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, albeit polygenic, genetic basis. Whereas approximately half of the accountable genetic effect of psoriasis maps to the major histocompatibility complex, >70 other loci have been identified, many of which implicate nuclear factor-κB, interferon signalling and the IL-23–IL-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 systems, with important roles for dendritic cells and T cells, among other cells. Frequent comorbidities are rheumatological 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 that target specific disease mediators have become a mainstay in the treatment of moderate-to-severe disease, whereas advances in the treatment of mild-to-moderate disease have been limited.

Psoriasis is a chronic, immune-mediated disorder that mainly affects the skin and joints and has a complex genetic architecture, with an estimated global prevalence of 2–3%[1]. Psoriasis is predominantly a skin disease, which can manifest as various 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 generalized pustular psoriasis), palmoplantar psoriasis and erythrodermic psoriasis. Multiple phenotypes might occur in the same individual. Psoriasis vulgaris is the most common manifestation[2] (FIG. 1). Symptoms that are 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 an increased release of pro-inflammatory cytokines from immune-related cells and chronic activation of the innate and adaptive immune systems are mechanisms that cause long-term damage to multiple tissues and organs. Psoriasis has been associated with numerous comorbidities, including rheumatological (psoriatic arthritis (PsA)), cardiovascular and psychiatric complications (BOX 1), and has well-described negative effects on patient quality of life (QOL)[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 QOL.

Epidemiology
Prevalence and incidence
Psoriasis affects >125 million people worldwide (FIG. 2). Women and men are affected equally. Psoriasis can manifest at any age, but onset usually occurs between 18 and 39 years of age or between 50 and 69 years of age[5]. Age of onset might be affected by genetic and environmental factors. Psoriasis is less common in children than in 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 seems to be increasing over time. In a retrospective cohort of adults, the incidence increased from 50.8 cases per 100,000 population between 1970 and 1974 to 100.5 cases per 100,000 individuals between 1995 and 1999 (REF. 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].

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The National Psoriasis Foundation has defined mild psoriatic skin disease as having <3% body surface area (BSA) affected, moderate disease as 3–10% affected and severe disease as >10% affected[8]. Additional classifications of psoriasis severity include the Psoriasis Area Severity Index (PASI) and the Physician Global Assessment (PGA)[9], among others. Whereas both the PGA and BSA are used in clinical practice, the PASI is typically limited to the clinical trial setting.

PsA

Among psoriatic comorbidities, PsA is one of the most frequent, affecting 0.3–1% of the global population[10]. Depending on the study, 11%[11], 20.6%[12] or 30%[13] of patients with psoriasis are estimated to have concomitant PsA. Men and women are affected equally, and the peak age of onset is between 35 and 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[14]. There is no direct correlation between the severity of joint and skin manifestations.

Cardiovascular and psychiatric comorbidities

Psoriasis has been associated with an increased prevalence of clinical[15] atherosclerosis and systemic and vascular inflammation (FIG. 3).

Comorbid cardiovascular diseases remain the leading cause of death among patients with psoriasis[16]. 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 (BMI)[17,18]. Patients with severe psoriasis have an approximately sevenfold increased risk of myocardial infarction compared with matched controls for age, sex, BMI and cardiovascular risk factors[18]; the risk of cardiovascular mortality is increased by 57%[18]. In addition, a dose–response correlation between the severity of psoriasis and the odds of having a myocardial infarction has been demonstrated, and an age interaction has been shown, in which a 30-year-old patient with severe psoriasis has an approximate twofold increase in the risk of experiencing a first myocardial infarction[18].

However, the correlation 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[19] or ischaemic heart disease hospitalization[20]. 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[21].

Mechanisms/pathophysiology

Genetics

Psoriasis has a strong genetic component, which was initially assessed by epidemiological studies involving twins and families[22,23]. Twin studies have found a substantially higher (2–3.5-fold) concordance of psoriasis in monozygotic twins than in dizygotic twins[24], and estimates of heritability (the proportion of variance in overall disease liability accounted for by genetic factors) have ranged between 50% and 90% in populations of European descent[23,25]. Recurrence rates (disease prevalence among relatives compared with the general population) range between 4% and 19% in first-degree relatives of individuals with psoriasis[26–28]. Even greater genetic effects have been reported for PsA, with estimates of heritability between 80% and 100%[26,27] and the risk of developing PsA said to be 30–49-fold greater if a first-degree relative has PsA[26–29]. The role of genetic factors has been confirmed by linkage studies (which measure the transmission of alleles through generations) in families and genetic association studies (which compare allele frequencies between cases and controls)[30,31]. Although >70 genes associated with psoriasis have been identified, they only account for 30% of overall psoriatic heritability, which might be explained by the cumulative effects of many genetic variations, whose individual effects are small and currently undetectable, as well as the existence of gene–gene and/or gene–environment interactions.

