activity (78,79). Galiximab is a primatized monoclonal antibody that binds to CD80 found on certain T-cells and antigen-presenting cells (80).

2. Physical therapy

In addition to the use of drugs, physical therapy and ergotherapy are regarded as definite parts of the multimodal therapy concept for PSA. An overview is given in table 7.

Table 7. Physical therapies in PSA

Treatment	Mechanisms and techniques	References
Kinesiotherapy	passive methods include positioning, mobilization, stretching, tractions, Maitland's oscillatory mobilization, active kinesiotherapy deals with isometric tensing, exercises, complex or axial movements, movements, against low level resistance, movements in water bath, kinesiotherapy with devices and gait analysis	(81–83)
Manual therapy	frictions at the muscle and tendon regions, "deep frictions" by Cyriax applied diagonally to the fiber, lines of muscles and tendons	(81,84)
Thermotherapy	mainly practiced in chronic stages	(85)
Cryotherapy	local cryotherapy often used in acute arthritis, cryotherapy (15°C to –180°C) for 1–3 min, for pain relief, normalization of muscular tonus, and active hyperemia, longer application (3–30 min) reduces pain, edemas, and inflammation	(86–88)
Therapeutic ultrasound/ phonophoresis	therapeutic ultrasound is analgetic, anti-inflammatory, muscular relaxing, phonophoresis = combination of ultrasound, antiphlogistic lipophilic drugs, higher efficacy	(89,90)
Electrical stimulation	galvanization, i.e., application with a frequency of 0 Hz, constant current (CC)-wiring and constant voltage (CV)-wiring are known; electrical flow, two- or four-chamber bath, iontophoresis = galvanization for directed drug transport, transcutaneous electrical nervous stimulation (TENS; f = 20–100 Hz), interferential electrical stimulation (100 Hz, carrier frequency 4000 Hz), short-wave therapy (27 MHz) = high-frequency electrical stimulation with a condenser field method	(91–95)
Massage therapy	classic massage, reflex zone massage; gadget massage (e.g., hydromassage), and lymphatic drainage	(96,97)
Balneotherapy	application of natural and specific local healing remedies during complex rehabilitation, often in combination with climatotherapy; thermal salts therapy (26–28% saturated salt brine with pH 5.6), sulfurated bath (alkaline-muriatic sulfur springs), or radon baths	(98,99)
Ergotherapy	functional orientated kinesiotherapy of the extremities for preserving personal independence	(79,99)

Conclusions and outlook

During the last decade understanding and treatment options in PSA have developed remarkably. Nevertheless there are still some open questions:

(i) Although neuropeptides and NGF are involved in inflammatory joint disease and related pain, drugs with specific activity in this field are not established yet.

(ii) Although most drugs have been investigated in RCTs as monotherapy, clinical practice is the combination of treatment modalities. The critical evaluation of combined treatments is still underrepresented.

(iii) Treatment of early RA has become a strategy to prevent a disabling course of the disease and probably achieve healing. The concept of early (systemic) treatment in PSA seems to be attractive but needs evaluation.

(iv) Most recent placebo-controlled trials with biologics revealed ACR20 responses of the placebo group in around 10% to 20% of patients. A better understanding of spontaneous remissions in a subset of PSA patients might facilitate targeted treatment.

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