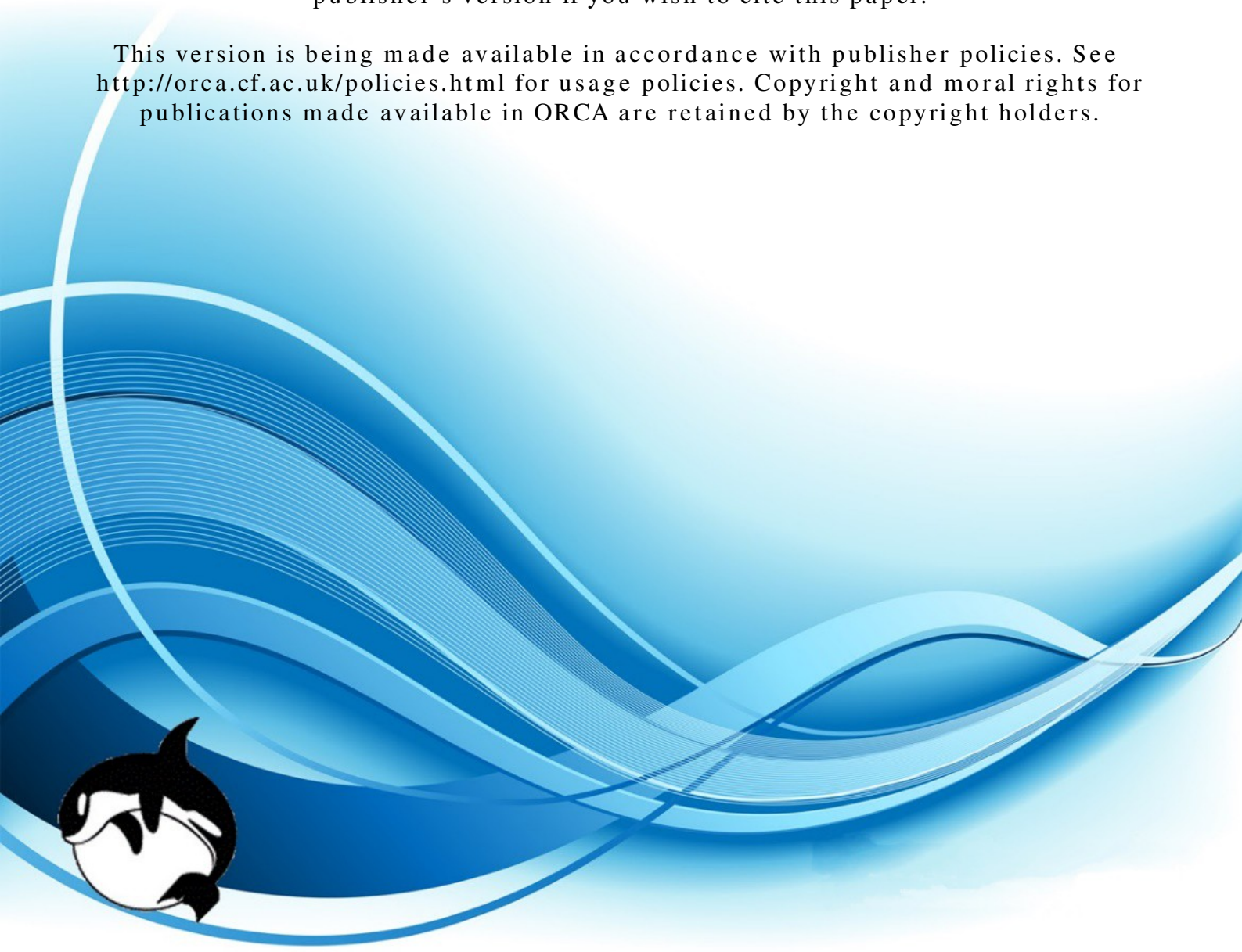

Psoriasis

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Abstract | Psoriasis is a chronic, immune-mediated disorder with cutaneous and systemic manifestations and substantial negative effects on patient quality of life. Psoriasis has a strong genetic basis, still mostly unknown; the majority of the identified genes linked to psoriasis belong to the human leukocyte antigens complex and others including interleukin 23 and the interleukin 23 receptor axis.Psoriasis pathophysiology is characterized by abnormal keratinocyte proliferation and immune cell infiltration in the dermis and epidermis involving the innate and adaptive immune system, with important roles for dendritic cells and T cells among others. Frequent comorbidities are rheumatologic and cardiovascular in nature, in particular psoriatic arthritis. Current treatments for psoriasis include topical agents, photo-based therapies, traditional systemic drugs, and biologic agents. Treatments can be used in combination or as monotherapy. Biologic therapies targeting specific disease mediators have become a mainstay in treatment of moderate-to-severe disease, whereas advances in the treatment of mild-to-moderate disease have been limited.

[H1] Introduction

Psoriasis is a chronic, immune mediated disorder that mainly affects the skin and joints and that has a complex genetic architecture, with an estimated global prevalence of 2-3%.(1) Psoriasis is predominantly a skin disease, phenotypes including plaque-type psoriasis (further referred to as psoriasis vulgaris), guttate psoriasis, inverse psoriasis, pustular psoriasis (including palmoplantar pustulosis, acrodermatitis continua of Hallopeau, and generalised pustular psoriasis), palmoplantar psoriasis, and erythrodermic psoriasis. Multiple phenotypes may occur in the same individual. Psoriasis vulgaris is the most common manifestation, (Figure 1).(2) Symptoms shared by all phenotypes can include itching, burning, and soreness. The extent of skin involvement is variable. Most types of psoriasis have a cyclic evolution, flaring for a few weeks or months, then subsiding for some time or even going into a period of remission.

Psoriasis is a systemic, inflammatory disease, in which increased release of pro-inflammatory cytokines from immune-related cells and chronic activation of the innate and adaptive immune system are mechanisms causing long-term damage to multiple tissues and organs. Psoriasis has been associated with numerous co-morbidities, including rheumatologic (psoriatic arthritis [PsA]), cardiovascular, and psychiatric complications (Box 1), and has well-described negative effects on patient quality of life. (3) (4)

In this Primer, we describe the epidemiology, pathophysiology and diagnosis of psoriasis, the available therapeutics and agents in the developmental pipeline and the potential of new treatments to positively affect patient quality of life.

[H1] Epidemiology

[H2] Prevalence and incidence Psoriasis affects over 125 million people worldwide (Figure 2). Women and men are affected equally. Psoriasis can manifest at any age, but onset usually occurs between 18–39 years of age or between 50–69 years of age.(5) Age of onset may be affected by genetic and environmental factors. Psoriasis is less common in children than adults; the prevalence among children ranged from 0% in Taiwan to 2.1% in Italy(5), and the incidence estimate reported in the United States was 40.8 per 100,000 person-years.(6) Psoriasis incidence in adults varied from 78.9 per 100,000 person-years in the United States to 230 per 100,000 person-years in Italy.(5)

The incidence of psoriasis appears to be increasing over time. In a retrospective cohort of adults, the incidence increased from 50.8 cases per 100,000 population between 1970–1974 to 100.5 cases per 100,000 individuals between 1995–1999.(7) In a retrospective cohort of children with psoriasis, the incidence increased from 29.6 to 62.7 cases per 100,000 in the same period.(6)

The National Psoriasis Foundation has defined mild psoriatic skin disease as having < 3% body surface area affected, moderate disease as 3–10%, and severe disease as > 10%.(8). Additional classifications of psoriasis severity include psoriasis-area-

severity-index (PASI) and physician global assessment (PGA), among others. While both BSA and PGA are used in the clinical practice of some authors, PASI is typically limited to the clinical trial setting.

[H2] PsA

Among psoriatic comorbidities, PsA is one of the most frequent, affecting 0.3–1% of the global population.(9) Depending on the study, 11%, (10)20.6%(11) or 30%(12) of patients with psoriasis are estimated to have concomitant PsA. Males and females are affected equally, and peak age of onset is between 35–45 years of age. In most patients with psoriasis who also develop PsA, the onset of arthritis occurs approximately 10 years after the onset of their skin disease. However, 15% of patients develop arthritis before cutaneous manifestations of psoriasis appear. **(13)** There is no direct correlation between the severity of joint and skin manifestations.

