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Frontiers in Dermatology and Venereology

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PSORIASIS

Theme Editors:

Lone Skov and Enikö Sonkoly

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REVIEW ARTICLE

Psoriasis and Genetics

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Psoriasis is a common inflammatory skin disease caused by the interplay between multiple genetic and environmental risk factors. This review summarises recent progress in elucidating the genetic basis of psoriasis, particularly through large genome-wide association studies. We illustrate the power of genetic analyses for disease stratification. Psoriasis can be stratified by phenotype (common plaque versus rare pustular variants), or by outcome (prognosis, comorbidities, response to treatment); recent progress has been made in delineating the genetic contribution in each of these areas. We also highlight how genetic data can directly inform the development of effective psoriasis treatments.

Key words: psoriasis; genetics; precision medicine; disease progression; treatment outcome.

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SIGNIFICANCE

Psoriasis has benefited greatly among dermatological conditions from genome-wide association studies (GWAS) of increasingly large, clinically well-described samples. Sixty-five regions of the genome have been linked to psoriasis risk in Europeans, with the largest contribution due to *HLA-C*06:02*, a variant of an important gene involved in immunity. Other regions implicate numerous immune and skin barrier processes in psoriasis development. Recent GWAS-based research has shown that genetics can help distinguish subgroups of psoriasis patients characterised by type (pustular vs. plaque psoriasis), development of joint disease or response to various drugs. This may help inform future tailored treatment strategies for individuals with psoriasis.

Dermatological research has made extraordinary progress over the past 100 years. This has been matched – if not exceeded – by advances in the field of genetics, particularly in the two decades since the initial mapping of the human genome (1, 2). Recent insights into the genetic basis of the common skin disease psoriasis illuminate the translational potential of genetic studies, having directly informed the design of several powerful biologic therapies and small molecule inhibitors.

Psoriasis is a chronic immune-mediated inflammatory disease that affects around 2% of the world's population (3). It has been designated a serious non-communicable disease by the World Health Organisation and its increasing prevalence represents a substantial global public health burden (4). Genetic research has delivered critical insights into the biology of psoriasis. We now know that psoriasis is a multifactorial disease caused by the interplay between multiple inherited alleles (**Box 1**) and environmental risk factors. Indeed, it has a particularly strong genetic component among complex diseases, with heritability estimated to exceed 60% (5).

Unlike other biological features, the genome is fixed at birth and does not vary by cell or tissue type, or in response to stimuli: in this sense it reveals the causal biology of psoriasis. In this review, we describe how genetic studies have helped to disentangle pathogenic mechanisms of psoriasis and informed the selection of therapeutic targets. We also highlight the potential of genetic biomarkers as a stratification tool for the effective clinical management of psoriasis.

GENETICS OF PLAQUE PSORIASIS

Early genetic findings

It has long been observed that the incidence of psoriasis is significantly higher among first- and second-degree relatives of sufferers than the general population (6, 7), and it is more concordant among monozygotic than dizygotic twins (8–10).

Linkage studies identified at least 9 genomic regions (loci) that co-segregated with psoriasis (*PSORS1-9*) in multiplex pedigrees. However, most of these findings could not be replicated, which underscores the limitations of linkage approaches for the analysis of multifactorial conditions (11). A notable exception is the *PSORS1* region, which maps to the class I interval of the major histocompatibility complex (MHC) that primarily encodes genes involved in antigen presentation (12–14). The region also contains the candidate gene corneodesmosin (*CDSN*), which encodes a desmosomal protein involved in keratinocyte cohesion and desquamation (15). *PSORS1* has the largest effect size and accounts for 35–50% of disease heritability explained by known

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Box 1 – Genetic terminology

Alleles: Alternative variants of a gene (or other segment of DNA).

Single nucleotide polymorphism (SNP): A DNA sequence change affecting a single genomic position.

Linkage disequilibrium (LD): Genetic variants are in LD if they are in close proximity on the same chromosome and therefore less likely to be separated by recombination during meiosis, tending to be inherited together and being correlated in the population.

Susceptibility loci: Genomic regions that contain variants showing statistically significant association in a disease susceptibility GWAS (usually more than one variant due to LD).

Imputation: The statistical ascertainment of an individual's probable genotype at known genetic variants that exist in between markers genotyped on a GWAS chip. This requires large panels of reference genomes in which genotypes are available for the "missing" variants.

Polygenic risk score (PRS): A composite measure of genetic risk for a disease. Once a susceptibility GWAS has been completed, the polygenic risk for any genotyped individual (who may not have been included in the original GWAS) can be calculated by summing the number of risk alleles they carry at each susceptibility locus (usually weighted by the effect size observed at that locus).

Genetic correlation: The degree to which the genetic influences on two different traits are similar.

Mendelian randomisation: An approach to assess how far one trait (typically representing a modifiable exposure) is causal of another trait (typically a health outcome) by estimating the effects of genetic variants associated with the first trait on the second.

Next-generation sequencing: High-throughput and highly parallelised DNA sequencing, typically of the whole genome or exome (the protein coding portion of the genome).

loci. Despite the complex correlation structure across the MHC due to extensive linkage disequilibrium (Box 1) (16), *HLA-C*06:02* is now confidently considered the most likely causal susceptibility allele, since single nucleotide polymorphisms (SNPs; Box 1) that tag this allele have generated the most significant association signals in subsequent case-control studies (17, 18). Fine mapping studies have suggested the presence of additional association signals within *PSORS1*, some of which are population-specific (19–22).

The only other successfully validated linkage results are the *PSORS2* and *PSORS4* loci on chromosomes 17q25 and 1q21, respectively. The most likely susceptibility gene in *PSORS2* is *CARD14*, which encodes a nuclear factor-κB (NF-κB) activator and harbours variants associated with rare and common forms of psoriasis (23–25). *PSORS4* contains the late cornified envelope (LCE) genes, which encode stratum corneum proteins involved in terminal epidermal differentiation. This locus has been implicated in psoriasis susceptibility in genome wide association studies of both European and Chinese populations (26, 27).

Psoriasis in the GWAS and post-GWAS era

Genome-wide association studies (GWAS) use highly optimised microarrays that can efficiently and robustly genotype several million genetic markers across the genome. With sufficiently large sample numbers, GWAS allows even small differences in allele frequencies between disease cases and unaffected controls to be detected, making it a much more powerful approach than linkage analysis. As such, GWAS have fundamentally changed the genetic dissection of common complex diseases such as psoriasis. By 2010, initial GWAS efforts in psoriasis had identified 21 susceptibility loci in Europeans (17, 18, 28, 29).

One inherent limitation of GWAS, however, is that it only uncovers statistical relationships. The genetic variants identified by GWAS may actually, by virtue of linkage disequilibrium, be tagging a separate 'causal' variant that exerts a biological effect and modifies disease risk. To refine GWAS signals and thus identify potential causal susceptibility alleles, genotyping arrays with dense coverage in regions of interest have been employed. The immunochip included 200,000 SNPs focused in known susceptibility loci for a range of immune-mediated diseases (30). In psoriasis, meta-analysis of immunochip data almost doubled the number of known susceptibility loci and uncovered candidate causal variants at 10 loci including in the innate immunity genes *DDX58* and *CARD14* (31).

More recently the exome chip aimed to comprehensively genotype protein-altering variants, including rare variants. Exome chip meta-analysis of 12,000 psoriasis cases and 29,000 controls highlighted potential functional SNPs within 11 known psoriasis susceptibility loci. This study provided novel insights into the complex role in psoriasis susceptibility of rare variants in the type I interferon signalling genes *IFIH1* and *TYK2* (32).

Rather than physically genotyping additional SNPs that are not included in GWAS arrays, however, it is becoming standard practice to perform genome-wide imputation (Box 1) using freely-available computational resources (33, 34). Imputation has been critical in facilitating the larger psoriasis meta-analyses, which combine data generated by different GWAS platforms (35–37). Indeed, an improved imputation strategy revealed a novel psoriasis susceptibility locus at *DLEU1*, linked to apoptosis, in previously analysed GWAS data (37).

Finally, combining datasets from international collaborations in meta-analyses of genome wide association studies has been essential to enhance statistical power and uncover novel disease susceptibility loci (18, 28, 29, 31, 38). A recent meta-analysis of psoriasis GWAS with a combined effective sample size of > 39,000 individuals identified 16 novel disease-associated regions (36).

PATHOGENIC INSIGHTS FROM GENETIC DISCOVERIES

As a result of GWAS, targeted association and meta-analysis efforts, the number of independent genomic loci contributing to susceptibility to common plaque psoriasis in populations of European ancestry now stands at 65 (32, 36, 37). More than 30 loci have been implicated in Han Chinese individuals (39). Although these susceptibility loci can span many genes, many of the lead SNPs lie in proximity to genes involved in specific adaptive and innate immune pathways. These include genes involved

in antigen presentation (*HLA-C, ERAP1*), T17 cell activation (*IL23R, IL23A, IL12B, TRAF3IP2*), innate antiviral immunity/type I interferon signalling (*RNF114, IFIH1*) and skin barrier function (*LCE3B/3D*) (**Fig. 1**) (17, 18, 26, 28, 40–42). The coding variants in genes such as *IL23R, TYK2* and *TNFSF15* uncovered by targeted association analyses further underscore the involvement of the interleukin (IL)-23/T17 axis in disease pathogenesis (31, 32, 38, 39, 43).

Genetic studies have thus provided important mechanistic insights into the aetiology of psoriasis, and support a pathogenic interplay between immune activation and disruption of skin barrier function (44). There is also evidence of gene-gene interactions (epistasis) contributing to disease heritability, since variants in *ERAP1* (encoding an enzyme that trims peptide antigens for loading onto MHC class I molecules) only confer disease susceptibility in individuals also harbouring the *HLA-C* risk allele (18). Once GWAS association summary statistics are in hand, there are several additional *in silico* approaches that can help to pinpoint relevant causal genes and variants before costly hypothesis-driven functional experiments are undertaken.