The genetic landscape of psoriasis is dominated by variation in the psoriasis susceptibility 1 locus (HLA-C; previously known as PSORS1), which comprises genes in the major histocompatibility complex (MHC) that encode human leukocyte antigens (HLAs). The MHC contributes approximately 40% of the detectable heritability of psoriasis, with smaller contributions from a multitude of other genetic loci[32]. Linkage-based and family-based association strategies have enabled important advances in the genetic dissection of the associations between HLA genes and psoriasis[33,34], including the differential analysis of cutaneous psoriasis and PsA[35]. The strongest HLA-related associations in psoriasis have consistently mapped to HLA-C*06 in white[34] and Chinese[36] populations, particularly in patients with early-onset and more-severe disease who have a positive family history[37]. HLA-C*06 has a particularly strong
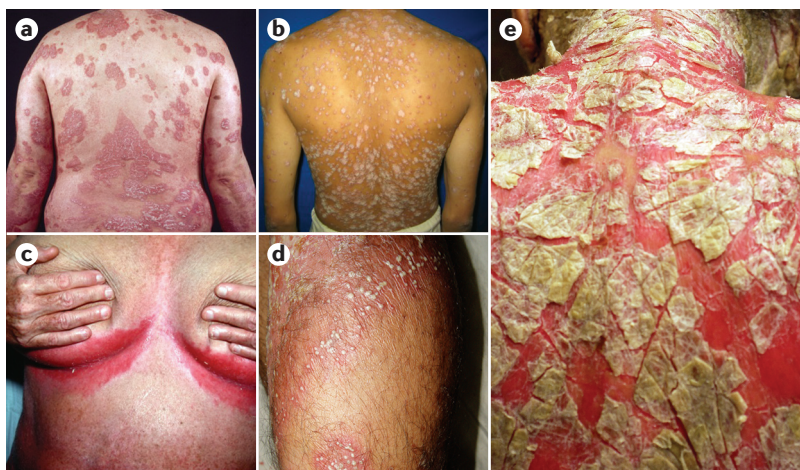
Figure 1 | **Skin manifestations of psoriasis. a** | Psoriasis vulgaris is the most common type of psoriasis and is characterized by well-defined areas of erythematous and indurated plaques with overlying silvery scale; the knees, elbows, scalp and trunk are the most commonly affected skin areas. **b** | 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 owing to increased moisture in these areas, patients often lack scales. 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 might be related to hypocalcaemia. **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. Images in part **a** and part **c** courtesy of J. J. Voorhees, University of Michigan, Ann Arbor, Michigan, USA. Images in part **b** and part **d** courtesy of T. Tejasvi, University of Michigan, Ann Arbor, Michigan, USA. Image in part **e** courtesy of J. E. Gudjonsson, University of Michigan, Ann Arbor, Michigan, USA.

association with streptococcal pharyngitis and guttate psoriasis[38]. However, regression analyses have identified at least seven independent genetic signatures for psoriasis in the MHC based on single-nucleotide polymorphism (SNP) genotyping, which have been mapped by imputation to *HLA-C*, *HLA-B*, *HLA-A* and *HLA-DRA*[35]. Notably, amino acid 45 of the *HLA-B*-encoded HLA class I histocompatibility antigen, which maps to the B pocket of the peptide-binding groove, discriminates cutaneous psoriasis from PsA across several different *HLA-B* alleles[35]. Besides the MHC, linkage-based strategies have identified 17 susceptibility loci[39–41], 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. Genetic linkage signals subsequently confirmed by association and/or sequencing (see below) include mutations in the psoriasis susceptibility 2 (*PSORS2*) region (17q24–q25) spanning the caspase recruitment domain-containing protein 14 (*CARD14*) gene[42], *PSORS4* in the epidermal differentiation complex[43], *PSORS7* on chromosome 1p spanning the IL-23 receptor (*IL23R*) locus[44] and *PSORS6* on chromosome 19p13 spanning the tyrosine kinase 2 (*TYK2*) locus[45].

As dense SNP 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[46]. By 2016, case–control association studies in populations of European and Chinese descent have identified 87 psoriasis susceptibility regions, including population-specific and shared loci[32,47–50]. This strategy has also been successful for PsA, revealing allelic variation between PsA and cutaneous psoriasis at known susceptibility regions[51,52]. New PsA loci have also been identified by SNP microarrays, including protein-tyrosine phosphatase, non-receptor type 22 (*PTPN22*), which is not associated with cutaneous psoriasis in the cohort studied[53].

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[54]. A prime example is the identification of *CARD14* (REFS 55,56). Targeted and whole-exome DNA sequencing also had key roles in the identification of mutations in the genes adaptor-related protein complex 1 σ3 subunit (*AP1S3*) (on chromosome 2q23)[57] and IL-36 receptor antagonist (*IL36RN*) (on chromosome 2q13)[58–60], which are linked to generalized pustular psoriasis, a highly inflammatory subtype of psoriasis that is characterized by systemic inflammation. However, not all patients with pustular psoriasis carry one of these mutations, particularly patients with concomitant psoriasis vulgaris[61].

Unlike the high-penetrance and high-effect size mutations emerging from the sequencing-based studies described above, biologically 'interesting' candidate genes that reside in psoriasis-associated loci cannot simply be assumed to have a causative role. Indeed, the identification of biological processes underlying these genetic associations is a major focus of current research in psoriasis and other complex genetic disorders[62]. Various methods have been developed to measure the overlap between observed genetic signals and corresponding functions and pathways. For example, functional enrichment analysis methods use statistical tests to identify over-represented subgroups of genes or proteins that might be associated with disease phenotypes[63].

Box 1 | **Psoriasis-associated comorbidities**

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

Figure 2 | **Global prevalence of psoriasis.** A systematic review of international, population-based studies demonstrated a global prevalence of psoriasis in adults ranging from 2.7% in the United States to 8.5% in Norway[5]. A study that analysed 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 owing to the level of ultraviolet exposure[200]. The lowest prevalence rates were observed in Latin-American Indians[201], Native Americans[202] 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[203] to as high as 2.4% in the Philippines[204]. Data from REFS 5,205–207.

One such study identified 87 significantly enriched functions or pathways, many of which are immune-related, such as lymphocyte differentiation and regulation, type I interferon (IFN) signalling and pattern recognition and nuclear factor-κB (NF-κB) signalling[32]. Another analysis focusing on transcription factor-binding sites also implicated numerous genes involved in immune regulation[64].

Immune response

Psoriasis is a disorder of both the innate and the 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 streptococcal infection) and medications (such as β-blockers, IFNα 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, which are the primary source of IL-17) and enhanced IL-17 response, which promotes the host's immune response and infiltration of immune cells (FIG. 4).