[H2] Cardiovascular comorbidities

Psoriasis has been associated with an increased prevalence of clinical (14) atherosclerosis and systemic and vascular inflammation (Figure 3).

Comorbid cardiovascular diseases remain the leading cause of death among patients with psoriasis.(15) Large scale, population-based epidemiological studies have demonstrated that psoriasis is associated with an increased risk of cardiovascular events beyond traditional risk factors and body mass index.(16, 17) Patients with severe psoriasis have an approximately 7-fold increased risk of myocardial infarction compared to age-, sex-, BMI-, and cardiovascular risk factor-matched controls.(17); risk of cardiovascular mortality is increased by 57%.(17) In addition, a dose response correlation between severity of psoriasis and odds of having a myocardial infarction has been demonstrated and an age-interaction has been shown whereby a 30-year-old patient with severe psoriasis has an approximate 2-fold increase in the risk of experiencing a first myocardial infarction.(17)

However, the association between psoriasis and cardiovascular comorbidities remains controversial and not all reports support the mentioned associations. Some articles have reported that patients with psoriasis are not at increased risk for atherosclerosis, coronary heart disease, stroke, heart failure(18) or ischemic heart disease hospitalization.(19) Thus, it has been suggested that such correlation might only apply to patients with severe psoriasis.

Furthermore, a higher prevalence of psychosocial distress or psychiatric disorders including stigmatization, social discomfort, anxiety and depression has been demonstrated in individuals with psoriasis.(20)

[H1] Mechanisms/pathophysiology

[H2] Genetics

Psoriasis has a strong genetic component, initially assessed by epidemiologic studies involving twins and families (21, 22). Twin studies have found a substantially higher (2–3.5-fold) concordance of psoriasis in monozygotic compared

with dizygotic twins (23), and estimates of heritability (the proportion of variance in overall disease liability accounted for by genetic factors) have ranged between 50–90% in populations of European descent.(22, 24) Recurrence rates (disease prevalence among relatives compared with the general population) range between 4–19% in first-degree relatives of individuals with psoriasis(25-27). Even higher genetic effects have been reported for PsA, with estimates of heritability between 80–100% (25, 26) and risk of developing PsA said to be 30–49-fold greater if a first-degree relative has PsA.(25-28) The role of genetic factors has been confirmed by linkage studies (which measure transmission of alleles through generations) in families and genetic association studies (which compare allele frequencies between cases and controls).(29, 30) Although over 40 genes associated with psoriasis have been identified, they only explain 30% of psoriatic heritability, which may be explained by cumulative effects of many genetic variations whose individual effects are small, as well as gene-gene and/or gene-environment interactions..

The genetic landscape of psoriasis is dominated by mutations in the psoriasis susceptibility locus 1 (*PSORS1*), which comprises genes in the human leukocyte antigens (HLA) complex (encoding the major histocompatibility complex proteins), with smaller contributions from a multitude of other genetic loci (Table 1). Linkage and family-based association strategies have enabled important advances in the genetic dissection of the associations between HLA genes and psoriasis (31, 32), including the differential analysis of cutaneous psoriasis and PsA. (33) The strongest HLA-related associations in psoriasis have consistently mapped to HLA-C*06 in white (32) and Chinese (34) populations, particularly in patients with early-onset and more-severe disease who have a positive family history.(35) However, regression analyses have identified at least seven independent HLA genetic signatures for psoriasis based on single-nucleotide polymorphism (SNP) typing, which have been mapped by imputation to HLA-C, HLA-B, HLA-A and HLA-DRA.(33) Notably, amino acid 45 of HLA-B, which maps to the B pocket of the peptide-binding groove, discriminates cutaneous psoriasisfrom PsA across a number of different HLA-B alleles. (33) Besides the HLA complex, linkage-based strategies have identified 17 susceptibility loci,(36-38) although only a few genes have been confirmed by subsequent linkage and/or association studies, because of the smaller effect sizes of genetic signals of non-HLA genes. Confirmed associations include mutations in the *PSORS2* region (17q24-q25) spanning the *CARD14* gene, (39) *PSORS4* in the epidermal differentiation complex, (40) *PSORS7* on chromosome 1p spanning the *IL23R* locus (41) and *PSORS6* on chromosome 19p13 spanning the *TYK2* locus (42)

As dense single nucleotide polymorphism microarrays and ever-increasing sample sizes became available, the new millennium marked a strategic shift from linkage to association studies, which are more powerful in the search for common susceptibility alleles in psoriasis and other complex genetic disorders.(43) By 2016, case-control association studies in population of European and Chinese descent have identified 87 psoriasis susceptibility regions, including population-specific and shared loci.(44-48) This strategy has also been successful for PsA, revealing allelic

variation between PsA and cutaneous psoriasis at known susceptibility regions.(49, 50) Novel PsA loci have also been identified by SNP microarrays, including PTPN22, which is not associated with cutaneous psoriasis in the cohort studied.(51)

Whereas SNP-based association strategies are suitable for identifying common but low-penetrance variants, traditional and next-generation sequencing techniques have been fruitful for identifying rare but highly penetrant alleles.(52) A prime example is the identification of the *CARD14* gene at the *PSORS2* locus.(53) (54) Targeted and whole-exome DNA sequencing also had key roles in the identification of mutations in *AP1S3* (chromosome 2q23) (55) and *IL36RN* (chromosome 2q13) genes, (56-58) which are linked to generalized pustular psoriasis, a highly inflammatory subtype psoriasis characterized by systemic inflammation. However, a genetic heterogenicity exists, particularly among patients with both generalized pustular psoriasis and psoriasis vulgaris.(59)

Unlike the high-penetrance and high-effect-size mutations emerging from the sequencing-based studies described above, 'interesting candidate' genes, in the proximity to loci commonly associated with psoriasis cannot simply be assumed to play a causative role. Thus, the identification of biological processes that can explain the genetic associations is a major focus of current research in psoriasis and other complex genetic disorders. (60) Various methods have been developed to measure the overlap between observed genetic signals and corresponding functions and pathways. For example, functional enrichment analysis is a method that uses statistical tests to identify over-represented subgroups of genes or proteins that might be associated with disease phenotypes. One study identified 87 significantly enriched functions or pathways, many of which are immune-related, such as lymphocyte differentiation and regulation, type I interferon signalling and pattern recognition, and nuclear factor κβ (NF-κβ) signalling.(61) In fact, the genetic signature uncovered by genome wide association studies in psoriasis revealed genes involved in immune regulation.(21) (62)

[H2] Immune response

Psoriasis is a disorder of both the innate and adaptive immune systems, in which keratinocytes, dendritic cells, and T cells have central roles. Psoriasis can be triggered by various factors in genetically susceptible individuals, including trauma, infection (such as HIV and streptococcal), and medications (such as β-blockers, IFN-α, and lithium).(2) Many abnormalities have been observed involving antigen presentation, activation of NF-κB signalling pathways, differentiation of T helper (T_H) cell populations (especially T_H17 cells, the primary source of IL-17) and enhanced IL-17 response, which promotes the host's immune response and infiltration of immune cells (Figure 4).