Statistical fine-mapping jointly considers correlated groups of associated variants to estimate the likely causality of each (45). This has been undertaken for several psoriasis susceptibility loci, revealing multiple independent association signals (46).

Pathway analysis methods look for known biological pathways for which gene annotations are enriched across multiple susceptibility loci. NF-κB and type I interferon signalling pathways have thus been implicated in psoriasis pathogenesis (36).

If GWAS summary results are available from other studies that have assessed the genetic basis of relevant molecular traits, colocalisation with the disease association signal can be assessed (47, 48). In particular, expression quantitative trait loci (eQTLs) are SNPs associated with the level of expression of a gene in a specific tissue. Colocalisation of a psoriasis susceptibility signal and a skin- or immune-based eQTL would thus provide strong evidence that the variant directly modifies psoriasis risk and suggest a probable mechanism of action. This powerful approach has been successfully employed in GWAS studies of acne (49) and atopic dermatitis (50) but has yet to be employed systematically in a large psoriasis dataset, with only suggestive colocalisations being reported in cross-disease studies (51, 52).

It is worth remarking that all of these approaches rely to a greater or lesser extent on *open science*: the continuing efforts of research groups around the world that are committed to making reference data, summary results, annotations, tools and computational resources publicly available in the interests of collaborative science.

TRANSLATION OF GENETIC DISCOVERIES INTO NOVEL THERAPEUTICS

The genetic insights gained from large-scale association analyses have paved the way for transformative novel therapeutics in psoriasis. Indeed, it has been shown in general that pipeline drugs whose mechanisms are supported by direct genetic evidence are more likely to reach the clinic (53, 54). Based on the mechanistic insights that have emerged from genetic studies in psoriasis, the IL-23/T17 axis has been a particular focus for drug development. Biologic agents such as ustekinumab (targeting the common p40 subunit of IL-12 and IL-23), secukinumab and ixekizumab (targeting IL-17A), and newer monoclonal antibodies targeting the p19 subunit specific to IL-23 (including guselkumab and tildrakizumab), have shown progressively increasing efficacy rates in clinical trials (55). These agents are now licensed for use in the USA and Europe and have impressive effectiveness and tolerability in real world practice (55, 56).

In addition to informing the targets of biologic medications, genetic studies have opened new avenues for small molecule therapeutics. Following genetic association data highlighting *TYK2* as a causal allele (31, 32), an oral, selective

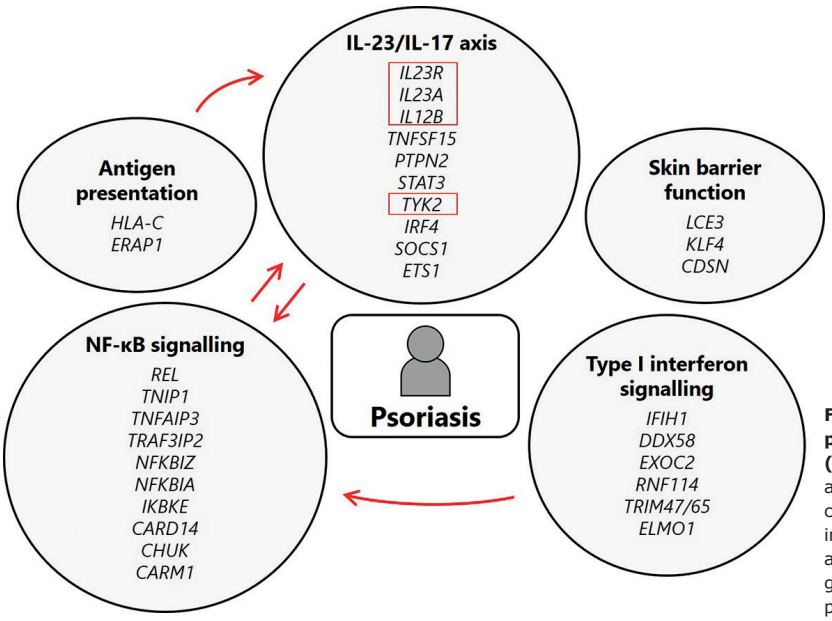

Fig. 1. Biological pathways implicated in psoriasis pathogenesis via genome wide association studies (GWAS). Candidate causal genes from selected disease-associated loci identified by GWAS. *Arrows* signify the crosstalk between the immune pathways shown (e.g. interleukin (IL)-17 and type I interferon signalling both activate nuclear factor-κB (NF-κB) pathways). *Red boxes:* genes involved in mechanisms currently targeted by psoriasis treatments.

inhibitor was developed, which has shown promising efficacy in phase II trials (57).

Missing heritability

Despite the recent progress in psoriasis genetics, less than a quarter of heritability is thought to be explained by the susceptibility loci identified to date (32). There are several reasons for this missing heritability.

A substantial fraction of heritability may arise from rare variants that are not genotyped or well tagged by GWAS arrays. A recent analysis of 22,000 whole genomes makes a compelling case for this, since the heritability of both height and body mass index could be almost fully explained when very rare variants are accounted for (suggesting also that pedigree-based estimates of heritability are not overestimated) (58). The same may be true for psoriasis susceptibility, although sequencing efforts will need to surpass those performed to date (59) to confirm this.

More generally, the estimated heritability explained at a GWAS-identified locus may be underestimated where the lead GWAS SNP is a poor tag for the true causal variant, or where there are multiple true causal variants (60).

Another explanation could be high polygenicity, where many common SNPs across the genome may modify psoriasis risk, but with effect sizes too small to have been identified with current GWAS sample sizes. Although increasingly large case-control study populations will help to address this (61), sufficient numbers to fully elucidate the role in psoriasis pathogenesis of every individual common SNP are impractical. One approach to overcoming this limitation is to consider genetic variation aggregated according to known biological function. For example, functional network-based analyses have been applied to suggest novel mechanisms involved in psoriasis (36, 62).

It could also be the case that psoriasis risk attributable to individual genetic variants does not accumulate additively and independently, so that simple GWAS association tests mask more complex causal biology. Alternative models of genetic architecture have been explored (63), including genetic interactions genome-wide (64, 65) (recall the *HLA-C/ERAP1* interaction described previously).

Missing heritability in genetic studies could be due in part to epigenetic variation: DNA modifications that can cause differences in gene expression even when no differences are present in DNA sequence. Numerous studies have begun to explore the role of epigenetics in psoriasis, although the types of modification and study designs have varied widely, making it difficult to assess their overall contribution to heritability (66).

The complex genetic nature of psoriasis and the unresolved missing heritability have implications for the growing industry of direct-to-consumer genetic testing. While genetic risk profiles can offer additional information beyond family-history based risk estimates (67), this information will likely be insufficiently precise or consistent to offer substantial clinical utility (68, 69) and it is vulnerable to misunderstanding by the public (70, 71).

As we shall describe, however, the genetic risk profiles of larger cohorts still hold great potential to refine our understanding of the biology and to inform effective clinical management of psoriasis.

BEYOND DISEASE SUSCEPTIBILITY

The possibilities of GWAS-based analysis have now moved beyond the study of simple susceptibility and towards disease stratification. With large collections of genotyped and deeply phenotyped individuals, the genetic basis of many other aspects of psoriasis natural history and treatment response can be characterised (**Fig. 2**). These collections could comprise psoriasis patients (e.g. PSORT (72)) or be derived from the general population with phenotype data from linked electronic medical records (e.g. UK Biobank (73)).

These "post-susceptibility" genetic studies still currently utilise much smaller samples than the susceptibility GWAS meta-analyses described above. However, they can benefit from numerous methods that incorporate or compare genetic information (typically GWAS summary statistics) from related traits to make novel inferences. Relevant methods include polygenic risk scores (PRS) (74) and genetic correlation (75, 76) to assess shared genetic associations, Mendelian randomisation (77) to assess causality, and methods for deconvoluting genome-wide association signals into functionally relevant constituents (78) (Box 1). While findings from psoriasis susceptibility studies offer a natural starting point (and efforts to accurately document and annotate these associations are ongoing (79, 80)), the utility of these methods are greatly enhanced by the availability of GWAS summary results for thousands of other traits, including physiological, disease-based and molecular traits (81).

We offer here a brief overview of recent progress in psoriasis genetics beyond susceptibility.

Onset

It remains unclear how genetic susceptibility variants interact with environmental risk factors such as infection, ultraviolet exposure, smoking, alcohol, and psychological stress to trigger psoriasis onset (82). Initial findings suggest that the risk attributable to *HLA-C*06:02* may be modified by smoking and stress (83). The pathogenic contribution of smoking may also be mediated via variants in *CYP1A1*, a key gene in the aryl hydrocarbon receptor signalling pathway (84). The availability of large datasets with environmental exposure and GWAS