Overlapping pathological mechanisms might also occur in the development of PsA. Key mediators in the disease process include infiltration of T_H cells, particularly T_H17 cells, and overproduction of pro-inflammatory cytokines; this inflammatory environment leads to excessive bone remodelling. IL-22 and IL-23 stimulate bone formation, tumour necrosis factor (TNF) enhances bone resorption and IL-17A stimulates both processes[65].

Secreted factors. In psoriasis pathogenesis, a primary initiation phase that triggers pathological inflammation is followed by a chronic inflammatory phase that is perpetuated by feedback loops and amplification signals. Key disease mediators include antimicrobial peptides (AMPs) — cationic proteins and members of the innate immune system that assist in the protection against pathogens — such as cathelicidin antimicrobial peptide (CAMP), pro-inflammatory cytokines and chemokines (for example, TNF, IL-17, IL-22 and CC-chemokine ligand 20 (CCL20), among numerous others) and angiogenic factors. CAMP production is absent in healthy keratinocytes and upregulated during processes that cause epithelial damage[66]. Complexes that are formed by CAMP and self-nucleotides can evade recognition and subsequent intracellular degradation by dendritic cells. Through this process, a wound-healing phenotype can be expressed. Conversely, when CAMP binds to viral DNA, an IFN-driven antiviral response is triggered. In psoriatic lesions, CAMP expression is uncontrolled. This increased CAMP production, in the setting of keratinocyte damage and the release of self-nucleotides, triggers pathological IFN signalling cascades and the activation of dendritic cells, which result in uncontrolled inflammation[66]. The expression of AMPs leads to the clinical manifestations of psoriasis: for example, acanthosis (an increase in the thickness of the stratum spinosum of the epidermis) has been linked to cytokines, such as IL-22 (REF. 67), and the Auspitz sign (that is, punctate bleeding upon the removal of a scale) to angiogenic factors, among others[68]. Mutations involved in pustular variants of psoriasis might

lead to increased activity of IL-8, a neutrophil chemotactic factor, and aggregation of neutrophils[69]. Mutations associated with pustular variants of psoriasis might also enhance reactivity of IL-36 and activation of NF-κB[69]. These underlying signalling processes are typically self-sustaining and maintain the chronic course of psoriasis until one or several crucial disease mediators, such as TNF or IL-17, are inhibited, leading to a temporary improvement of clinical manifestations. Even among patients who are clear of active psoriatic plaques, clinical evaluation of normal-looking skin can unveil abnormal signalling involving key inflammatory pathways[70].

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 cells and regulatory T cells (T_{reg} cells)[71]. 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 cells are associated with IFNγ and IL-12, T_H17 cells with IL-17 and IL-23 and T_H22 cells with IL-22, whereas TNF is not specific to a single T_H cell profile. Although this traditional paradigm of separate T cell lineages might predominate, there is also heterogeneity, with secretion of the same factors from multiple different T cell lines, and plasticity, with switching between T cell lineages under certain conditions[72]. Internal and external factors, such as the balance of local cell populations or the introduction of therapies that dampen or accentuate certain signatures, can shift the cytokine milieu towards a different T cell phenotype. Within the natural disease course, T cell predominance can also change, switching from a T_H1 cell profile during the initiation phase of psoriasis to a T_H17 cell profile in the chronic, inflammatory phase.

The role of keratinocytes in psoriasis also extends beyond its association with the classic psoriasis histological phenotype of epidermal hyperplasia and acanthosis[67]. 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 the amplification of psoriasis[73] (FIG. 4).

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 the innate and adaptive immune systems[74]. Plasmacytoid dendritic cells are components of the innate immune system that circulate in the blood; they can detect viral and other antigens and respond by releasing type I IFNs during the initiation phase of inflammation in psoriasis, whereas myeloid dendritic cells promote the expansion of specific T_H cell populations through the production of cytokines, such as IL-12 and IL-23.

Diagnosis, screening and prevention
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[75]. Several types of skin manifestations associated with psoriasis have been described (FIG. 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 (FIG. 5). Cutaneous disease severity can be rated by measures, such as the PGA[9] (a 0–5 composite score of erythema (redness of the skin), induration (thickening or elevation of the skin) and scales), BSA (the percentage of BSA affected by psoriasis, with one palm of the patient equivalent to 1%) and the PASI (a 0–72 composite score of erythema, induration and scale, with a multiplier based on the total affected BSA); in both the PGA and the PASI scoring systems, higher scores correspond to more-severe disease[76]. 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.
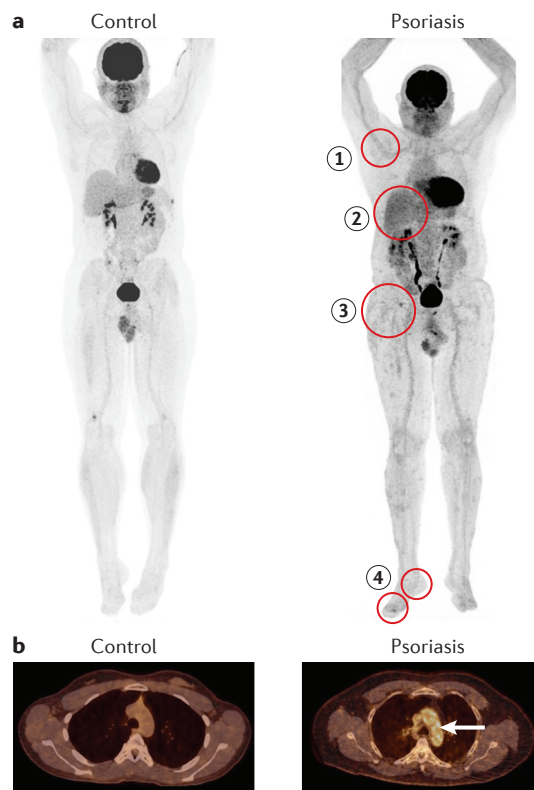
Figure 3 | **Evidence of systemic inflammation in patients with psoriasis. a** | Frontal reconstructions of ^{18}F-fludeoxyglucose (FDG) PET-CT images of individuals matched for age, sex and body mass index with (right) or without (left) psoriasis. High levels of tracer (FDG) uptake (darker areas, red circles) correspond to the presence of vascular (1), liver (2), skin (3) and joint (4) inflammation. **b** | Transverse FDG PET-CT images at the level of the aortic arch depict a higher tracer uptake (arrow) in the aorta of a patient with psoriasis (right) than in a healthy control (left), which is consistent with vascular inflammation. Images courtesy of N.N.M., National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA.