Overlapping pathologic mechanisms may also occur in the development of PsA. Key mediators in the disease process include infiltration of T_H cells, particularly T_H17, and overproduction pro-inflammatory cytokines; this inflammatory environment

leads to excessive bone remodelling. IL-23 and IL-22 stimulate bone formation), TNF enhanced bone resorption, and IL-17A stimulates both processes.(63)

[H3] Secreted factors

In psoriasis pathogenesis, a primary initiation phase that triggers pathologic inflammation is followed by a chronic inflammatory phase perpetuated by feedback loops and amplification signals. Key disease mediators include anti-microbial peptides (AMPs) —cationic proteins and members of the innate immune system that assist in protection against bacteria, viruses, fungi and parasites — such as cathelicidin (CAMP), pro-inflammatory cytokines and chemokines (for example TNF-α, IL-17, IL-22, and CCL20 (among numerous others)) and angiogenic factors. CAMP production is absent in healthy keratinocytes and upregulated during processes that cause epithelial damage.(64) Complexes formed by CAMP and self-nucleic acids can evade recognition and subsequent intracellular degradation by dendritic cells, Through this process, a wound healing phenotype can be expressed. On the other hand, when CAMP binds to viral DNA IFN -driven anti-viral response is triggered. CAMP expression is upregulated during processes that cause epithelial damage(64); levels are undetectable in healthy keratinocytes but uncontrolled in psoriatic lesions. This, in the setting of keratinocyte damage and self-nucleotides release, triggers pathologic IFN signalling cascades and activation of dendritic cells, resulting in uncontrolled inflammation.(64) Expression of AMPs leads to the clinical manifestations of psoriasis: for example, acanthosis has been linked to cytokines such as IL-22(65) and Auspitz sign (punctate bleeding upon the removal of a scale) to angiogenic factors, among others.(66) Mutations involved in pustular variants of psoriasis might lead to increased activity of IL-8, a neutrophil chemotactic factor, and aggregations of neutrophils.(67) Mutations associated with pustular variants of psoriasis might also enhance reactivity of IL-36 and activation of NF-κB.(67) These underlying signalling processes are typically self-sustaining, and maintain the chronic course of psoriasis until one or multiple critical disease mediators, such as TNF or IL-17, are inhibited, leading to a temporary improvement of clinical manifestations. Even among patients clear of active psoriatic plaques, clinical evaluation of normal-looking skin can unveil abnormal signalling involving key inflammatory pathways.(68)

[H3] Cellular mediators

T cell signalling is essential in understanding the pathogenesis, treatment and comorbidities associated with psoriasis. Multiple T cell lineages have been described, including T_H1, T_H2, T_H9, T_H17, T_H22, and regulatory T_{reg} cells.(69) Each T cell lineage produces its own signature cytokines and processes signals through a set of transcription factors. At the most rudimentary level, T_H1 is associated with IFNγ and IL-12, T_H17 with IL-23 and IL-17 and T_H22 with IL-22, whereas TNF is not specific to a single T_H cell profile. Although this traditional paradigm of separate T cell lineages may predominate, there are exists heterogeneity with secretion of factors from multiple different T cell lines and plasticity with switching between T cell lineages under certain conditions.(70)

The role of keratinocytes in psoriasis also extends beyond its association with the classic psoriasis histologic phenotype of epidermal hyperplasia and acanthosis (increase in the thickness of the stratum spinosum of the epidermis).(65) Although the primary physiological function of keratinocytes is the establishment and maintenance of the skin barrier, they also produce inflammatory cytokines such as TNF, express IL-17 receptors and participate in both the initiation and amplification of psoriasis (Figure 4).(71)

Finally, among other innate immune cells, dendritic cells are essential not only as professional antigen presenters and cytokine producers, but also as a bridge between innate and adaptive immune systems.(72) Plasmacytoid dendritic cells are components of the innate immune system circulating in the blood; they can detect viral and other antigens and respond by releasing type 1 interferons during the initiation phase of inflammation in psoriasis, whereas myeloid dendritic cells promote the expansion of specific T_H cell populations through production of cytokines such as IL-12 and IL-23.

[H1] Diagnosis, screening and prevention

[H2] Cutaneous involvement in psoriasis

The majority of patients with psoriasis initially present with cutaneous involvement, with a minority, approximately 15%, experiencing joint symptoms such as swelling or pain prior to skin involvement.(13) Several types of skin manifestations associated with psoriasis have been described (Figure 1). Although the diagnosis of psoriasis vulgaris can often be made based exclusively on clinical signs, further investigation including histological examination of a skin biopsy might be helpful in diagnosis (Figure 5). Cutaneous disease severity can be rated by measures such as the physician global assessment (PGA) (a 0–5 composite score of erythema (redness of the skin), induration (thickening or elevation of the skin), and scale, body surface area (BSA) (a percentage of body surface area affected by psoriasis with one palm of the patient equivalent to 1%) and the psoriasis area and severity index (PASI) (a 0–72 composite score of erythema, induration and scale, with a multiplier based on the total affected body surface area); in both scoring systems higher scores correspond to more severe disease.(73) Although absolute PASI score is often used to define severity, percentage response rate is often used to define response to treatment. For example, PASI 75 indicates the percentage of patients who have achieved a >75% reduction in PASI scores from baseline.

Given that psoriasis vulgaris is the most prevalent subtype, we will use this as an example to explain characteristic features of skin involvement in psoriasis. Psoriasis vulgaris typically manifests as well-circumscribed, symmetric, pink-to-erythematous, scaly plaques on the scalp, trunk and extremities. Extensor surfaces (for example, the elbows, knees, and sacral area, although any area might be affected. Psoriatic plaques might exhibit the Auspitz sign (pinpoint bleeding with removal of scale) and Koebner phenomenon (appearance of psoriasis at sites of

trauma; Figure 6), although these signs are not specific for psoriasis. Other features can include changes in the nails observed in 50% of patients**,** such as pitting (depressions in the nail plate due to involvement in the proximal nail matrix), leukonychia (whitening of the nail plate due to mid-matrix involvement), onycholysis (detachment of the nail plate from the nail bed), subungual hyperkeratosis (excessive proliferation of keratinocytes in the nail bed), and oil drop sign (due to onycholysis involving a more proximal part of the nail)(74) (Figure 6)(75)

The differential diagnosis of cutaneous involvement in psoriasis includes various disorders (Box 2). Although clinical history and examination might be sufficient to distinguish these disorders from psoriasis, other tests such skin biopsy to assess histologic findings, anti-nuclear antibodies for autoimmune conditions, flow cytometry or T cell clonality studies for abnormal T cell populations, and potassium hydroxide test to evaluate for fungal infection might be required to rule out other conditions and guide therapeutic decision-making.(76)

[H2] Psoriatic arthritis

PsA is observed in a substantial proportion of patients with psoriasis(77)(Figure 6C)(75) and usually presents after diagnosis of cutaneous psoriasis. In patients with psoriasis, risk factors for developing PsA include severe skin involvement, nail lesions, the presence of certain *HLA* alleles and elevated acute phase proteins and matrix metalloproteinase 3 in the serum.(78) (79) (80) PsA presents with inflammatory joint pain and erythema over the affected joint and is associated with prolonged morning stiffness (>45 minutes), which improves with activity and worsens with rest. Although any joint might be affected, the most common sites (in order of decreasing frequency) are the feet, hands, knees, ankles, shoulders and elbows. Early disease is typically characterized by asymmetric involvement of a few joints, with subsequent polyarticular involvement of >5 joints. In addition, axial inflammation might limit mobility of spine. Almost 50% of patients develop both peripheral and axial disease, whereas only 2–4% experience isolated axial disease. Other characteristic features of PsA include dactylitis (inflammation of the whole digit) and enthesitis (inflammation at the insertion point of tendons and ligaments into bone).(13) Group for Research and Assessment of Psoriasis and Psoriatic Arthritis recommends thorough evaluation of multiple PsA domains, including peripheral arthritis, axial arthritis, enthesitis, dactylitis and skin and nail disease, which might affect disease management.(81)

The diagnosis of PsA has been facilitated by the Classification Criteria for PsA (CASPAR) developed through an international study with a large sample size (Box 3).(82) These criteria are 91% sensitive and 99% specific for disease identification, compared with the gold standard (physician's expert opinion based on clinical and when necessary radiographic examination). Although such criteria function very well in both early and late disease, many cases require rheumatologic expertise for definitive diagnosis. A delay in consultation for PsA by only 6 months can result in

adverse outcomes, including physical disability and peripheral joint erosions, an observation that underscores the importance of early diagnosis and treatment of PsA.(83)

Since psoriasis is a common condition, it might co-exist with forms of arthritis other than PsA (that is, rheumatoid arthritis, osteoarthritis, and gout, which can be usually differentiated by the distribution of the affected joints (Box 4, and Box 5).