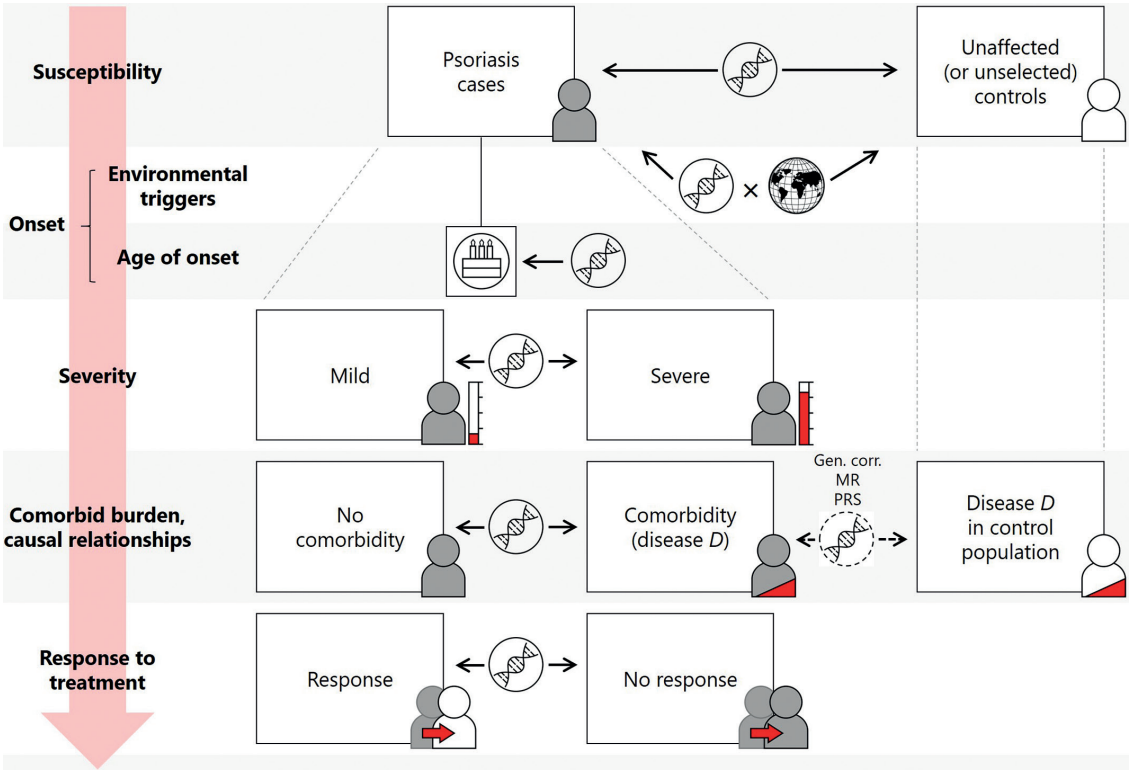

Fig. 2. Psoriasis genetics beyond susceptibility. Various strategies are employed to study the genetic factors that influence the conceptual trajectory from risk of psoriasis through disease onset and prognosis to patient outcomes (red arrow). *Susceptibility*: allele frequencies are compared between psoriasis cases and controls to reveal genetic variants contributing to psoriasis risk. *Onset:* gene × environment studies may integrate genetic data with environmental exposures (indicated by globe symbol) to identify relationships between genes and environmental triggers; age-of-onset is also influenced by genetic factors and this can be investigated where age-of-onset data (denoted by birthday cake symbol) are available for psoriasis cases. *Severity:* genetic profiles can be compared between psoriasis patients with mild and severe disease; severity may also be studied as a continuous outcome. *Comorbidities*: genetic profiles are compared between psoriasis patients with and without comorbid disease *D*; more sophisticated methods will also consider the genetic basis of disease *D* in the wider population. *Response to treatment*: genetic profiles can be compared between psoriasis patients responding and not responding to a treatment; response may also be studied as a continuous outcome. Gen. corr.: genetic correlation; MR: Mendelian randomisation; PRS: polygenic risk score.

data (such as UK Biobank (73)) now offers the opportunity to study gene-environment interactions in a more systematic manner, and this is an active area of research in the field. Age of onset is better studied. It is well established that the *HLA-C*06:02* susceptibility allele is associated with earlier disease onset (85, 86). Tsoi et al. used PRS analysis to show that a greater burden of psoriasis susceptibility variants is associated with earlier disease onset, even when only non-HLA susceptibility loci are considered (36).

Comorbidities

Psoriatic arthritis (PsA), with prevalence estimates ranging from 6–41% among individuals with psoriasis (87), has been the subject of large genetic studies as a disease in its own right (88–90). Particularly revealing, however, are studies comparing individuals with psoriasis and PsA against cutaneous-only psoriasis cases, (either directly or with reference to unaffected controls). Several studies focusing on the HLA region suggest that certain *HLA-B* alleles, including *HLA-B*27*, are associated with increased PsA risk in the presence of psoriasis (21, 91, 92), while *HLA-C*06:02* is not (91). Genome-wide analysis has identified additional associations of interest, including independent alleles in known psoriasis susceptibility loci (including at *IL23R* and *TNFAIP3*) (93). The translational potential of these approaches was recently explored using a "risk score" of 200 genetic markers that proved predictive of PsA development (area under the receiver operator curve = 0.82) (37). While this finding requires replication and may benefit from phenotype refinement (there are at least five recognised subtypes of PsA (94)), it offers a first step towards prognostic genetic risk profiling.

Obesity and related cardiometabolic traits have also been studied. While a large GWAS-based investigation found the genetic architectures of psoriasis and cardiometabolic traits to be largely distinct (95), an epidemiological association with obesity is well established (96, 97) and twin studies suggest a genetic correlation (98). Based on psoriasis and body mass index (BMI) GWAS data, Mendelian randomisation reveals a causal relationship: higher BMI increases the risk of psoriasis, whereas psoriasis does not have a causal effect on BMI (99, 100). Given the relatively large effect that *HLA-C*06:02* exerts

on psoriasis risk, it may be interesting to examine the causal role of BMI separately in patients positive and negative for this allele.

In principle, the shared genetic aetiology between psoriasis and any other associated condition can be readily explored at scale via GWAS data. A recent example looked at psoriasis alongside 4 other inflammatory diseases (ankylosing spondylitis, Crohn's disease, primary sclerosing cholangitis and ulcerative colitis), finding genetic overlap between the conditions that may drive co-occurrence, but with the qualification that patients affected by multiple conditions are likely to be genetically distinct from those with a single disease (101). Shared genetic factors have been found to extend beyond inflammatory disease, such as the positive genetic correlation observed between psoriasis and schizophrenia (102).

Stratified medicine

Genomic information has an exciting role in potential future personalised models of disease prevention and treatment (103). Although highly discriminative genetic prediction for complex diseases such as psoriasis (which are influenced by many genetic factors of modest effect) is unlikely (74), there remains ample opportunity to "stratify" individuals into broader groups according to distinct risk and response profiles, thus leading to more effective and economical care.

Effective deployment of expensive biologic therapies is an area of promise in psoriasis. Patients positive for the *HLA-C*06:02* psoriasis susceptibility allele demonstrate better response to ustekinumab than *HLA-C*06:02*-negative patients, particularly during the initial months of treatment (104, 105). Numerous candidate gene studies (and one small GWAS (106)), have tested for genetic associations with response to TNF antagonists such as etanercept, adalimumab and infliximab, often pooling observations for multiple drugs. Robust associations have until recently been scarce, but we are beginning to see better-powered investigations; a recent Danish study found significant associations with anti-TNF response in several immune genes (107). We recently showed via a comparative approach that *HLA-C*06:02* status could inform choice of treatment between adalimumab and ustekinumab, particularly when used in combination with clinical factors. Specifically, we found that *HLA-C*06:02*-negative patients with psoriatic arthritis were significantly more likely to respond to adalimumab than ustekinumab after 6 months (odds ratio, 5.98; $p = 6.89 \times 10^{-5}$), with no such difference observed in *HLA-C*06:02*-positive patients (108). This has promising clinical utility.

PRS may also help to define strata relevant to the management of psoriasis. Several studies have explored the predictive ability of PRS in psoriasis susceptibility (36, 109, 110) but the true translational benefits of this approach may lie in identifying and characterising groups of patients with very high or very low PRS scores (74). More research in this area in psoriasis is therefore warranted.

PUSTULAR PSORIASIS

Pustular psoriasis is a rare subtype characterised clinically by the presence of sterile pustules on variably erythematous skin, and histologically by diffuse dermal neutrophilic infiltration (111). It can be classified as either acute generalised (generalised pustular psoriasis (GPP)) or chronic localised disease (palmoplantar pustulosis (PPP) and acrodermatitis continua of Hallopeau (ACH)) (112). Pustular psoriasis has a distinct genetic architecture to plaque psoriasis, underscored by a lack of association with the *PSORS1* locus (113). The severity and rarity of the clinical phenotype indicate that pustular psoriasis could be associated with rare alleles of moderate to large effect, which has been supported by the identification of three disease genes (*IL36RN, AP1S3* and *CARD14*) using next-generation sequencing technologies (Box 1).

Linkage studies of consanguineous pedigrees and exome sequencing of unrelated GPP patients identified autosomal recessive loss of function mutations in *IL36RN* (114, 115). *IL36RN* encodes the IL-36 receptor antagonist (IL-36Ra), which modulates the activity of the IL-1 family cytokines IL-36α, -β and -γ. The screening of expanded patient resources subsequently identified a spectrum of *IL36RN* mutations that are distributed throughout the length of the protein and are associated with pustular psoriasis in a variety of populations (116, 117).

Genotype-phenotype analyses indicate that *IL36RN* disease alleles are less common in individuals with PPP (frequency 0.03) than GPP (0.19) and ACH (0.16) (116). Although recessive *IL36RN* alleles are typically observed in patients presenting with a severe clinical phenotype (early-onset GPP characterised by a high risk of systemic involvement) (118), deleterious *IL36RN* variants have also been associated with localised pustular disease (119). Individuals harbouring a single *IL36RN* mutation are occasionally affected, and they classically present with disease at a later age, indicating a dose-dependent effect (116, 118). Thus, genotype-phenotype analyses provide evidence for variable penetrance of disease alleles and a potential role for genetic modifiers and environmental factors.

Since *IL36RN* mutations are only found in a minority (~25%) of pustular psoriasis cases (118), exome sequencing was undertaken to gain a better understanding of the genetic basis of the disease. This uncovered two recurring founder mutations in the *AP1S3* gene (120). While these defects were found to account for 12% of pustular psoriasis cases of European descent, no AP1S3 mutations were found in Asian patients. AP1S3 encodes the σ1 subunit of AP-1, an evolutionarily conserved

hetero-tetramer that has been implicated in the formation of autophagosomes (specialised vesicles that mediate autophagy). Autophagy is an intracellular degradation pathway for misfolded proteins and damaged organelles (121) and has been shown to regulate cutaneous immune responses (122, 123). *AP1S3* mutations may lead to defective autophagy, causing accumulation of p62 (an adaptor protein that mediates NF-kB activation) and upregulation of IL-36 mediated cutaneous inflammation (124). Therefore, mutations in different disease genes converge on the de-regulation of IL-36 signalling in pustular psoriasis, highlighting IL-36 blockade as a promising therapeutic strategy regardless of the specific gene affected.