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 (especially extensor surfaces, such as the elbows, knees and sacral area), although any area might be affected. Psoriatic plaques might exhibit the Auspitz sign and Koebner phenomenon (the appearance of psoriasis at sites of trauma; FIG. 6), although these signs are not specific for psoriasis. Other features can include changes in the nails,
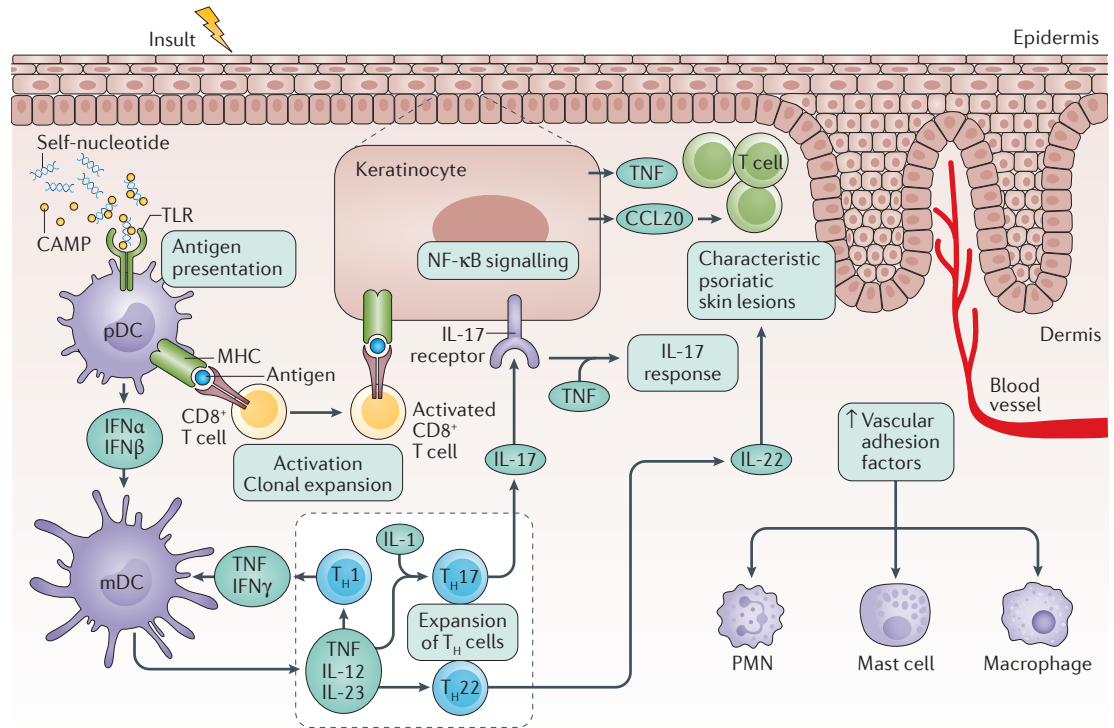
Figure 4 | **Mechanisms of psoriasis.** External insults, such as trauma, infection or medication, can cause the release of self-nucleotides, especially in genetically predisposed individuals. Self-nucleotides can form complexes with antimicrobial peptides (AMPs) that are released from keratinocytes, such as, for example, cathelicidin antimicrobial peptide (CAMP), which can bind to receptors on antigen-presenting cells, including Toll-like receptor 7 (TLR7) and TLR9 on the surface of plasmacytoid dendritic cells (pDCs). This binding triggers antigen presentation by pDCs, which prompts 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 major histocompatibility complex (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-α (IFNα) and IFNβ, which stimulate myeloid DCs (mDCs) to secrete additional pro-inflammatory mediators, such as IL-12, IL-23 and tumour necrosis factor (TNF). These innate immunity mediators stimulate the activities of key T cell populations, such as T helper 1 (T_H1), T_H17 and T_H22 cells, which release additional cytokines and chemokines. In particular, T_H17 cell response to IL-23 is potentiated by IL-1. IL-17 acts on keratinocytes (which express IL-17 receptor), stimulating them to produce TNF and CC-chemokine ligand 20 (CCL20; a chemotactic for T cells and DCs[208]). In combination with TNF and/or other pro-inflammatory cytokines, IL-17 stimulates the production of defensins and chemokines, which promotes host defence and leads to the recruitment of additional inflammatory cells into the lesion. IL-22 contributes to the characteristic psoriatic histological phenotype, including epidermal hyperplasia, acanthosis and parakeratosis (incomplete keratinization with retention of nuclei). Key transcription factors in psoriasis include cyclic AMP, the Janus kinase (JAK)–signal transducer and activator of transcription (STAT) family and nuclear factor-κB (NF-κB); their activation leads to further production of factors, such as TNF and IL-17, and downstream amplification loops. The expression of vascular endothelial growth factor receptors on endothelial cells induces vascular proliferation and the expression of adhesion molecules in the endothelium to recruit additional inflammatory cells into the skin. Among other changes, these angiogenic factors lead to the characteristic tortuous (twisting) papillary dermal vessels of lesional psoriatic skin, which contribute to the development of the Auspitz sign. A symptomatic, chronic phase of psoriatic inflammation is then established, which typically continues until a therapeutic intervention that targets key pathological regulators (for example, TNF or IL-17) breaks the cycle (although, in some cases, disease activity can naturally wax and wane in the absence of treatment). However, after the withdrawal of treatment, a susceptible patient can relapse to the chronic phase with actively inflamed skin. In some cases, there can be a prolonged disease resolution when off treatment, but in most cases psoriasis activity eventually returns. PMN, polymorphonuclear leukocyte.