[H2] Cardiovascular comorbidities

Individuals with severe psoriasis should be routinely counselled and screened for cardiovascular risk factors. Traditional risk factors include hypertension, hyperlipidemia, smoking, diabetes and family history of premature myocardial infarction (< 55 years of age). The Framingham Risk Score(84), which is routinely used to estimate the 10-year risk for cardiovascular events, is increased by 6% when psoriasis is present(85). The 2013 American College of Cardiology and American Heart Association guidelines for cardiovascular risk screening do not consider psoriasis as a risk**(86)**; however, the European Society of Cardiology guidelines note that the increased risk of CV disease observed in patients with psoriasis.(87) Furthermore, the U.S.-based Adult Treatment Panel of the National Cholesterol Education Program(88) state that inflammatory diseases might be considered emerging risk factors, and warrant earlier and more-frequent screening. Thus, age appropriate normal screening algorithm recommendations for cardiovascular risk factors should be followed after a diagnosis of psoriasis, including monitoring resting blood pressure, measurement of the body mass index to assess for obesity and cholesterol and glucose serum concentration. After diagnosis such tests should be done every five years between 18–40 years of age, and then annually**.** Patients with psoriasis with body surface area exceeding 10% should be educated of their heightened risk and might require more-regular cardiovascular risk screening.

No guidelines endorse screening for subclinical coronary artery disease. Nevertheless, emerging data suggest that patients with psoriasis who have ≥2 cardiovascular risk factors might benefit from non-invasive imaging exams to assess coronary atherosclerosis burden, such as CT assessment of coronary calcification or carotid intimal medial thickness measurement with ultrasonography. If atherosclerosis is suspected, dyslipidemia therapy, including lifestyle changes and lipid-lowering agents, might be recommended. Finally, despite accumulating evidence that aggressive treatment with anti-TNF biologic agents of psoriasis leads to improved surrogate markers for cardiovascular disease such as intima medial thickness and vascular inflammation (89) (90) and reduced risk of myocardial infarction (14, 91); Randomized clinical trials to confirm these associations are still ongoing.(92) (93)

[H1] Management

The treatment approach for psoriasis depends on multiple factors. The body areas involved determine the formulation and dose of the topical treatments. Selection of

an appropriate therapy is also substantially influenced by the presence of comorbidities. In patients with PsA, systemic treatments with, methotrexate or biological agents that target both the skin and joints are the most appropriate therapies. Concomitant conditions such as HIV, hepatitis B or hepatitis C infection; alcoholism; cardiovascular disease or a history of malignancy also influence the choice of therapies. Age is another factor to be considered, as some treatments (for example, methotrexate) are excreted less efficiently in elderly patients than in younger patients, and certain treatments (for example, acitretin) are not safe for use in children or women of childbearing age who have a child wish because of their teratogenic effects. Recent management guidelines with useful treatment algorithms exist in the United States(94) and Europe.(95)

[H2] Topical therapy

For patients with mild disease (<10% body surface area) and without PsA, topical therapy is usually adequate. Historically, dithranol (also known as anthralin),which induce keratinocyte apoptosis, and tars, which reduce IL-15 production and nitric oxide synthase activity, were the only treatments available.(96, 97)

Although these treatments are still used, corticosteroids are the mainstay of topical psoriasis therapy nowadays. Many different formulations exist. Solutions, foams, sprays, shampoos and gels are prescribed for the scalp, whereas ointments or creams are typically used for the face, torso and extremities. Even corticosteroid-impregnated patches. Steroid-sensitive sites, such as the face and intertriginous areas, typically require lower-potency topical corticosteroids or steroid-sparing agents, (medications given in addition to or instead of steroid therapy to decrease the amount of steroid required) — such as topical vitamin D or its analogues or topical calcineurin inhibitors — to minimize adverse effects. More-potent corticosteroids can be used for areas of thicker skin, such as the palms, soles, elbows and knees. Adverse effects associated with topical corticosteroid use includes cutaneous atrophy and and dyspigmentation.

Several topical vitamin D analogues (for example, calcitriol, calcipotriene, tacalcitol and maxacalcitol) are approved for psoriasis used as monotherapy or combination with corticosteroids and act through immune modulation and normalization of keratinocyte maturation. Although these agents are less effective than corticosteroids, their adverse effect profile is favorable.(98) Topical retinoids, which normalize keratinocyte differentiation and supress the immune response**,** are effective but irritating, and therefore are most often used in combination with topical corticosteroids.(99) Topical calcineurin inhibitors, although not approved for the treatment of psoriasis, are also widely used in managing psoriasis in steroid-sensitive areas, owing to their suppression of T cell activation and proliferation.(100)

[H2] Phototherapy

For patients with moderate-to-severe disease, typically characterized by BSA >10%, and without PsA, phototherapy can be an effective option when topical application

to a large area is impractical. Phototherapy acts through multiple mechanisms: inducing apoptosis of inflammatory cells (such as antigen presenting cells), increasing production of the anti-inflammatory cytokine IL-10 and stimulating T_H1 switching, T_H17 suppression and T_H2 and T_{reg} activation. (101) Broadband ultraviolet B (UVB) radiation has been used since the 1920.(102) It has not been associated with an increase in skin cancers(103), likely because the spectrum of light used does not include the most carcinogenic short wavelengths found in sunlight, and phototherapy dose is gradually increased to limit burns. In addition, the most skin cancer-prone areas such as the face are usually protected during phototherapy. Narrowband UVB, which includes only the most effective spectrum of light wavelengths for the treatment of psoriasis, has gained popularity and largely replaced broadband UVB. Both broadband and narrowband UVB are administered 2-3 times per week(103). Proximity to a phototherapy center used to be a limiting factor, but home phototherapy units have become a popular alternative to in-office treatments and have demonstrated comparable efficacy.(104) Considerable insurance and co-pay costs, photosensitivity, or use of photosensitizing medications, are reasons why patients might be reluctant to use phototherapy.

Psoralen combined with UVA (PUVA) treatment is a regimen in which 8-methoxsalen is administered orally followed by exposure to UVA light 75–120 minutes later. Although still in use, particularly in patients with skin types with lower risk of developing skin cancers, this treatment is less frequently prescribed because of its photocarcinogenic effects and association with cutaneous squamous cell carcinoma and malignant melanoma.(105),(106)

[H2] Systemic therapy

For patients with moderate-to-severe psoriasis (>10% BSA), both phototherapy and systemic therapy (oral or injectable therapies) may be prescribed, but patients often prefer systemic therapy over phototherapy. Systemic therapy might be appropriate even for patients with <10% BSA, especially when the face, scalp, palms or soles are affected, which can be debilitating or when PsA is also present.(107)

[H3] Methotrexate

Administered orally or intramuscularly, methotrexate is the oldest systemic therapy for psoriasis and is widely used owing to its low cost. As an anti-inflammatory agent, methotrexate inhibits the enzyme 5-aminoimidazole-4-carboxamide ribonucleotide transformylase, leading to downstream increases in adenosine which leads to reduced tumor necrosis factor, nuclear factor NF-kappa-B p105 subunit, and transcription factor p65 expression.(108, 109) Key inflammatory cytokines and chemokines, including IL-17, IL-23, CCL20 and IL-22, are down-regulated by methotrexate. Low-dose methotrexate treatment might also be associated with reduced risk of cardiovascular disease, and has been shown to lower the expression of atherogenic genes in lesional psoriatic skin.(110)

Methotrexate is teratogenic and therefore contraindicated during pregnancy. The most common life-threatening adverse effect associated with methotrexate is bone

marrow toxicity; pancytopenia or death was reported in 1.4% of patients with rheumatoid arthritis receiving low-dose methotrexate and identified risk factors included elevated blood urea nitrogen and creatinine, lowered serum albumin, infection, drug-drug interactions and advanced age.(111) Because methotrexate interacts with numerous medications, a thorough medication history is essential, and patients must be warned to seek advice from their doctor before starting any other new medications while on methotrexate. For example, the combination of methotrexate with antibiotics such as trimethoprim-sulfamethoxazole might substantially increases drug toxicity leading to pancytopenia and potentially death.(112) Another serious side effect of methotrexate is the development of cirrhosis. In one study, hepatic fibrosis was observed in patients with psoriasis who were treated with methotrexate; 14 out of 15 of those were obese, 7 out of 7 had diabetes, and 9 out of 9 had excessive alcohol intake (exceeding 30 grams).(113) Risk factors for methotrexate-induced hepatic toxicity include the persistently abnormal liver function tests, a history of chronic hepatitis B or hepatitis C, hyperlipidemia, diabetes, and lack of folate supplementation.(114) Oral folic acid supplementation can prevent some methotrexate side effects, such as nausea and macrocytic anemia.