CARD14 was subsequently confirmed as a third disease gene for GPP (25). *CARD14* is highly expressed in keratinocytes and encodes a scaffold protein that, upon oligomerisation, mediates TRAF-2 dependent activation of NF-κB signalling. A deleterious gain-of-function substitution in *CARD14* has been associated with GPP in an extended case series and shown to cause spontaneous CARD14 oligomerisation *in vitro* (25). The same variant was also found in two patients with PPP (125), which provides further evidence for an overlap in the genetic basis of generalised and localised forms of pustular psoriasis. Indeed, gain-of-function *CARD14* mutations have been detected in cases of familial plaque psoriasis (23, 24), indicating shared aetiological mechanisms in plaque and pustular subtypes of disease.

There is a substantial unmet need for effective treatments for pustular psoriasis (111). The conventional systemic agents used for the treatment of plaque psoriasis are often ineffective in pustular phenotypes and there is a paucity of robust clinical trial data, such that current guidelines are mostly based on isolated case reports (111). However, recent exciting progress in this area shows a clear throughline from genetic discovery to treatment advances. IL-1 blockers are being investigated as potential treatments for pustular psoriasis and a multicentre double-blind randomised controlled trial of anakinra in PPP is currently underway (http://apricot-trial.com/). In GPP, anakinra has been shown to cause initial rapid clinical improvements in case reports (126, 127), although full disease remission was seldom achieved. This incomplete response supports the notion that IL-1 itself is not the dominant disease driver but participates in positive regulatory feedback loops driven by IL-36 (128).

In vivo and *ex vivo* research has validated IL-36 signalling as a powerful therapeutic target in psoriasis, and indicates that IL-36 blockade would not substantially compromise host defences (129). A recent phase I proof of concept study of 7 patients demonstrated that blockade of the IL-36 receptor (using a single intravenous dose of a monoclonal antibody) reduced the severity of GPP over a 20-week period (130). The agent was efficacious irrespective of the presence of known causal genetic variants and larger scale clinical trials of IL-36 antagonists in pustular psoriasis are currently underway.

FINAL THOUGHTS

Non-European ethnicities

We have shown that genetics will be instrumental in moving healthcare provision towards stratified, and even personalised, models. However, such progress is dependent on robust genetic associations with disease susceptibility, clinical outcomes and other related traits. The majority of genotyping efforts to date have focused on populations of European, and to a lesser extent Han Chinese, origin, meaning the translational potential of GWAS is largely limited to these groups at present.

A trans-ethnic GWAS meta-analysis of psoriasis susceptibility demonstrated heterogeneous genetic associations between European and Han Chinese populations (20). Other ethnic groups in which smaller GWAS and candidate gene studies have been undertaken include Indian (131), Japanese (132) and Omani Arab (133) populations. We are unaware of genetic studies of psoriasis in people of African descent. While lower prevalence might make psoriasis a smaller population burden among predominantly non-white populations (134) the disease burden for individual psoriasis patients is high, and large-scale genetic studies across ethnic groups are warranted.

Such endeavours will benefit from recent community efforts to generate the necessary supporting resources, including statistical tools for trans-ethnic meta-analysis (135), reference panels for genome-wide (136) and HLA allele (137) imputation, and GWAS summary results for common traits (138).

The future of genetics in psoriasis

As with other complex diseases, we believe that genetics will be at the heart of future success in translational psoriasis research. Increasingly large GWAS studies will improve power to detect genetic variants with small effects on psoriasis risk, refining our understanding of the genetic basis of the disease. This increased resolution should allow more accurate deconvolution of susceptibility associations into functional mechanisms of disease, aided by a growing catalogue of systematically derived and publicly available GWAS datasets for intermediate molecular traits. There is also an increasing awareness in the investigative dermatology community of the importance of precise phenotyping. When combined with genetic data, larger and more detailed clinical datasets will help reveal genetic differences between patients that differ in phenotypic presentation or outcome and therefore inform the development and deployment of effective therapies. Finally, as patients become more likely to undergo GWAS profiling or whole-genome sequencing as part of standard healthcare provision, there will almost

certainly be benefits to be derived from PRS or related genome-wide measures. These benefits are unlikely to come from very precise diagnostic or prognostic predictions but rather from prioritising individuals for early screening or closer monitoring, thus making optimal use of clinical resources and reducing the significant disease burden of psoriasis at the population level.

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REVIEW ARTICLE

The Woronoff Ring in Psoriasis and the Mechanisms of Post-inflammatory Hypopigmentation

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The Woronoff ring is a ring-like hypopigmentation zone around regressing psoriasis lesions. Although it was first described more than 100 years ago, its aetiology has remained a mystery. Recent insights into the pathogenesis of psoriasis can now explain the origin of the Woronoff ring. Psoriasis involves an HLA-class I-restricted autoimmune response of CD8⁺ T cells against melanocytes in the epidermis. The pathogenic CD8⁺ T cells are not cytotoxic, but are characterized by the production of interleukin-17, interleukin-22 and tumour necrosis factor-α. Interleukin-17 and tumour necrosis factor-α act synergistically on melanocytes by increasing proliferation while inhibiting melanogenesis. This reduces the cellular melanin content despite an increased number of melanocytes in psoriatic lesions. As a consequence, during healing the prior influence of interleukin-17 and tumour necrosis factor-α, despite the increased density of melanocytes, leaves a hypopigmented zone at the edge of regressing psoriasis lesions, which becomes visible as the Woronoff ring. This mechanism can explain a long-discussed puzzling phenomenon in dermatology.

Key words: psoriasis; Woronoff ring; melanocytes.

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SIGNIFICANCE

The Woronoff ring is a depigmented zone arising around healing psoriasis plaques. Analysed in detail for the first time approximately 100 years ago, our current understanding of the pathogenesis of psoriasis enables its explanation due to the cytokine pattern of the T-cell-mediated pathogenic melanocyte-specific psoriatic autoimmune response. The production of interleukin-17 and tumour necrosis factor-α causes suppression of melanin synthesis with a simultaneous increase in melanocyte proliferation. This results in an inflammation-induced hypopigmentation surrounding the healing psoriasis lesions. The emergence of the phenomenon is thus coherently integrated into our immunological understanding of psoriatic pathogenesis.

Nearly 100 years ago, Dr D. L. Woronoff, a dermatologist at the clinic for skin diseases of Moscow University in Russia, published his investigations on a pale annular zone that was known to appear around healing psoriasis lesions, and was thought to be caused by a spastic vessel contraction or hypopigmentation (1). He described the clinical appearance of these rings as a "pseudoatrophic" annular zone surrounding acanthotic psoriatic plaques, and gave a precise histological description (**Fig. 1**). He reported that this zone was histologically distinct from both the psoriasis plaque and the surrounding normal skin due to the absence of parakeratosis in the stratum granulosum, a broadened stratum Malpighii due to more layers of living cells leading to increased epidermal thickness, and irregularly shaped papillae without dilation of the capillaries. He concluded

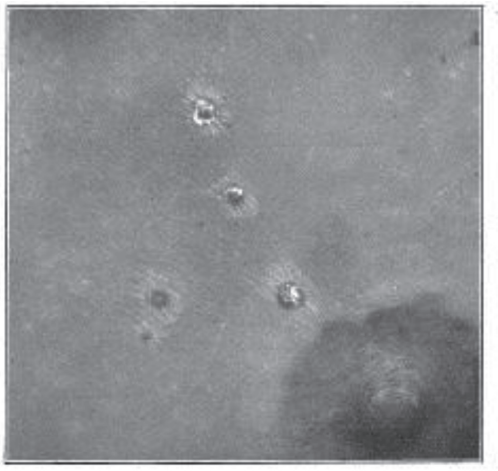

Abb. 1.

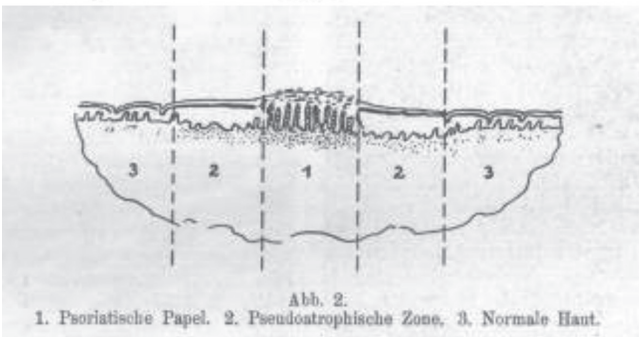

Abb. 2.
1. Psoriatische Papel. 2. Pseudoatrophische Zone. 3. Normale Haut.

Fig. 1. The pseudoatrophic zone around the psoriatic papules and scheme of histological changes. From the original publication by Woronoff, 1926 (1).

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that this zone, which he sketched in a scheme (Fig. 1), inhibited further development of the psoriatic plaque and was more likely to result in regression of psoriasis lesions. Since he also observed these changes around corymbiform syphilitic skin lesions, he concluded that these "achromatic phenomena" were to the utmost extent better able to withstand all possible pathological stimuli than normal skin.

Based on these studies, the annular zones of hypopigmentation developing around psoriatic skin lesions are referred to as the Woronoff ring. The Woronoff ring is a phenomenon that is mentioned in major dermatological textbooks as a morphologically distinct alteration of healing psoriasis plaques, and it has been occasionally addressed in the medical literature with only a few photographic illustrations. The width is usually between 2 and 6 mm, with regional fluctuations, and increases with the size of the central psoriatic plaque (2). The Woronoff ring has been observed after ultraviolet (UV) phototherapy or photochemotherapy (3), topical treatment, such as anthralin (4) or glucocorticosteroids, or systemic treatments including fumaric acid esters (5) or the tumour necrosis factor (TNF)-α antagonist adalimumab (6), but it may also occur spontaneously. The nature of the Woronoff ring is still not fully explained. This article discusses the aetiology of the Woronoff ring in terms of new insights into the pathogenesis of psoriasis, using the example of a patient who developed Woronoff rings around regressing psoriasis plaques under UV (311 nm) radiation therapy.