observed in 50% of patients, such as pitting (depressions in the nail plate due to proximal nail matrix involvement), 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)[2,77] (FIG. 6).

The differential diagnosis of cutaneous involvement in psoriasis vulgaris includes various disorders (BOX 2). Although clinical history and examination might be sufficient to distinguish these disorders from psoriasis, other tests, such as skin biopsy to assess histological findings, antinuclear 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 to guide therapeutic decision making[78].

PsA

PsA is observed in a substantial proportion of patients with psoriasis[2,79] (FIG. 6c) and usually presents after the 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 increased serum levels of acute-phase proteins and matrix metalloproteinase 3 (REFS 80–82). 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 more than five joints. In addition, axial inflammation might limit mobility of the 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 the bone)[14]. The 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[83].

The diagnosis of PsA has been facilitated by the Classification Criteria for Psoriatic Arthritis (CASPAR), which were developed through an international study with a large sample size[84] (BOX 3). These criteria are 91% sensitive and 99% specific for disease identification compared with the gold standard (that is, the 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 rheumatological expertise for definitive diagnosis. A delay in consultation for PsA by only 6 months can result in adverse outcomes, including physical
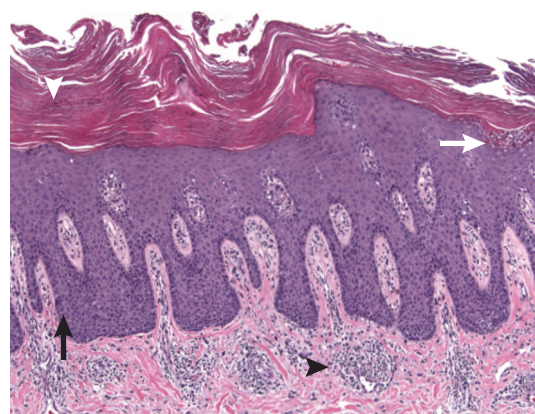
Figure 5 | **Skin biopsy obtained from a patient with psoriasis vulgaris.** Histological examination with haematoxylin and eosin staining demonstrates acanthosis (black arrow), Munro microabscesses (an accumulation of neutrophils in the epidermis; white arrow), alternating neutrophils (isolated neutrophils within the stratum corneum) and parakeratosis in the stratum corneum (white arrowhead) and infiltration of mononuclear cells in the dermis and epidermis (black arrowhead)[2]. Figure from *Fitzpatrick's Dermatology in General Medicine*, 8th Edition, Goldsmith, L. A., Katz, S. I., Gilchrest, B. A., Paller, A. S., Lefell, D. J. & Wolff, K., © (2012) McGraw-Hill Education.

disability and peripheral joint erosions, an observation that underscores the importance of early diagnosis and treatment of PsA[85].

Because psoriasis is a common condition, it might coexist with forms of arthritis other than PsA (that is, rheumatoid arthritis, osteoarthritis and gout), which might be differentiated by the distribution of the affected joints (BOXES 4,5).

Cardiovascular comorbidities

Individuals with severe psoriasis should be routinely counselled and screened for cardiovascular risk factors. Traditional risk factors include hypertension, hyperlipidaemia, smoking, diabetes and a family history of premature myocardial infarction (<55 years of age). The Framingham Risk Score[86], which is routinely used to estimate the 10-year risk for cardiovascular events, is increased by 6% when psoriasis is present[87]. The 2013 American College of Cardiology and American Heart Association guidelines for cardiovascular risk screening do not consider psoriasis as a risk factor[88]; however, the European Society of Cardiology guidelines note an increased risk of cardiovascular disease observed in patients with psoriasis[89]. Furthermore, the Adult Treatment Panel of the National Cholesterol Education Program[90] based in the United States claims that inflammatory diseases might be considered as emerging risk factors, and warrants 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 BMI to assess for obesity and measurement of
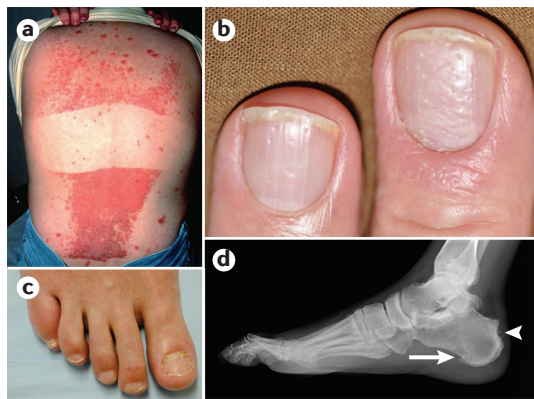
Figure 6 | **Clinical markers of psoriasis. a** | Koebner phenomenon occurs when a new area of psoriasis develops in injured skin. Psoriatic plaques can be seen in a distribution of skin damage secondary to a sunburn. **b** | Nail pitting, the most common nail finding in psoriasis, occurs as depressions 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 as a result of joint, tendon and soft tissue inflammation). **d** | Enthesitis (inflammation of the sites where tendons or ligaments insert into the bone) showing an erosion and fluffy periostitis at the site of new bone formation (at the insertion of the Achilles tendon into the calcaneous; arrowhead) as well as a plantar spur (arrow). Image in part **a** courtesy of J. E. Rasmussen. Image in part **b** courtesy of A. T. Bruce. Images in part **c** and part **d** courtesy of D.D.G., Toronto Western Hospital, Toronto, Ontario, Canada.