Routine monitoring during methotrexate therapy includes complete blood count as well as liver and renal function tests, both at baseline (before the start of the treatment) and at regular follow-up intervals. Monitoring for hepatotoxicity is controversial; some guidelines recommend liver biopsies or enzymatic testing in at-risk patients.(114) (115)

[H3] Acitretin.

Acitretin is an oral retinoid that reduces the activity of T_H1 and T_H17 cells and normalizes keratinocyte differentiation; it is particularly effective in palmoplantar psoriasis.(116) It is modestly effective as monotherapy, but is commonly used in combination with phototherapy; this combination results in greater and rapid improvement in psoriasis compared with phototherapy or acitretin alone.(117, 118) Like methotrexate, acitretin is teratogenic and is typically avoided in women of childbearing age, as its teratogenic effect prolongs over the years because the drug is stored in the adipose tissue. Periodic monitoring of blood parameters is done, owing to the risk of hyperlipidemia, especially hypertriglyceridemia, and liver toxicity. Mucocutaneous side effects, including hair loss, cheilitis (inflammation of the lips), dry and sticky skin, pyogenic granulomas and thinning of the nail plates, are common and often dose-limiting.(119)

[H3] Cyclosporine

Cyclosporine is one of the most effective therapies for psoriasis by inhibiting T cell activity. After forming a complex with cyclophillin, cyclosporine inhibits calcineurin, a phosphatase that activates three nuclear factor of activated T cells isoforms (NFAT1, NFAT2, and NFAT4). NFAT is a transcription factor that promotes the expression of IL-2, a key pro-inflammatory cytokine.(120) The use of cyclosporine is limited by its adverse effects, particularly nephrotoxicity, and numerous drug-drug

interactions. All patients show evidence of nephrosclerosis on kidney biopsies within two years of starting cyclosporine treatment.(121) Thus, most guidelines limit the use of cyclosporine to one to two years.(107) Other adverse effects include hypertension, hypomagnesemia, hyperkalemia, hyperlipidemia, hypertrichosis and increased risk of lymphoma and squamous cell carcinoma with long-term use. Frequent monitoring, particularly of serum creatinine levels and blood pressure, is essential.

[H3] Apremilast

Apremilast is a phosphodiesterase-4 inhibitor that limits the degradation of cAMP, reduces nitric oxide synthase, TNF-α, and IL-23 and increases IL-10 levels.(122) It was approved as an oral treatment for psoriasis by the United States Food and Drug Administration in 2014 and by the European Medicines Agency in 2015. The main barrier to its use is insurance coverage, as apremilast is more costly than many of the other available oral agents, although it is still substantially less expensive than the biologics (see below). Adverse effects include nausea, weight loss and diarrhea, which usually occur within the first 15 days after the start of treatment, and in most instances, lasts up to 15 days, but in some patients can persist longer.(123) Apremilast efficacy is lower than that of many biologic therapies, with 33% of patients achieving PASI 75 by week 16 of therapy.(124) However, because it is administered orally and has not been associated with an increased risk of infections or malignancy, its use has been growing in the United States.

[H3] Fumarates

Oral fumarates are approved in Germany for the treatment of moderate-to-severe psoriasis and are used as an off-label treatment for psoriasis in other countries.(125) Believed to down regulate TNF-α and interleukin 12 and 23 production,(126), fumarates have demonstrated greater improvement in PASI scores than placebo although the comparative efficacy of fumarates and methotrexate remains unclear. Common adverse effects include gastrointestinal disturbances, flushing, eosinophilia and proteinuria; further characterization of their long-term safety profiles is needed.

[H3] Biologic therapies

A biologic medication should be considered as first-line therapy for moderate-to-severe disease with significant quality of life impacts, or if there is concomitant PsA; biologics should be considered in other cases of moderate-to severe-disease when a traditional systemic therapy fails to achieve disease control, or when a patient is unable to tolerate the traditional systemic due to side effects. Eight injectable biologic therapies are currently approved for moderate-to-severe psoriasis or PsA (**Table 1**), and several other agents, including some targeting IL-23, are in various stages of the developmental and approval process. Patient sex(127), BMI, C-reactive protein levels (as a marker for inflammation), prior use of biologic therapies and concomitant hepatitis B or hepatitis C might affect the response to and selection of biologic therapy. TNF-blockers have been particularly effective in patients with concomitant PsA.(128)

Several anti-TNF agents, that either bind TNF-α thereby inhibiting receptor binding or block TNF receptor activation, are available to manage psoriasis and PsA (Table 2). In addition, evidence from registry studies showing that anti-TNF agents are protective against cardiovascular disease, supports their use, particularly in individuals at high risk of cardiovascular events.(91) (129) Other biological agents might also provide cardiovascular protection, but there is no clear evidence yet. Anti-TNF agents have safety profiles different from those of traditional systemic agents and are considered safe during pregnancy.(130) Anti-TNF agents have been associated with an increase in infections and certain malignancies, particularly cutaneous squamous cell carcinoma(131), whereas these correlations have not been observed with ustekinumab or any of the IL-17 blockers.(132) Paradoxical worsening of psoriasis has been reported as an adverse effect of anti-TNF agents and often resolves with treatment discontinuation.(133) Patients treated with biologics agents have an increased risk of developing tuberculosis, and annual tuberculosis screening has therefore been recommended. (134)

Ustekinumab (IL-12 and IL-23 specific antibody), secukinumab (anti IL-17A antibody) and ixekizumab (anti IL-17A antibody) have been approved for the treatment of PsA. (135), (136), (137) Early data on brodalumab, have been favorable; (138) however, before potential approval, further evaluation of the possible association between suicidal ideation and brodalumab is required and ongoing. IL-17 blockers have been associated with the development of candida infections, which are easy to treat, and suicidal ideation for brodalumab .(139), (140) (141) Ustekinumab and IL-17 blockers can be used safely in patients with heart failure and personal or family history of demyelinating diseases, unlike TNF blockers, which could cause the development of worsening of advanced congestive heart failure and multiple sclerosis **.(142)**

Head-to-head comparisons of biologics are limited in number. Ustekinumab was shown to be more effective than entanercept(143) but less effective than secukinumab(144) for cutaneous disease; secukinumab was more effective than adalimumab for PsA.(145) The development of anti-drug antibodies and the associated reduced efficacy of biologics remain important concerns.(146) The potentially protective role of biologics-methotrexate combination therapies in limiting the emergence of anti-drug antibodies in psoriasis needs further evaluation. Finally, biosimilars are now approved in Europe, Canada, the United States, and Korea and etanercept biosimilar is approved in Europe. Infliximab and etanercept biosimilars seem to demonstrate similar efficacy to the original agent and will likely reduce the cost of biologics and improve patient access to these medications. (147) (148)

[H1] Quality of life

Psoriasis often has profound effects on patient quality of life (QoL).(149) Individuals with psoriasis have higher rates of depression, anxiety, suicidal ideation, and

experience feelings of shame, anger and worry more frequently and/or severely than the general population.(20). The degree to which psoriasis affects QoL depends on both the individual patient's outlook and personality and the severity of the symptoms, which account for 80% of the disease burden. In addition, psoriasis severity and age of onset are inversely correlated with QoL and directly associated with greater risk of depression and social stigmatization.(150) Furthermore, psoriasis influences pivotal life decisions, such as choice of partner, career and residence. (151) The lives of the patients' family members or partners might also be widely disrupted, which should be taken into account when evaluating overall disease burden.(152)

[H2] Measurement

Quantifying the effect of psoriasis on QoL is essential, as it informs therapeutic decisions (including decisions on therapy initiations and treatment goals), highlights the aspects of the disease that are most important to the patient and helps assess and communicate patient satisfaction. Psoriasis registries also routinely record QoL data.(153) Among the several tools measuring QoL in patients with psoriasis (**Box 6**), the Dermatology Life Quality Index is the most widely used. (154) (155) EuroQoL 5 Dimension Health Questionnaire, a general health measure, was used to compare the burden of psoriasis with that of other conditions and to measure the cost effectiveness of novel therapies. The study has demonstrated that the negative effect of psoriasis is equal to that of other severe systemic chronic diseases.(156)

[H2] Effect of treatment on QOL

Treatment with biologic agents can substantially improve the disease course and QoL sustained over years, although high baseline Dermatology Life Quality Index scores might portend treatment discontinuation.(157) Cyclosporine and methotrexate improve QoL to a lesser extent than biologic agents do, and educational interventions have demonstrated limited effect on QoL.(158, 159) Evaluating the effect of psoriasis on patient QoL is essential when discussing therapeutic options and allocating healthcare funding, as QoL impairment is associated with poor treatment adherence and clinical outcomes. Thus, by addressing patient QoL, we might enhance therapeutic success and ultimately improve patient care.