CASE REPORT

A 71-year-old female patient with a long history of psoriasis had undergone phototherapy with UVB (311 nm) radiation. The resolving psoriasis plaques developed annular zones of hypopigmentation and, further outward, circumferential hyperpigmentation (**Fig. 2**A). A biopsy from a whitish Woronoff ring showed a dense population of c-Kit$^+$ melanocytes in the basal epidermal layer (Fig. 2B) compared to lesional and normal skin (Fig. 2 C, D).

DISCUSSION

Different approaches have tried to explain the aetiology of the Woronoff ring. Disturbed vascularization, as discussed in early descriptions, appeared unlikely as a cause, since injections of prostaglandin E_2 (7), histamine phosphate and metacholine chloride (8) produced wheals with surrounding red flare involving both the Woronoff ring and adjacent normal skin. Furthermore, by measuring the cutaneous and subcutaneous blood flow in the Woronoff ring by the ^{133}Xe washout method, cutaneous vasoconstriction corresponding to a white dermographism could be excluded as the cause of the white discoloration (9). A major cause of the Woronoff ring was suspected in alterations in prostaglandin metabolism. Observation of a decreased level of prostaglandins in the tissue corresponding to the Wornoff ring has led to the hypothesis that UV therapy induces an inhibitor of prostaglandin synthesis, which causes the white ring by reducing inflammation (10). In addition, diminished inflammation in the Woronoff ring was attributed to a decreased level of endoglin, a scavenger of transforming growth factor beta (11). A histological study using the Masson-Fontana stain observed a marked decrease in the amount of basal-zone epidermal melanin in both the halo and the psoriatic lesions (8).

Recent insights into the psoriatic pathogenesis now provide another explanation for the aetiology of the Woronoff ring. The HLA-class I allele, HLA-C*06:02, is the main psoriasis risk gene (12). Psoriasis develops upon epidermal recruitment, activation and clonal expansion of CD8$^+$ T cells (13, 14). CD8$^+$ T cells recognize peptides that are presented by HLA-Class I molecules. Because the peptide antigens are derived from intracel-

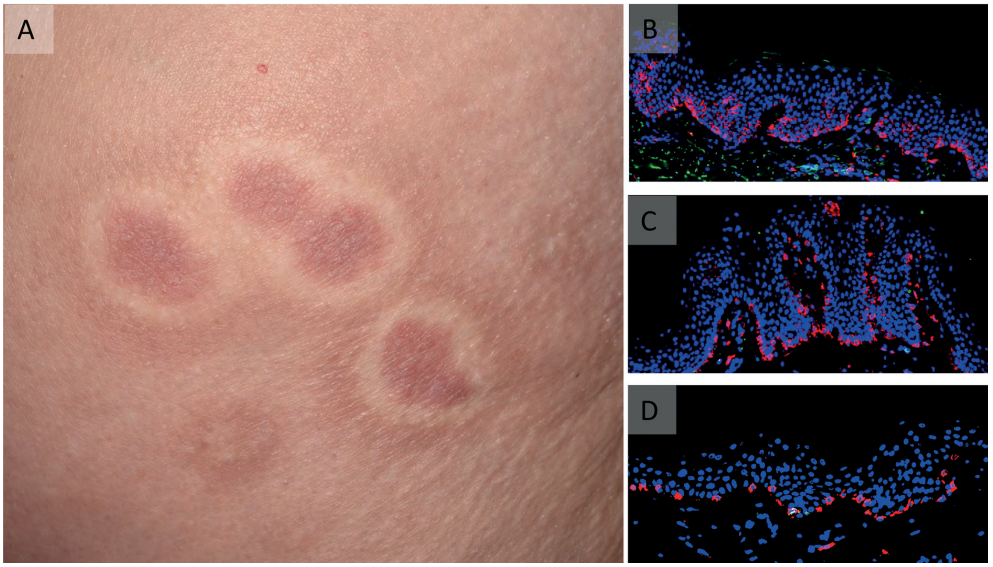

Fig. 2. Clinical features and immunostaining of melanocytes in patient and control skin. (A) Woronoff rings developing as depigmented zones around regressing psoriasis lesions during UVB (311 nm) radiation on the buttocks. Note the slight hyperpigmentation surrounding the depigmented halo. (B) Dense population of c-Kit+ melanocytes (red) in the basal epidermal layer of a biopsy from a Woronoff ring compared with (C) a psoriasis lesion or (D) normal skin; blue: DAPI. Staining by Akiko Arakawa, MD, PhD. Original magnification ×25.

lular proteins, an HLA-class I-restricted pathogenic $CD8^+$ T-cell response is primarily directed against a particular target cell type expressing the parent protein of said antigenic peptides (15, 16). In fact, in psoriasis HLA-C*06:02 mediates an autoimmune response against melanocytes through autoantigen presentation as the underlying pathomechanisms of T-cell mediated chronic inflammation (17).

The pathogenic psoriatic $CD8^+$ T cells represent a particular subtype of epidermal $CD8^+$ tissue-resident memory cells. Such $CD8^+$ T cells are characterized by the expression of CD103 and by CD69, and develop in the skin from epithelium-infiltrating precursor cells (18). CD103 is the α subunit of the $\alpha_E\beta_7$ integrin receptor, binds E-cadherin, which is highly expressed on epithelial cells and thus promotes lodging of $CD8^+$ T cells in the epidermis (19), while CD69 inhibits egress of T cells from tissue via the sphingosine 1-phosphate receptor 1 (20, 21). The epidermal psoriatic $CD8^+$ T cells belong to the $T_{helper/cytotoxic}17$ ($T_{h/c}17$) T cell type and produce the cytokines interleukin (IL)-17, TNF-α and IL-22 (22), which are the signature cytokines of the lesional psoriatic immune response (23). These cytokines promote the epithelial hyperplasia, accumulation of neutrophilic granulocytes and production of antimicrobial peptides, and thus convey the clinical manifestation of psoriasis with the scaly erythematous squamous plaques.

In addition to these clinically apparent cytokine effects, IL-17 and TNF-α have another impact: they alter the functional state of melanocytes. IL-17 and TNF-α synergize in reducing skin pigmentation while promoting melanocyte proliferation (24). They inhibit pigmentation-related signalling and melanogenesis by suppressing pigmentation-related genes and lowering cellular tyrosinase levels in melanocytes, thereby reducing cellular melanin content. IL-17 and TNF-α further jointly induce the expression of melanocyte mitogens, including CXCL1 and IL-8, thus enhancing melanocyte proliferation. In psoriasis, epidermal melanocytes are under the constant influence of IL-17 and TNF-α. Accordingly, the combined effect of these 2 cytokines causes hypopigmentation and, at the same time, increases the number of melanocytes by stimulating melanocyte proliferation, which is reflected by the expression of the proliferation marker Ki67 on melanocytes in psoriatic lesions (24). This impact on melanocytes can now explain the emergence of the Woronoff ring. During healing, the effect of IL-17 and TNF-α leaves a hypopigmented zone on the edge of regressing lesions, where melanogenesis is still suppressed despite the increased density of melanocytes along the basement membrane (Fig. 2B) seen in lesional psoriatic skin (24, 25). The progressive recovery of pigmentation genes, along with the numerically increased melanocytes can then lead to an abundant melanin production and thus cause post-inflammatory hyperpigmentation. This is already evident here as a hyperpigmented zone around the Woronoff ring (Fig. 2A) and can eventually induce hyperpigmentation of the entire lesion. Accordingly, selective therapeutic blockade of TNF-α or IL-17 caused rapid recovery of pigmentation and post-inflammatory hyperpigmentation in healing psoriatic lesions of treatment responders (24). The ring may develop if the psoriasis plaques regress centripetally and not evenly over the entire lesion, so that a remaining central plaque is surrounded by a healed skin zone. If the psoriasis lesions evenly heal, either a uniform post-inflammatory hyperpigmentation or hypopigmentation may remain at the site of the former psoriasis plaque, as is often observed.

At the same time, these findings raise the question of how psoriasis differs from vitiligo. Both diseases are based on an autoimmune response against melanocytes. The pathogenic T cells of vitiligo correspond with the expression of $CD8^+CD103^+CD49a^+$ to a tissue-resident memory phenotype, which is characterized by a high production of interferon (IFN)-γ and has the protective purpose to mediate local immunity to viruses (26). CD49a is the α-subunit of the $\alpha_1\beta_1$ integrin receptor and is expressed on ~15% of all skin-derived T cells (27). The $CD8^+CD103^+CD49a^+$ T cells express cytotoxic granules including granzymes and perforins and have a high cytotoxic potential, which can be further amplified by IL-15 (26). When activated in an autoimmune response against melanocytes they promote T-cell-mediated killing of melanocytes and induce the persistent depigmentation of vitiligo through the permanent elimination of melanocytes. The melanocyte-specific $CD8^+CD103^+$ psoriatic T cells are clearly distinguished from the melanocyte-specific $CD8^+$ T cells of vitiligo by the absence of the expression of CD49a, by a different cytokine transcription profile and a lack of cytotoxicity, which even IL-15 cannot overcome (26). Instead, they belong to the $T_{h/c}17$ phenotype, whose actual role is the antimicrobial immune defence against extracellular bacteria and fungi (23, 28). When activated against melanocytes in psoriasis, they are not cytotoxic, but induce an antimicrobial, yet sterile, immune reaction. Psoriasis can therefore be considered as a T-cell-mediated antibacterial defence reaction against melanocytes (29, 30). The reason for the different functional outcomes of the melanocyte-specific autoimmune response in psoriasis and vitiligo may lie in the different genetic predisposition of the 2 diseases. According to genome-wide association studies, psoriasis and vitiligo arise on a different genetic background and HLA-association, which may then decide the respective functional differentiation of the pathogenic immune response (31, 32).