cholesterol and glucose serum concentrations. After diagnosis, such tests should be carried out every 5 years between 18 and 40 years of age, and then annually[90]. Patients with psoriasis with a BSA 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 indicate that patients with psoriasis who have two or more cardiovascular risk factors might benefit from non-invasive imaging examinations to assess coronary atherosclerosis burden, such as CT assessment of coronary calcification or measurement of carotid intimal medial thickness with ultrasonography. If atherosclerosis is suspected, dyslipidaemia therapy, including lifestyle changes and lipid-lowering agents, might be recommended. Finally, despite accumulating evidence that aggressive treatment of psoriasis with anti-TNF biologic agents leads to improved surrogate markers for cardiovascular disease, such as intimal medial thickness and vascular inflammation[91,92], and reduced risk of myocardial infarction[15,93], randomized clinical trials to confirm these associations are still ongoing[94,95].

Management

The treatment approach for psoriasis depends on several 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 biologic agents that target both the skin and the 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 wish to have a child because of their teratogenic effects. Recent management guidelines with useful treatment algorithms exist in the United States[96] and Europe[97].

Topical therapy

For patients with mild-to-moderate disease (<10% BSA) and without PsA, topical therapy might be adequate. Historically, dithranol (also known as anthralin), which induces keratinocyte apoptosis, and tars, which reduce IL-15 production and nitric oxide synthase activity, were the only treatments available[98,99].

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 are available. Steroid-sensitive sites, such as the face and intertriginous areas, typically require lower-potency topical corticosteroids or steroid-sparing agents (medications that are given in addition to or instead of steroid therapy to decrease the amount of steroid required) — such as topical vitamin D, 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 include cutaneous atrophy and dyspigmentation.

Several topical vitamin D analogues (for example, calcitriol, calcipotriene, tacalcitol and maxacalcitol) are approved for psoriasis, used as monotherapy or in 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 favourable[100]. 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[101]. 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[102].

Phototherapy

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

- 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

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 cell suppression and activation of T_H2 and T_{reg} cells[103]. Broadband ultraviolet B (UVB) radiation has been used since the 1920s[104]. It has not been associated with an increase in skin cancers[105], probably because the spectrum of light used does not include the most carcinogenic short wavelengths that are found in sunlight, and the 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[105]. Proximity to a phototherapy centre used to be a limiting factor, but home phototherapy units have become a popular alternative to in-office treatments and have demonstrated comparable efficacy[106]. 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[107,108].

Evidence of inflammatory articular disease, namely, arthritis, spondylitis or enthesitis, and at least 3 points from the following categories:

- Current psoriasis (2 points) or a personal history or family history (first-degree or second-degree relative) of psoriasis (1 point)
- Current dactylitis or a history of dactylitis (1 point)
- Radiographic evidence of juxta-articular new bone formation (1 point)
- Rheumatoid factor negative (1 point)
- Current nail dystrophy, including pitting, onycholysis and hyperkeratosis (1 point)

CASPAR, Classification Criteria for Psoriatic Arthritis.

Systemic therapy

For patients with moderate-to-severe psoriasis (>10% BSA), both phototherapy and systemic therapy (oral or injectable therapies) might 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[109].

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 the levels of adenosine, which lead to reduced levels of TNF and two NF-κB subunits that are involved in the mechanism of action (nuclear factor NF-κB p105 subunit and transcription factor p65)[110,111]. Key inflammatory cytokines and chemokines, including IL-17, IL-22, IL-23 and CCL20, are downregulated by methotrexate. Preliminary results indicate that low-dose methotrexate treatment might also be associated with reduced risk of cardiovascular disease, and it has been shown to lower the expression of atherogenic genes in lesional psoriatic skin[112].

Methotrexate is teratogenic and, therefore, contraindicated during pregnancy. The most common life-threatening adverse effect associated with methotrexate is bone marrow toxicity; pancytopaenia or death was reported in 1.4% of patients with rheumatoid arthritis who received low-dose methotrexate, and identified risk factors included increased blood urea nitrogen and creatinine levels, lowered serum albumin levels, infection, drug–drug interactions and advanced age[113]. 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 increase drug toxicity, leading to pancytopaenia and potentially death[114]. Another serious adverse 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 g)[115]. Risk factors for methotrexate-induced hepatic toxicity include persistently abnormal liver function tests, a history of chronic hepatitis B or hepatitis C infection, hyperlipidaemia, diabetes and lack of folate supplementation[116]. Oral folate supplementation can prevent some methotrexate adverse effects, such as nausea and macrocytic anaemia.

Routine monitoring during methotrexate therapy includes complete blood count as well as liver and renal function tests, both at baseline (before the start of treatment) and at regular follow-up intervals. Monitoring for hepatotoxicity is controversial; some guidelines recommend liver biopsies or enzymatic testing in at-risk patients[116,117].

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[118]. 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[119,120]. 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 should be done, owing to the risk of hyperlipidaemia, especially hypertriglyceridaemia, and liver toxicity. Mucocutaneous adverse 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[121].