[H1] Outlook

Despite advances in the genetic and mechanistic understanding of psoriasis and developments in clinical care and treatment modalities, gaps in our knowledge and management of this complex, multifactorial disease remain.(160) A multidisciplinary approach involving patients, dermatologists, rheumatologists, cardiologists, geneticists, pharmacologists, immunologists, and researchers in all these fields is necessary to further elucidate the immunopathogenesis of psoriasis and continue to develop novel treatments to improve patient QoL (Table 3).

Our understanding of psoriatic comorbidities, such as cardiovascular disease, requires further investigation. It is not yet known whether controlling inflammation in early psoriasis decreases the risk of PsA development(161) (162) (163), or reducing immune activation with biological and oral agents such as methotrexate can mitigate cardiovascular morbidity and mortality.(164) Large-scale, innovative studies, designed in cooperation with regulatory agencies, are necessary to answer these clinically meaningful questions.(161)

[H2] Genetics

Despite providing remarkable insights into disease pathogenesis, genetic studies of psoriasis and other autoimmune disorders pose several challenges. In addition to the modest odds ratios associated with most susceptibility loci, approximately 90% of these genetic variations do not appear to encode changes in protein structure, but rather in gene regulation (transcription level, splicing and mRNA stability).(60) Moving forward, the translation of disease-associated genetic variation into biologic effects will require innovative use of available resources to decipher the complex relationship between the landscapes of chromatin structure and gene regulation and the underlying genetic variation.

Mapping of the psoriatic genome is currently underway in a study headed by the International Psoriasis Council and upon completion will enable susceptibility gene characterization beyond the ~50 known disease loci.(165) Similarly, new technologies (such as next generation sequencing), genomic mechanisms (such as copy number variation) and epigenetics are being applied to psoriasis and PsA to gain a deeper knowledge of their genetic bases.(166) A new taxonomy for psoriasis based on molecular targets might also be able to guide treatment decisions.(167) The responses to treatment of the different disease endotypes (disease subtype with a distinct functional mechanism) are being mapped to create pathobiological algorithms for a personalized approach to psoriasis that minimizes treatment toxicity and maximizes clinical response and cost efficacy.(168) (169)

[H2] Biomarkers

Currently no biomarkers are available to evaluate disease prognosis or treatment response for patients with psoriasis or PsA. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis and Outcome Measures in Rheumatology have prioritized the prospective identification and validation of a PsA biomarker through the Psoriatic Arthritis Biomarkers for Joint Damage (PsA BioDam) effort.(170) (171) Flow cytometry, proteomics, and molecular signalling techniques are being applied to identify potential biomarkers with adequate sensitivity and specificity.(172) The ability to predict the likelihood that patients with PsA will develop joint destruction and to identify which patients with psoriasis will develop PsA will allow early and aggressive interventions to slow or prevent debilitating disease outcomes.

[H2] Management

From a healthcare standpoint, discrepancies between treatment guidelines and clinical practice should be corrected, including the large number of patients with

moderate-to-severe cutaneous disease who receive either no treatment or only topical monotherapy(173) because of multiple factors including high treatment costs**.** The introduction of infliximab biosimilars in Europe and Canada has led to a price reduction of infliximab by up to 33%. In addition, the transition of biologic production from batch-based to a more-sophisticated continuous process with greater implementation of single-use technologies has the potential to reduce costs without sacrificing product quality.(174) The use of biosimilars and manufacturing innovation might reduce health care expenditures and undertreatment rates by ultimately passing these savings on to the community. Furthermore, the development of outcome measures for clinical practice, which address the needs of all stakeholders (patients, health care providers, payers, drug developers, and policy regulators) is crucial in improving the quality of care and encouraging further drug development for psoriasis and PsA.(175)

[H2] New treatment targets

A growing understanding of psoriasis pathophysiology has led to the development of several novel topical, systemic and biologic agents, now in various stages of approval (Table 2).(176) (177) As chronic treatment with topical agents is the most common form of treatment in patients with mild-to-moderate disease, further exploration of new targets for topical formulations and innovative delivery systems with favorable side effect profiles that facilitate treatment outcomes is warranted.(178) Although new biologic agents provide exciting therapeutic options for individuals with moderate-to-severe disease, key limitations of these drugs include primary and secondary treatment failures and challenging risk-benefit analysis.

Possible solutions are targeting of differentially expressed genes and more specific disease mechanisms termed 'psoriasis response elements' using sophisticated methods like decoy oligonucleotide therapy (selective inhibition of the expression of specific genes).(179) (180) (62) Gene expression profiling of lesional skin has enabled the definition of differentially expressed genes characteristic of psoriasis and subsequent identification of the upstream psoriasis response elements, genomic sequences thought to have a regulatory role in disease development. Isolation of these sequences might lead to the development of novel decoy oligonucleotides (ODNs) that can recognize and bind transcription factors central to psoriasis.(62) Such efforts have demonstrated the ability of ODNs to inhibit the onset and reverse established psoriatic lesions in psoriatic mouse models.(181)

Current and emerging treatments focus primarily on targeting key mediators involved in the chronic phase of psoriasis. Although psoriasis has been generally considered a primarily T_H1- IFN-γ driven disorder, this pathway might be more essential in the initiation phase of the disease.(182) IFN-γ inhibition has not shown substantial clinical benefit.(183) Thus, the T_H1 axis might be more critical in the pathogenic mechanisms of psoriasis as a bridge between the innate and adaptive immune responses. The T_H17 axis, with its signature cytokines IL-17 and IL-23, has emerged as a key driver of the chronic disease process and has become a focus of

drug development, as agents targeting this pathway have achieved improved clinical outcomes. Table 2 lists some of the biological agents currently being assessed. Selective IL-23 inhibition (tildrakizumab, guselkumab and risankizumab) (184) and combined IL-12 and IL-23 inhibition (ustekinumab, Table 1)(185) produces substantial beneficial responses of skin and joints in psoriasis. The T_H22–IL-22 axis is also an important mediator of the psoriatic phenotype, and therefore could be a potential therapeutic target. However, phase I investigation of an IL-22 inhibitor (fezakinumab) was terminated early.(186) Although current drug development specifically targeting the innate immune system is less advanced, mediators such as CAMP are thought to be essential in the pathogenesis of psoriasis.(64)(Figure 4).

As the molecular and genetic pathological mechanisms of psoriasis continue to be unravelled, additional therapeutic targets will be developed, perhaps on an individualized basis.

Box 1 | Psoriasis associated comorbidities

- Psoriatic arthritis
- Autoimmune disease
- Cardiovascular disease
- Obesity
- Metabolic syndrome
- Chronic obstructive pulmonary disease
- Sleep apneaLiver disease
- Psychiatric illness
  Addictive behaviour: smoking and alcohol abuse

Box 2 | Differential diagnosis of psoriasis vulgaris.

- Inflammatory disorders: atopic dermatitis, lichen planus, nummular eczema, pityriasis rubra pilaris, pityriasis lichenoides chronica, lupus erythematosus, sarcoidosis, pityriasis rosea and seborrheic dermatitis
- Reactive processes: allergic contact dermatitis, lichen simplex chronicus, drug hypersensitivity reaction and erythema annulare centrifugum
- Infectious disorders: tinea, syphilis and crusted scabies
- Neoplastic processes: mycosis fungoides (a cutaneous T cell lymphoma)**,** and extramammary Paget disease

Box 3 | CASPAR criteria for the diagnosis of PsA.