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REVIEW ARTICLE

Psoriasis and Treatment: Past, Present and Future Aspects

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The management of psoriasis has evolved considerably over the past 100 years. This has occurred in parallel with our understanding of the pathogenesis of this common, complex and enigmatic disease. It should be celebrated as an outstanding example of successful translational research. With precise targeting of immune pathways for the treatment of psoriasis with new biologics and small molecules has come the realisation that the most effective approach to patient management is a holistic one which encompasses the biopsychosocial nature of the disease. This involves a stratified medicine approach to identifying the best drug for an individual allied to patient education, screening for comorbidity, and regular review as both the clinical presentation and the patient's needs will change over time. Although there is not yet a cure for psoriasis – the whole person, systems approach to patient management, that is in part dependent on early intervention, should help to ensure an optimal outcome.

Key words: psoriasis; treatment.

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SIGNIFICANCE

Psoriasis is a common and disfiguring chronic skin condition. Over the past 100 years, our understanding of the disease has improved and as a direct result, more effective therapies have been developed. In addition to the cutaneous manifestations, it is associated with an increased risk of psoriatic arthritis, depression and cardiovascular disease. The best approach to care is an individualised one which focuses on improving the physical symptoms of the rash while proactively screening for and treating any associated comorbidities to minimise the impact of the disease and empower patients to live well.

This psoriasis-themed edition of *Acta Dermato-Venereologica* provides an opportunity to reflect on the progress which has been made in the treatment of psoriasis over the intervening 100 years since the journal was established in 1920.

The first volume of the journal featured a patient with 'psoriasis universalis' (1); a case which would fit with our current definition of erythrodermic psoriasis. The patient was treated with, a to us unusual, combination of bran baths, borvaseline emollient and injections of sterilised milk. An improvement was noted after the third cycle of injections, at which point cignolin (dithranol) was introduced to treat the remaining plaques. Fortunately, therapies for patients have evolved greatly in terms of efficacy, safety and tolerability. Over the past century therapies for psoriasis were more commonly discovered by chance and recommendations were largely based on anecdote. Today, serendipity still plays a role in the advancement and discovery of therapies but the reductionist approach to targeted therapies and evidence-based guidelines hold sway (2).

One hundred years ago, psoriasis was recognised as a relapsing and remitting skin condition for which temporary remission, but not cure, was possible with treatment (3). Although a cure remains elusive, treating psoriasis as an isolated skin disease is widely viewed as an outdated approach. The condition is now accepted as a systemic immune-mediated inflammatory disease associated with several comorbidities including psoriatic arthritis, mood disorders and cardiovascular disease. When selecting therapy, several factors should be considered in addition to the extent and clinical severity of the cutaneous involvement. These include psoriasis phenotype and previous treatment history, clinical severity and psychosocial impact, presence of psoriatic arthritis and other comorbidities, concomitant medications, conception plans and of course individual preferences and treatment goals. An effective approach to treatment is holistic, recognising the multi-faceted nature of the disease, and should be flexible as this chronic disease evolves and patient needs change over time.

The evolution of psoriasis treatment over the past century is an excellent example of successful translational research whereby an enhanced understanding of the pathogenesis of the disease has facilitated the development of increasingly precise targeting of therapies. Biologics are the proof of concept in this modern approach to drug design and development and the management of patients with moderate-severe disease has been transformed by these therapies. Complete skin clearance or psoriasis area and severity index (PASI) 100 has become a realistic treatment goal with use of the recently available anti-interleukin (IL) 23p19 therapies. Despite this progress, patients face many challenges including timely access

to appropriate care; the cost of under-treatment to the individual and to society remains and is considerable (4).

This review outlines the major treatments used for psoriasis over the past 100 years, focusing on important milestones through the decades. It illustrates a shift in approach from serendipity to science, as modern-day drug development is based on targeting key effector molecules in psoriasis, and a shift to a whole patient approach to care.

1920's

Even a hundred years ago, a variety of treatments, both systemic and topical, were available for psoriasis and salicylic acid, coal tar and dithranol preparations were all in use. **Fig. 1** illustrates those therapies which were available 100 years ago and tracks major therapeutic developments to the present day.

In the 19th century, arsenic became established as a popular treatment for psoriasis. It was trialled for a variety of dermatological conditions but appeared to be most effective for psoriasis. It was taken orally or applied topically – and even added to spa water. A narrow therapeutic range meant it was usually ineffective at low doses, and high doses were associated with clinically significant ocular and gastrointestinal tract disturbances (5). With more widespread prescription, the adverse effects associated with chronic use became more apparent. Cutaneous adverse effects including hyperpigmentation, keratotic and cancerous growths were noted towards the end of the 19th century but it continued to be used to treat psoriasis during the first half of the 20th century. Today, arsenic toxicity is well recognised (6).

Balmanno Squire first described the use of Goa powder (chrysarobin), a forerunner of dithranol (anthralin), for the treatment of psoriasis and published this in the British Medical Journal in 1876 (7). Produced from the araroba tree in Brazil, Goa powder had been used for centuries to treat fungal infections. Squire used Goa powder for a patient with psoriasis who he thought had tinea corporis; the psoriasis cleared prompting his accidental discovery of it as an effective treatment for the condition. Importing this product from Brazil to Europe became difficult during World War 1; in 1916, a synthetic version known as cignolin or dithranol was synthesized which seemed more efficacious than the natural variant. There is a correlation between efficacy and side-effects of irritancy and discoloration of skin, nails, clothes. In 1953, Ingram suggested using dithranol as a photosensitiser with ultraviolet-B radiation (UV-B) (8). The use of short contact dithranol became popular in the early 1980's. This involves applying a concentrated version of dithranol which is washed off after a few minutes and so is more practical and acceptable for patients. Nowadays dithranol is used only rarely by outpatients with most cases being treated in day treatment centers or as inpatients.

X-rays were first used to treat psoriasis at the beginning of the 20th century. Carcinogenic and other side effects became apparant over time, and so this method was phased out by the 1950's (3, 9). The beneficial effects of heliotherapy in treating psoriasis were first reported in 1923 (10), although patients had been aware, for centuries, that sunlight improves their psoriasis. In 1925, Goeckerman used a high-pressure mercury lamp to produce artificial broadband UV-B and demonstrated that the effect of UV-B was enhanced with prior application of crude coaltar as a photosensitiser (11).

1950's

Corticosteroids were discovered in 1950 and two years later, the first report of a topical steroid (17 hydroxycorticosterone-21-acetate) used to treat two patients with psoriasis was published; it did not have any noticeable

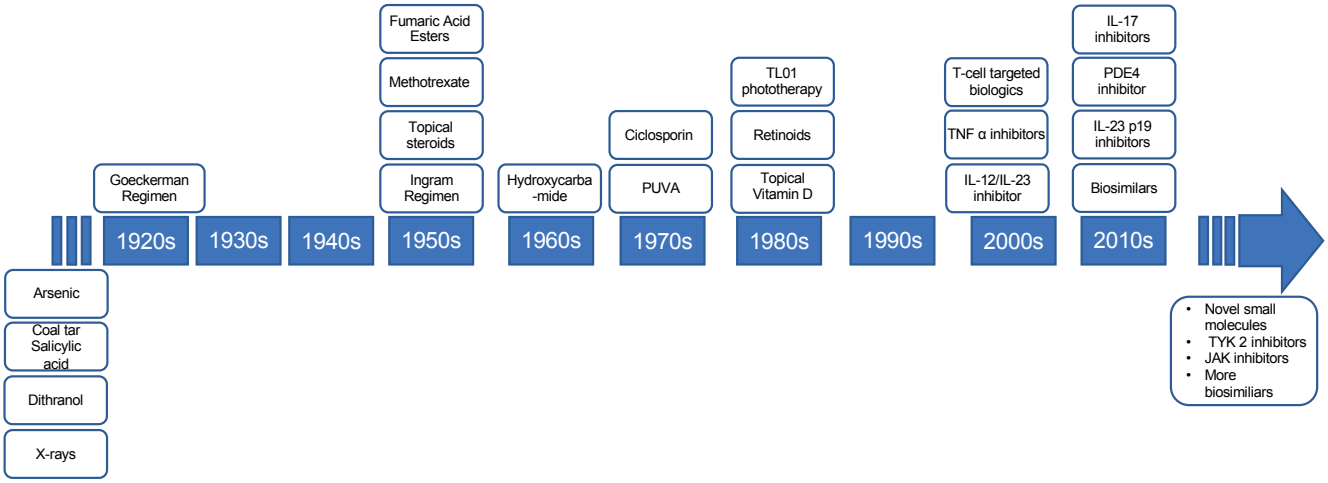

Fig. 1. Advances in the treatment of psoriasis over the past century. This timeline illustrates the major pharmacological advances which have occurred in the management of psoriasis over the past 100 years. It also speculates as to what may be the important therapies in the near future. IL: interleukin; PDE: phosphodiesterase; PUVA: psoralen plus ultraviolet (UV)-A; TNFα: tumour necrosis factor alpha; TYK: tyrosine kinase; JAK: janus kinase.

effect which may have been due to its low potency (12). Following this report, the structure of the compound was modified and by the end of the 1950's, a variety of local and systemic corticosteroid drugs had been developed. Prednisolone and triamcinolone were both shown to be moderately effective when taken orally (3). In the early 1960's, potent topical steroid preparations were developed including betamethasone 17-valerate (Betnovate®) and fluocinolone acetonide (Synalar®) marking a significant breakthrough in the treatment of dermatoses in general. We now know that potent steroids only suppress psoriasis temporarily. Today, topical corticosteroids are the acknowledged first line recommended topical therapy either alone or in combination with vitamin D analogues (2). They are known to have an anti-inflammatory, immunosuppressive, and anti-proliferative mechanism of action in psoriasis. Steroid-related side effects are well recognised however, and include skin atrophy with increasing potency, tachyphylaxis, suppression of the pituitary-adrenal axis, and a rebound phenomenon which may lead to psoriasis becoming unstable or pustular.