Cyclosporine. Cyclosporine is one of the most effective therapies for psoriasis that act 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 (NFAT) isoforms (*NFATC1*, *NFATC2* and *NFATC4*). NFAT is a transcription factor that promotes the expression of IL-2, a key pro-inflammatory cytokine[122]. 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 2 years of starting cyclosporine treatment[123]. Thus, most guidelines limit the use of cyclosporine to 1–2 years[109]. Other adverse effects include hypertension, hypomagnesaemia, hyperkalaemia, hyperlipidaemia, 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.

Apremilast. Apremilast is a phosphodiesterase 4 inhibitor that limits the degradation of cyclic AMP, reduces nitric oxide synthase, TNF and IL-23 levels and increases IL-10 levels[124]. It was approved as an oral treatment for psoriasis by the US FDA 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 diarrhoea, 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[125]. Apremilast efficacy is lower than that of many biologic therapies, with 33% of patients achieving PASI 75 by week 16 of therapy[126]. 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.

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[127]. Believed to downregulate TNF, IL-12 and IL-23 production[128], 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.

Biologic therapies. A biologic medication should be considered as first-line therapy for moderate-to-severe disease with profound effects on QOL 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 therapy because of adverse effects. Eight injectable biologic therapies are currently approved for moderate-to-severe psoriasis or PsA (TABLE 1), and several other agents, including some that target IL-23, are in various stages of the developmental and approval process. Patient sex[129], BMI, C-reactive protein levels (as a marker for inflammation), prior use of biologic therapies and concomitant hepatitis B or hepatitis C infection might affect the response to and selection of biologic therapy. TNF blockers have been particularly effective in patients with concomitant PsA[130].

Several anti-TNF agents — which either bind to TNF, thereby inhibiting receptor binding, or block TNF receptor activation — are available to manage psoriasis and PsA (TABLE 1). In addition, evidence from

registry studies showing that anti-TNF agents are protective against cardiovascular disease supports their use, particularly in individuals who are at high risk of cardiovascular events[93,131]. Other biologic agents might also provide cardiovascular protection, but there is no clear evidence yet.

Anti-TNF agents have safety profiles that are different from those of traditional systemic agents (such as less-severe risk of liver, kidney or bone marrow suppression) and are considered safe during pregnancy[132]. Anti-TNF agents have been associated with an increase in infections and certain malignancies, particularly cutaneous squamous cell carcinoma[133], whereas these correlations have not been observed with ustekinumab (an anti-IL-12 and anti-IL-23 antibody)[134] or any of the IL-17 blockers. Paradoxical worsening of psoriasis has been reported as an adverse effect of anti-TNF agents and often resolves with treatment discontinuation[135]. Patients treated with biologic agents have an increased risk of developing tuberculosis; thus, annual tuberculosis screening has been recommended[136].

Ustekinumab, secukinumab (an anti-IL-17A antibody) and ixekizumab (an anti-IL-17A antibody) have been approved for the treatment of PsA[137–139]. Early data on brodalumab have been favourable[140]; 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[141–143]. Ustekinumab and IL-17 blockers can be used safely in patients with heart failure and a 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[144].

Head-to-head comparisons of biologics are limited in number. Ustekinumab was shown to be more effective than etanercept[145] but less effective than secukinumab[146] for cutaneous disease; secukinumab was more effective than adalimumab for PsA[147]. The development of anti-drug antibodies and the associated reduced efficacy of biologics remain important concerns[148]. The potentially

Table 1 | Biologic agents used in psoriasis

Drug	Structure	Mechanism of action	Indication*	Effectiveness (PASI 75‡)	Standard dosing regimen	Refs
Anti-TNF agents						
Etanercept	Fusion protein between the Fc portion of human IgG1 and the extracellular domain of human TNF receptor superfamily member 1B	TNF receptor antagonist	Psoriasis and PsA	49% at week 12	Subcutaneous injections twice per week for 12 weeks, then once per week	209, 210
Adalimumab	Human monoclonal antibody	Anti-TNF antibody	Psoriasis and PsA	53% at week 12	Subcutaneous injections; a loading dose first, then a regular dose regimen every 2 weeks	211, 212
Infliximab	Chimeric monoclonal antibody comprising human IgG1 with the mouse binding site for TNF	Anti-TNF antibody	Psoriasis and PsA	88% at week 10	Intravenous infusions over 2 hours at weeks 0, 2 and 6, then every 8 weeks	213–216
Certolizumab	Pegylated humanized fragment antigen-binding fragment	Anti-TNF antibody	PsA	75% at week 12	Subcutaneous injections; a loading dose first, then a regular dose every 2 weeks	217, 218
Golimumab	Human monoclonal antibody	Anti-TNF antibody	PsA	65% at week 52. Less effective against cutaneous psoriasis than other biologic agents	Subcutaneous injections once every 4 weeks	219
Others						
Ustekinumab	Human monoclonal antibody directed against the IL-12 subunit-β 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 injections at weeks 0 and 4, then every 12 weeks; weight-based dosing (<100 kg or ≥100 kg)	188
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	220
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	221
Brodalumab	Human monoclonal antibody	Anti-IL-17A receptor antibody	Approval for psoriasis pending; data for PsA are promising	At week 12, PASI 75 was 86.3%, PASI 90 was 70.3% and PASI 100 was 44.4%	Subcutaneous injections at weeks 0, 1 and 2, then every 2 weeks	140

PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; TNF, tumour necrosis factor. *In the United States, Canada and Europe. ‡PASI 75 reflects the number of patients who have achieved >75% reduction in PASI scores in response to treatment. §Approval pending in Canada.

protective role of biologic–methotrexate combination therapies in limiting the emergence of anti-drug antibodies in psoriasis needs further evaluation. Finally, infliximab biosimilars are now approved in Europe, Canada, the United States and Korea, and an etanercept biosimilar is approved in Europe. Infliximab and etanercept biosimilars seem to demonstrate similar efficacy to the original agents and will probably reduce the cost of biologics and improve patient access to these medications[149,150].