- Evidence of inflammatory articular disease, namely arthritis, spondylitis or enthesitis and at least 3 points from the following categories:
    - Current psoriasis (2 points), personal history or family history (first or second degree relative) of psoriasis (1 point)
    - Current or history of dactylitis (1 point)
    - Radiographic evidence of juxtaarticular new-bone formation (1 point)
    - Rheumatoid factor negative (1 point)
    - Current nail dystrophy, including pitting, onycholysis, and hyperkeratosis (1 point)

Box 4| Differential diagnosis of psoriatic arthritis

- Rheumatoid arthritis typically affects the proximal small joints of the hands and feet symmetrically, whereas psoriatic arthritis (PsA) more commonly affects the distal joints in an asymmetric distribution.
- Osteoarthritis affects the distal interphalangeal joints, but its clinical presentation is characterized by bony Heberden nodes, which are distinct from the soft tissue joint swelling in PsA.
- Gout can cause a diagnostic dilemma as both gout and PsA can affect the toes and the swollen digits in gout can mimick dactylitis. In these cases, joint aspiration and microscopic detection of crystals are helpful diagnostic tools.(13)

Box 5| Early screening of psoriatic arthritis

To facilitate early recognition of psoriatic arthritis (PsA), new screening instruments are being explored for non-experts, in particular patient questionnaires using lay definitions of inflammatory musculoskeletal disease (187).(188) Several instruments, including the Psoriasis Epidemiology Screening Tool, Psoriatic Arthritis Screening Evaluation and Psoriatic arthritis screening questionnaire, are validated for use among patients with psoriasis. However, sensitivity and specificity of these tools vary between different healthcare centers. An updated version of Toronto Psoriatic Arthritis Screen, Toronto Psoriatic Arthritis Screen 2, has been developed and validated; it was found to be highly sensitive and specific and might even serve to screen for PsA both in patients with psoriasis and in the general population.(189)

Box 6 | Questionnaires used to measure the effects of psoriasis on patient quality of life

[H1] Psoriasis-specific questionnaires(190)

- Psoriasis Disability Index
- Impact of Psoriasis Questionnaire (IPSO)
- Psoriasis Index of Quality of Life (PsoriQol)
- PsoDisk
- Psoriasis Life Stress Inventory
- Simplified Psoriasis Index (SPI)
- Psoriasis itch visual analogue scale (191)
- Psoriasis symptom inventory.(192)

[H1] Dermatology-specific questionnaries(190)

- Dermatology Life Quality Index (DLQI)
- Skindex (versions 16, 17, 29)

[H1] General health measures(190, 193)

- Short Form 36 (SF-36)
- General Health Questionnaire (GHQ)
- World Health Organization Quality of Life (WHOQOL)
- EuroQoL 5 Dimensions (EQ-5D)
- Pictorial Representation of Illness and Self Measure (PRISM)

[H1] Children-specific questionnaires

- Children's Dermatology Life Quality Index (CDLQI)(194)

[H1] Family-oriented questionnaires (195, 196)

- Psoriasis Family Impact (PFI)
- Family Dermatology Life Quality Index (FDLQI)
- Family Reported Outcome Measure (FROM-16)

Figure 1 | Skin manifestations of psoriasis.
A. Psoriasis vulgaris is the most common type and is characterized by well-defined areas of erythematous and indurated plaques with overlying silvery scale; knees, elbows, scalp and trunk are the most commonly affected skin areas. B. Guttate psoriasis, the second-most common type of psoriasis, is characterized by small, tear-shaped papules, often starts in childhood or young adulthood, and can be triggered by an infection such as streptococcal pharyngitis. C. Inverse psoriasis is characterized by erythematous plaques in the body folds, and due to increased moisture in these area often lack scale. Many individuals with inverse psoriasis also experience other subtypes of psoriasis simultaneously. D. Pustular psoriasis is characterized by sterile pustules on an erythematous base. It is primarily seen in adults, usually presents on the hands and feet, and tends to evolve through a cycle, with erythema followed by the formation of pustules and scaling. Appearance in pregnancy is termed impetigo herpetiformis and may be related to hypocalcemia E. Erythrodermic psoriasis is a severe form of psoriasis that can be life-threatening. It leads to widespread erythema over at least 90% of the body, which can cause severe itching and pain, and can be associated with desquamation of the skin in sheets. It affects about 3% of individuals with psoriasis, and generally occurs in patients with unstable psoriasis vulgaris.

Figure 2 |Global prevalence of psoriasis. A systematic review of international, population-based studies demonstrated a global prevalence of psoriasis in adults ranging from 2.2% in the United States to 8.5% in Norway.(5) A study that analyzed 22 population-based surveys, case-control studies and reviews from around the world found a weak positive correlation between higher latitude and greater psoriasis prevalence possibly due to level of UV exposure.(197) The lowest prevalence rates were observed in Latin American Indians(198), native Americans(199), and in African and Asian countries whereas the highest rates were reported in Europe. Even within Asia, prevalence ranged from as low as 0.3% in Hong Kong, Sendai, Japan and five major cities in mainland China(200) to as high as 2.4% in the Philippines.(201)
Map based on data from Refs(5),(202),(203),(204)

Figure 3| Evidence of systemic inflammation in patients with psoriasis

(A) Frontal reconstructions of 18-fludeoxyglucose (FDG) positron emission tomography (PET) – CT images of age, gender and body max index matched individuals with (right) or without (left) psoriasis. High levels of tracer (FDG) uptake (darker areas) correspond to the presence of vascular (1), liver (2) skin (3) and joint (4) inflammation.

(B) Transverse 18-FDG PET/CT images at the level of the aortic arch depict a higher tracer uptake in the aorta of a patient with psoriasis (left) compared with a healthy control (right), consistent with vascular inflammation.