Methotrexate was first used to treat psoriasis in the early 1950's. Aminopterine, a folic acid inhibitor which had been used to treat leukaemia, was shown to suppress arthritis experimentally. Thus, it was trialled in a group of patients with rheumatoid arthritis. One of these patients had psoriasis which improved markedly. The authors of this original report proposed that aminopterine probably worked via direct effect on epithelial cells; at the time, psoriasis was thought to be a disorder of keratinocytes (13). Ametopterine (methotrexate) a next generation folic acid antagonist was subsequently developed; it was shown to be as effective as aminopterine but less toxic (14). Methotrexate is currently recommended as first line therapy for most people with psoriasis who are eligible for systemics. It is also effective for psoriatic arthritis (15). It is typically given as a once weekly oral dose. Folic acid supplementation is recommended when prescribing methotrexate. Folic acid use may also decrease the gastrointestinal and mucosal side-effects of methotrexate (16) whilst having a protective effect against hepatotoxicity (17). Its specific mechanism of action remains uncertain. It is thought to exert an anti-inflammatory effect via adenosine pathways. Some of the immunomodulatory effects are mediated through the inhibition of nucleic acid synthesis in keratinocytes and activated T cells (18). A recent meta-analysis showed that 45% of patients achieve PASI75 at primary endpoint (12 or 16 weeks, respectively) (19). The side effect profile of methotrexate is well characterised, in particular the hepatotoxicity risk. Appropriate patient selection to minimise this risk is important (2) and subcutaneous administration may reduce gastrointestinal side-effects and enhance efficacy (20).

The German chemist Schweckendiek was the first to use fumaric acid esters FAE to treat psoriasis in the late 1950's. He postulated that psoriasis occurred due to a deficiency in fumaric acid levels leading to defects in the Krebs citric acid cycle, and that oral supplementation of fumaric acid might neutralize these defects. He suffered from psoriasis, and used esters of fumaric acid in self-experimentation (21). The drug was subsequently modified to produce Fumaderm®, which comprises dimethyl fumarate (DMF), and calcium, magnesium, and zinc salts of monoethyl hydrogen fumarate; licensed for oral use in Germany since 1994. A second oral product, Skilarence® (dimethyl fumarate as a single acid ester), was introduced to the European market for the treatment of psoriasis in 2017. The mechanism of action of (FAE) remains unclear, but evidence suggests that it has nothing to do with the Krebs cycle. Recent systematic reviews have investigated the efficacy and safety of FAE using data from randomised controlled trials (22, 23). Meta-analysis showed that a PASI50 response rate at 12–16 weeks was achieved by 64% receiving FAE compared to 14% in the control group – it was not possible to calculate PASI75. It is ineffective for treating psoriatic arthritis. Of note, 8–39% of patients discontinue FAE treatment owing to adverse events, mostly relating to intolerable gastrointestinal or flushing complaints (23).

1970's

Psoralens, photosensitisers extracted from plants, have been used for centuries to manage skin conditions such as vitiligo. The beneficial effect of topical and the subsequent use of oral psoralens combined with UVA (PUVA) in treating psoriasis was first reported in 1973 (24) and subsequently became widespread (25). It was the most effective systemic therapy in use for psoriasis in the 1980s. PUVA can increase the lifetime risk of cutaneous squamous cell carcinoma, and this limits its use (26); indeed the use of PUVA has diminished markedly in recent years as it has been usurped by narrow band UVB, which was introduced in the 1980s after it was found to be more effective than broadband UVB in the treatment of psoriasis (27, 28).

In 1979 it was reported, serendipitously, that ciclosporin improved psoriasis in patients with psoriatic arthritis (29). By this time, it was already known to be an immunosuppressant drug which exerted its effect through inhibition of T-cell proliferation and had transformed outcomes in solid organ transplant recipients (30), but the mechanism of action in treating psoriasis remained unclear. A few years later, the active selective recruitment of T-helper cells into psoriasis plaques was demonstrated (31, 32). The authors proposed that psoriasis should be considered a T-cell-mediated disease and this hypothesis was subsequently proven by the remarkable efficacy of ciclosporin in its treatment (33). Today, there is substantial evidence for efficacy of ciclosporin in psoriasis vulgaris (34) but its use is limited by a relatively narrow therapeutic index. Nephrotoxicity and hypertension

are the most significant common risks of ciclosporin. Nephrooxicity risk is directly related to the dose and duration of ciclosporin (35). Thus, single or intermittent short courses of up to 16 weeks are recommended to limit nephrotoxicity (34, 35). Ciclosporin is particularly effective for patients who need rapid or short-term disease control (for example a psoriasis flare), have palmoplantar pustulosis or are considering conception and systemic therapy cannot be avoided (2).

The discovery of ciclosporin marked a turning point in the history of psoriasis treatment and the direction of future translational research as it became clear that a deeper understanding and subsequent modulation of the immune system would lead to more effective disease control.

1980's

Vitamin D analogues were investigated in the 1980s for a range of dermatoses. Calcipotriol, a vitamin D3 analogue, was shown to be effective in reducing proliferation and inducing differentiation of epidermal keratinocytes, indicating potential efficacy when used topically for psoriasis (36, 37). This therapy was subsequently shown to be significantly more effective than either dithranol (38) or tar (39). Although not as effective as potent topical steroids, calcipotriol has the advantage of not being subject to the same side-effects. Calcipotriol may protect against corticosteroid-induced dermal atrophy (40). Local irritation at the site of application affects up to 20% of patients (41) and this may lead to discontinuation. The vitamin D analogue calcitriol tends to be less irritating than calcipotriol and so may be better tolerated on face and flexural sites (42). Combination of calciptriol and betamethasone valerate as either ointment, cream, gel, or, more recently, a foam spray preparation, has proven to be a highly effective topical preparation for psoriasis (43).

The importance of vitamin A in maintaining healthy skin was recognised over 100 years ago. Synthetic vitamin A drugs, retinoids, were subsequently developed and trialled for a variety of skin diseases. Etretinate was found to improve psoriasis but this was replaced by acitretin, its pharmacologically active metabolite, in the late 1980s, because of a more favourable and less lipophilic pharmacokinetic profile. The precise mechanism of action is not understood. It is believed to interfere with epidermal growth factor receptor gene expression which reduces epidermal cell proliferation and differentiation to a normal rate (44). Additional anti-inflammatory effects may be mediated through nitric oxide (45).There is considerable variability in reported effectiveness of acitretin and anecdotally, it tends to work best for the less common pustular and erythrodermic variants of psoriasis (46). Acitretin may be combined with PUVA which is more effective than PUVA alone, reducing the number of PUVA treatments needed and hence UVA exposure (47). The use of acitretin is limited by its safety profile. It is highly teratogenic and pregnancy should be avoided for at least 2 years after the last dose. These days, acitretin is recommended for adults and in exceptional cases for children and young people if other conventional systemics (ciclosporin and methotrexate) are not appropriate or have failed, and for cases of pustular psoriasis (2).

With the development of an increasing number of systemic therapies, it became apparent that a valid and objective approach to the assessment of cutaneous disease severity and response to treatment was needed for psoriasis. Fredriksson & Pettersson created the PASI in 1978 as an objective means to evaluate the clinical efficacy of retinoids for psoriasis (48). Today, it is the most widely recognised outcome measure in psoriasis management. The Dermatology Life Quality Index (DLQI), the first dermatology-specific health-related quality of life questionnaire, was published several years later in 1994 (49). Although not specific for psoriasis, it is widely used to assess the subjective effectiveness of psoriasis treatments and their effect on quality of life.

BIOLOGICS ERA

Biologics are a subgroup of drugs comprised of large complex protein molecules including monoclonal antibodies and receptor fusion proteins. Unlike the traditional systemics which are taken orally, these are administered parenterally – as they would otherwise be degraded by the gastrointestinal tract. These target specific components of the immune system that are involved in psoriasis pathogenesis.

Biologics are indicated for moderate-severe psoriasis which has not responded to conventional systemic therapies. This licensing reinforces the current stepwise approach to psoriasis treatment. Patients with mild or limited extent disease are typically prescribed topical therapy in the first instance. If this is not sufficient, they are deemed to have moderate-severe disease and phototherapy or conventional systemic therapies (methorexate, ciclosporin, acitretin) are used next. If these fail, small molecule therapies (FAEs, apremilast) or biologics are indicated. Unfortunately, we do not yet have the tools in clinical practice to predict which patient will respond favourably to a given drug. As a result, between 11 and 35% of patients do not respond sufficiently to their first biologic drug during the first year of treatment, either because the drug is not effective or adverse effects develop (50).

2000's

T-cell targeted biologics

Research on the mechanism of action of ciclosporin in treating psoriasis (29) affirmed it being a T-cell-mediated

disease, and subsequent mouse models added further evidence to the theory that immune cells are the primary effector cells in driving the disease (51). Ensuing from this, the first biologics to be developed for the treatment of psoriasis targeted T cells.

The first was alafacept, which was approved for psoriasis use in 2003. This is a human lymphocyte function-associated antigen (LFA)-3/immunoglobulin (Ig) 1 fusion protein. It binds to CD2 molecules on the surface of activated T cells, blocking their co-stimulation by antigen presenting cells. It selectively targets memory-effector T cells, blocking their activation and migration (52, 53). Despite high hopes resulting from the known mechanism of action of this drug and what was known about the pathogenesis of psoriasis at that time, the results of phase III studies indicated a modest overall efficacy (54, 55). The overall PASI75 response rate was 33%. Median duration of remission (time to retreatment or maintenance of PASI50) was 7 to 10 months in phase II and III studies (56). In 2011, alefacept was withdrawn from the market as it had become clear that more efficacious and cost-effective options had become available.

Efalizumab was the first biologic to be approved in the UK for the management of psoriasis in 2003. This drug is a humanized monoclonal IgG1 antibody, directed against CD11a, the α-subunit of LFA-1. This inhibits T-cell trafficking into the skin. In phase III studies, the PASI75 response rate was approximately 30% when compared to placebo (57, 58). Increasing the duration of treatment from 12 to 24 weeks resulted in a PASI75 of 44% (58). Post-marketing drug surveillance revealed an association between long-term treatment with efalizumab and progressive multifocal leukoencephalopathy (PML) which is a rare but life-threatening infection of the central nervous system (59). As a result, efalizumab was withdrawn from the market in 2009. This reminds us of the importance of monitoring drug safety in the post-marketing phase.