Quality of life

Psoriasis often has profound effects on patient QOL[151]. Individuals with psoriasis have higher rates of depression, anxiety and suicidal ideation, and experience feelings of shame, anger and worry more frequently and/or severely than the general population[21]. The degree to which psoriasis affects QOL depends on both the outlook and personality of the patient 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[152]. Furthermore, psoriasis influences pivotal life decisions, such as choice of partner, career and residence[153]. 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[154].

Box 6 | Psoriasis quality-of-life questionnaires

Psoriasis-specific questionnaires*
- 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‡
- Psoriasis Symptom Inventory§

Dermatology-specific questionnaires*
- Dermatology Life Quality Index (DLQI)
- Skindex (versions 16, 17 and 29)

General health measures*‖
- 36-Item Short-Form Health Survey (SF-36)
- General Health Questionnaire (GHQ)
- World Health Organization Quality of Life (WHOQOL)
- EuroQoL 5 Dimension Health Questionnaire (EQ-5D)
- Pictorial Representation of Illness and Self Measure (PRISM)

Children-specific questionnaires
- Children's Dermatology Life Quality Index (CDLQI)¶

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

*See REF. 193. ‡See REF. 194. §See REF. 195. ‖See REF. 196. ¶See REF. 197. #See REFS 198,199.

Measurement

Quantifying the effect of psoriasis on QOL is essential, as it informs therapeutic decisions (including decisions on therapy initiation and treatment goals), highlights the aspects of the disease that are most important to the patient and helps to assess and communicate patient satisfaction. Psoriasis registries also routinely record QOL data[155]. Among the several tools that measure QOL in patients with psoriasis (BOX 6), the Dermatology Life Quality Index is the most widely used[156–158]. The 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[159].

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[160]. Cyclosporine and methotrexate improve QOL to a lesser extent than biologic agents do, and educational interventions have demonstrated limited effect on QOL[161,162]. Evaluating the effect of psoriasis on patient QOL is essential when discussing therapeutic options and allocating health care 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.

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[163]. 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 to continue to develop new treatments to improve patient QOL (TABLE 2).

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[164–166], or whether reducing immune activation with biologic and oral agents, such as methotrexate, can mitigate cardiovascular morbidity and mortality[167]. Large-scale, innovative studies, designed in cooperation with regulatory agencies, are necessary to answer these clinically meaningful questions[164].

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

Table 2 | **Current clinical trials on biologic agents for psoriasis**

Therapeutic agent	Mechanism of action	Trial (status)	ClinicalTrials.gov identifier
Tofacitinib	JAK1 and JAK3 inhibition	Randomized trial versus etanercept (completed)	NCT01241591
Ruxolitinib (topical treatment)	JAK1 and JAK3 inhibition	Randomized vehicle controlled safety and efficacy trial (completed)	NCT00820950
Pazopanib (topical treatment)	VEGF antagonist	Randomized efficacy trial (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 etanercept (ongoing)	NCT01729754
Risankizumab	IL-23 inhibitor	Open-label safety and efficacy trial (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 (also known as CF101)	Adenosine A3 receptor agonist	Randomized safety and efficacy trial (completed)	NCT00428974

GM-CSF, granulocyte–macrophage colony-stimulating factor; JAK, Janus kinase; S1P1, sphingosine 1-phosphate receptor 1; TLR, Toll-like receptor; VEGF, vascular endothelial growth factor. Data from REF. 187.

do not seem to encode changes in protein structure, but rather in gene regulation (transcription level, splicing and mRNA stability)[62]. 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 approximately 50 known disease loci[168]. 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[169]. A new taxonomy for psoriasis based on molecular targets might also be able to guide treatment decisions[170]. The responses to treatment of the different disease endotypes (that is, a 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[171,172].

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[173,174]. Flow cytometry, proteomics and molecular signalling techniques are being applied to identify potential biomarkers with adequate sensitivity and specificity[175]. 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.

Management

From a health care 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[176] because of several 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[177]. 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[178].

New treatment targets

A growing understanding of psoriasis pathophysiology has led to the development of several novel topical, systemic and biologic agents, which are now in various stages of approval[179,180] (TABLE 2). 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 favourable side-effect profiles that facilitate treatment outcomes is warranted[181]. 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, such as decoy oligonucleotide therapy (that is, the selective inhibition of the expression of specific genes)[64,182,183]. Gene expression profiling of lesional skin has enabled the definition of differentially expressed genes that are characteristic of psoriasis and the subsequent identification of the upstream psoriasis response elements, which are genomic sequences that are thought to have a regulatory role in disease development. The isolation of these sequences might lead to

the development of novel decoy oligonucleotides that can recognize and bind to transcription factors that are central to psoriasis[64]. Such efforts have demonstrated the ability of novel decoy oligonucleotides to inhibit the onset and reverse established psoriatic lesions in psoriatic mouse models[184].

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–IFNγ-driven disorder, this pathway might be more essential in the initiation phase of the disease[185]. IFNγ inhibition has not shown substantial clinical benefit[186]. Thus, the T_H1 axis might be more crucial in the pathogenetic 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 that target this pathway have achieved improved clinical outcomes. TABLE 2 lists some of the biologic agents that are currently being assessed. Selective IL-23 inhibition (with drugs such as tildrakizumab, guselkumab and risankizumab)[187] and combined IL-12 and IL-23 inhibition (with ustekinumab; TABLE 1)[188] produce 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, a phase I investigation of an IL-22 inhibitor (fezakinumab) was terminated early[189]. 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[66] (FIG. 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.

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