Image courtesy of Mehta Lab, NHLBI, NIH

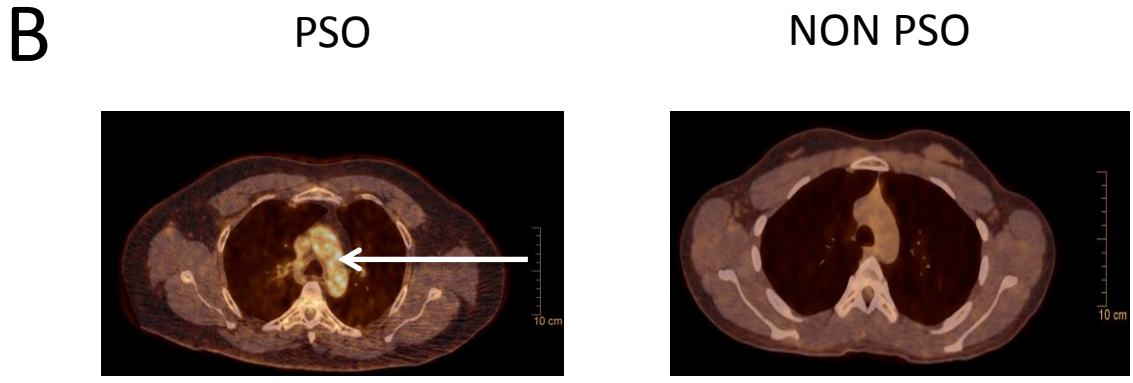

Figure 4 Mechanisms of psoriasis.
External insults such as trauma, infection or medication can cause the release of self-nucleotides, especially in genetically predisposed individuals. Self-nucleotides can form complexes with anti-microbial peptide (AMP) released from keratinocytes, for example cathelicidin (CAMP), which can bind to receptors on antigen presenting cells, including toll-like receptor (TLR) -7 and -9 on the surface of plasmacytoid dendritic cells (pDCs). This binding triggers antigen presentation by pDCs, which prompt the activation and clonal expansion of antigen-specific $CD8^+$ T cells. This process can occur in the dermis (activation of memory resident T cells) and local lymph nodes (activation of naive T cells). Subsequently, activated $CD8^+$ T cells migrate into the epidermis where they encounter class I MHC receptors on the surface of keratinocytes (or perhaps melanocytes) and trigger the local release of soluble factors, including cytokines, chemokines, and innate immune mediators, which could further increase local inflammation and stimulate keratinocyte proliferation. pDCs release the inflammatory mediators interferon (IFN) $-\alpha$ and $-\beta$, which stimulate myeloid dendritic cells (mDCs) to secrete additional pro-inflammatory mediators such as IL-12, TNF and IL-23. These innate immunity mediators stimulate the activities of key T cell populations such as T_H1, T_H17 and T_H22, which release additional cytokines and chemokines. IL-17 acts on keratinocytes (which express IL-17R) stimulating them to produce TNF, CCL20 (chemotactic for T cells and DCs(205)). In combination with TNF and/or other pro-inflammatory cytokines, IL-17 stimulates the production of defensins and chemokines, promoting host defence and leading to the recruitment of additional inflammatory cells into the lesion. IL-22 contributes to the characteristic psoriasis histologic phenotype, including epidermal hyperplasia, acanthosis and parakeratosis (incomplete keratinization with retention of nuclei). Key transcription factors in psoriasis include cAMP, the JAK-STAT family, and NF-κB; their activation leads to further production of factors such as TNF and interleukin-17 and downstream amplification loops.
Expression of vascular endothelial growth factor receptors on endothelial cells induces vascular proliferation and expression of adhesion molecules within the endothelium to recruit additional inflammatory cells into the skin. Among other changes, these angiogenic factors lead to the characteristic tortuous (twitsting), papillary, dermal vessels of lesional psoriatic skin, which contribute to the development of Auspitz sign.
A chronic phase is then established, which typically continues until a therapeutic intervention targeting key pathological regulators (for example, TNF or IL-17) breaks the cycle. However, after the withdrawal of treatment, a susceptible patient can relapse to the chronic phase with actively inflamed skin.

Figure 5 Skin biopsy obtained from a patient with psoriasis vulgaris. Histological examination demonstrates acanthosis Munro microabscesses (an accumulation of neutrophils in the epidermis), alternating neutrophils**,** and parakeratosis in the stratum corneum, infiltration of mononuclear cells (for example, $CD3^+$ T cells and $CD11c^+$ dendritic cells) in the dermis and epidermis, tortuous dermal papillary

vessels, increased mitotic activity of basal keratinocytes and abnormal keratinocyte marker expression.(75)

Figure 6: Clinical markers of psoriasis. (A) Koebner phenomenon occurs when a new area of psoriasis develops in injured skin. Psoriatic plaques seen in a distribution of skin damage secondary to a sunburn. (B) Nail pitting, the most common nail finding in psoriasis, occurs as depressions in the nail plate due to proximal nail matrix involvement. C. Psoriatic arthritis is an inflammation of the joints, which become sore and stiff. Dactylitis can also occur (swelling of the whole digit resulting from joint, tendon and soft tissue inflammation).
(D) Enthesitis showing an erosion and "fluff" at the insertion of the Achilles tendon into the calcaneous as well as a plantar spur.

Table 1 | Biologic agents used in psoriasis.

Drug	Structure	Mechanism of action	Indication*	Effectiveness (PASI 75‡)	Standard dosing regimen	Reference	
Anti-TNF agents							
Etanercept	Fustion protein between Fc portion of human IgG1 fused and the extracellular domain of human p75 TNF receptor	TNF receptor antagonist	Psoriasis and PsA	49% at week 12	Subcutaneous injections twice per week for 12 weeks, then once per week	Refs. (206), (207)	
Adalimumab	Human monoclonal antibody	Anti TNF-α antibody	Psoriasis and PsA	53% at week 12	Subcutaneous injections; a loading dose first, then a regular dose regimen every 2 weeks	Refs. (208), (209)	
Infliximab	Chimeric monoclonal antibody consisting of human IgG1 with the mouse binding site for TNF-α	Anti TNF-α antibody	Psoriasis and PsA	88% at week 10	Intravenous infusion over 2 at weeks 0, 2 and, 6, then every 8 weeks	Refs(210), (211),(212), (213)	
Certolizumab	Pegylated humanized	Anti	PsA	75% at week 12	Subcutaneous injection; a loading	Refs (214), (215)	

	Fab' fragment	TNF-α antibody			dose first, then a regular dose every 2 weeks		
Golimumab	Human monoclonal antibody	Anti TNF-α antibody	Psoriatic arthritis	65% at week 52. Less effective against cutaneous psoriasis compared to the other biologic agents.	Subcutaneous injection once every 4 weeks	Ref (216)	
Others							
Ustekinumab	Humanized monoclonal antibody directed against the p40 component of IL-12 and IL-23	Anti IL-12 and anti IL-23 antibody	Psoriasis and PsA	67% and 76% at week 12, patients weighing <100 kg and ≥ 100 kg, respectively	Subcutaneous injection at weeks 0 and 4, then every 12 weeks; weight-based dosing (< or ≥100 kg)	Ref (185)	
Secukinumab	Human monoclonal antibody	Anti IL-17A antibody	Psoriasis and PsA	At week 12, PASI 75 was 82%, PASI 90 was 59% and PASI 100 was 29%	Subcutaneous injections once a week for 5 weeks, then every 4 weeks	Refs (217)	
Ixekizumab	Humanized monoclonal antibody	Anti IL-17A antibody	Psoriasis[§]; data for PsA are promising	At week 12, PASI 75 was 90%, PASI 90 was 71% and PASI 100 was 41%	Subcutaneous injections every 2 weeks for 12 weeks, then every 4 weeks	Ref (218)	
Brodalumab	Humanized monoclonal antibody	Anti IL-17A receptor antibody	Approval for psoriasis pending; data for psoriatic arthritis are promising	At week 12, PASI 75 was 86.3%, PASI 90 was 70.3% and PASI 90 was 44.4%	Subcutaneous injections at weeks 0, 1 and 2, then every 2 weeks	Ref (138)	
[‡]PASI 75 reflects the number of patients who have achieved >75% reduction in PASI scores in response to							

treatment. PsA, psoriatic arthritis; PASI, psoriasis area and severity index *In the United States, Canada and Europe §Approval pending in Canada	

Table 2

Current clinical trials on biologics for psoriasis

Therapeutic agent	Mechanism of action	Trialand status	ClinicalTrials.gov identifier
Tofacitinib	JAK 1 and JAK 3 inhibition	Randomized trial versus entanercept Completed	NCT01241591
Ruxolitinib (topical treatment)	JAK 1 and JAK 3 inhibition	Randomized vehicle controlled safety and efficacy trial Completed	NCT00820950
Pazopanib	VEGF antagonist	Randomized trial of efficacy Completed	NCT00358384
Ponesimod	S1P1 receptor inhibition	Randomized safety and efficacy trial Completed	NCT01208090
Guselkumab	Il-23 inhibitor	Randomized trial versus adalimumab Ongoing	NCT02207244
Tildrakizumab	IL-23 inhibitor	Randomized trial versus entanercept Ongoing	NCT01729754
Risankizumab	IL-23 inhibitor	Open label safety and efficacy trial Not yet recruiting	NCT02772601
IMO-8400	TLR7, TLR8 and TLR9 inhibitor	Randomized dose-ranging trial Completed	NCT01899729
Namilumab	GM-CSF receptor antagonist	Randomized safety and efficacy trial Completed	NCT02129777
Piclidenoson (CF101)	A3 adenosine receptor agonist	Randomized safety and efficacy trial Completed	NCT00428974

Data from Ref. (184)

JAK, Janus kinase, VEGF, vascular endothelial growth factor; S1P1, sphingosine 1-phosphate receptor 1; TLR, toll-like receptor; GM-CSF Granulocyte macrophage colony stimulating factor

Competing interests

J. E. G. declares no competing interests.

A. M. G. declares no competing interests.

J. T. E. is currently serving as a Scientific Advisor for Janssen, a division of Johnson and Johnson. Since 2013 he has also served as a consultant or scientific advisor for Janssen, Novartis and Lilly and as a consultant for Pfizer.

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