Tumour necrosis factor-α inhibitors

Tumour necrosis factor (TNF)-α is recognised as a key effector cytokine in chronic immune-mediated inflammatory diseases, including psoriasis.

Etanercept was the first TNF-α inhibitor approved for treatment of psoriasis in 2004. It is a recombinant human TNF-receptor fusion protein. Each molecule can bind two TNF-α molecules. Phase III studies show that 100 mg weekly results in PASI75 at week 12 in 47–49% compared with placebo (60–62). Infliximab, a chimeric IgG1 monoclonal antibody which can bind to and neutralise soluble and membrane-bound TNF-α was approved for the treatment of severe psoriasis in 2006. This derived from the observation that it cleared the concomitant psoriasis of a patient in whom it had been administered for the management of Crohn's disease. Two phase III studies reported that intravenous infliximab 5 mg/kg at week 0, 2, and 6 resulted in PASI75 responses at week 10 of 75.5% and 80% compared with placebo (63, 64). This level of efficacy had not previously been recorded with any treatment for psoriasis. Adalimumab was approved for the treatment of psoriasis in 2005. Similar to infliximab, adalimumab is a fully human monoclonal antibody of the IgG1 isotype. PASI75 response rates of around 70% have been reported in clinical trials (65).

A meta-analysis has confirmed that infliximab is the most efficacious drug in this class in terms of PASI, followed by adalimumab (66). However, infliximab is associated with an increased risk of serious infection (67) and infusion reactions can occur.

Targeting TNF-α is particularly effective for treating psoriatic arthritis. Therefore, adalimumab is currently the recommended first line biologic for psoriasis with psoriatic arthritis (68). There are rare but potentially severe adverse events associated with this drug class including multiple sclerosis, congestive heart failure, opportunistic infection such as tuberculosis, and lupus. The risk of developing neutralizing anti-drug antibodies is well described for this class which in turn is associated with reduced clinical response to infliximab and adalimumab treatment (69).

Anti-TNFα therapies continue to develop and evolve. Certolizumab pegol (CZP) was licensed for psoriasis in 2018, and psoriatic arthritis in 2013. It is the only biologic agent with clinical trial data in its label supporting potential use in both pregnancy and breastfeeding. Prospective studies showed a lack of placental transfer of CZP from mothers to infants (70), and no to minimal transfer from plasma to breastmilk (71). The adalimumab and etanercept labels have recently been updated to allow potential use during pregnancy while acknowledging that they may cross the placenta (72). These recent developments have brought the issue of managing psoriasis in women of childbearing age into sharper focus, highlighting the specific challenges faced by this large group.

Ustekinumab anti-IL12/IL-23

Psoriasis was the first inflammatory disease for which ustekinumab was licensed by the US Food and Drug Administration (FDA) in 2009. It is a human IgG1 monoclonal antibody that targets the shared protein subunit p40 of IL-12 and IL-23. PASI75 response at week 12 in phase III studies was 66% (73) and 76% (74) and this was maintained at week 28. For patients with a bodyweight ≤100 kg the dose of ustekinumab is 45 mg and with a body weight of >100 kg the dose is 90 mg.

Registry data show that ustekinumab has a longer drug survival compared to the anti-TNF-α therapies (50, 75). Due to its effectiveness, weight-based dosing and safety record – it is recommended as first line biologic

for patients with psoriasis without psoriatic arthritis in the UK (68).

2010's

The current consensus is that psoriasis is a disease driven by the IL-23/TH17 cell pathway. For this reason, current therapeutic strategies are now focused on the development of novel agents that disrupt IL-23 or IL-17 cytokine signalling.

Three IL-17 pathway antagonists have been approved for the treatment of psoriasis: secukinumab was the first approved in 2015, and since then ixekizumab and brodalumab have come to market. Ixekizumab and secukinumab target IL-17A, while brodalumab targets the receptor subunit IL-17RA. Both secukinumab and ixekizumab have been approved for psoriatic arthritis. Phase III studies have demonstrated favourable efficacy and safety profiles. For the first time, significant numbers of patients are achieving PASI90 or PASI100 with treatment. In the CLEAR trial nearly 80% of patients treated with secukinumab achieved a PASI90 response at week 16 compared with only 58% in a comparison cohort treated with ustekinumab (76). The available safety information is overall reassuring, but there are specific adverse events associated with IL-17 inhibition, including increased risk of mucocutaneous candida and a slightly increased risk of developing inflammatory bowel disease (77). Four suicides were reported in clinical trials for brodalumab which raised some concern, but no causal relationship was demonstrated when these cases were reviewed (78). Bimekizumab is a novel drug in this class as it inhibits both IL-17A and IL-17F. The result of phase 3 comparative studies in patients with psoriasis and psoriatic arthritis are pending.

The latest biologic group to be licensed for the management of psoriasis are those which specifically target the p19 subunit of IL23. Three drugs have been licensed: guselkumab, rizankizumab and tildrakizumab. Guselkumab, the first of the 3 to be approved by the FDA in 2017, was compared to adalimumab in the VOYAGE 1 and 2 clinical trials. The PASI90 response at week 16 was 73% versus 50% (VOYAGE 1) and 70% versus 47% (VOYAGE 2), confirming the superior efficacy of guselkumab (79, 80). Guselkumab also showed superior long-term efficacy based on PASI90 at week 48 when compared with secukinumab (81).

In phase 3 studies comparing rizankizumab to ustekinumab at week 16, PASI90 was achieved by approximately 75% of patients receiving risankizumab versus 45% receiving ustekinumab and 4% receiving placebo (82). Pivotal trials for tildrakizumab selected PASI 75 at week 12 as the co-primary outcome measure. In one study, 64% of those who received the study drug achieved PASI75 compared to 9% of those who received placebo. In a subsequent clinical trial, 61% who received tildrakizumab and 48% who received etanercept achieved PASI75 (83).

The selective IL-23 p19 inhibitors have proved to be highly efficacious in clinical trials and no specific safety concerns have been raised to date (84). Although the depletion of IL17 by the anti-IL 17 biologics class has been associated with an elevated risk of opportunistic infections, mucocutaneous candida infections, and triggering or worsening of inflammatory bowel disease; the IL-23 p19 inhibitors have not been associated with these side effects (84). This is thought to be because residual IL17 is produced by non TH17 cells such as innate lymphoid cells and mast cells, so function is not clinically impaired. In addition, no increase in rates of malignancy, major adverse cardiovascular events, demyelinating disorders, active tuberculosis or reactivation of latent tuberculosis infection have been reported, although these have been associated with other biologic drug classes (84).

The real test will be how IL23p19 inhibitors perform in the real-world clinical setting. In addition to PASI90 and PASI100, other novel outcomes have been assessed for these drugs. For example, the efficacy of withdrawal and retreatment with guselkumab was assessed in VOYAGE 2 and it was shown that few patients required retreatment by week 48 (80). Amongst patients treated with guselkumab, efficacy was maintained at 2 years with continuous therapy while efficacy improved amongst those who switched from adalimumab to guselkumab at week 52. Reassuringly, there was no significant increase in adverse event rate compared with rates through week 48 (85).

The recent increase in published head to head comparator studies amongst biologic therapies is a welcome addition to the literature as this provides more meaningful results than placebo comparator alone.

Apremilast is a small molecule therapy which was licensed in 2014 to treat moderate–severe psoriasis and active psoriatic arthritis. It inhibits phosphodiesterase (PDE) 4 and thus reduces expression of proinflammatory mediators such as TNF-α and IL-23 (86). The PASI75 response to apremilast 30 mg twice/day ranges from 29–41% at week 16 in clinical trials (87). It is moderately effective for both psoriasis and psoriatic arthritis, with an efficacy level comparable to methotrexate. Advantages include its oral administration and it is anti-inflammatory rather than immunosuppressant. It also has a favourable safety profile, laboratory monitoring is not required and a potentially advantageous weight loss effect (88). Gastrointestinal intolerance is the most common adverse effect reported in clinical trials – diarrhoea (18%) and nausea (17%) (89) and rates appear higher in real world clinical practice (90). Apremilast has potentially been associated with an increased risk of depression, although the incidence is low – caution and close monitoring is advised in patients with a history of depression.

RECENT THERAPEUTIC DEVELOPMENTS

A variety of small molecule oral and topical drugs are in development for psoriasis. Indeed, the majority of drugs in the clinical trial pipeline for psoriasis are small molecules. The drugs listed below interfere with the IL-23/TH17 cell pathway that is key in driving the disease.

Tofacitinib is an oral Janus kinase (JAK) inhibitor targeting JAK1 and JAK3, thus regulating immune response via interruption of intracellular signalling pathways involved in the pathogenesis of psoriasis. A recent meta-analysis showed that approximately one third of those receiving tofacitinib 5 mg twice/day and half of those receiving tofacitinib 10 mg twice/day achieve PASI75 at week 12–16. Results to date indicate that it is generally well tolerated in treating psoriasis (91, 92). Although of modest efficacy, the favourable safety profile is appealing. JAK show efficacy in the topical treatment of psoriasis as well as atopic dermatitis and may have utility in facial and flexural disease as they are without corticosteroid side-effects (91). Research into this new topical therapy is welcomed as there has not been very much development in this area in recent decades.

Tyrosine Kinase 2 (TYK 2) signalling pathways are implicated in psoriasis pathogenesis and recent Genome Wide Association Studies have identified TYK 2 as a "druggable target". This molecule is an intracellular signalling enzyme which can activate functional responses of interleukin-12, interleukin-23, and interferon receptors – key cytokine pathways in psoriasis pathogenesis. A recent phase 2 study of TYK 2 inhibitor therapy for moderate to severe psoriasis has shown promising results (93). Several different doses were trialled and the primary outcome measure was PASI75 at week 12. This was achieved by 75% of patients on the maximal dose of 12 mg daily. Trials of longer duration and with a larger population are required to determine the longer-term safety and effectiveness of this agent.

MANAGEMENT OF PSORIASIS AS A COMPLEX CHRONIC DISEASE

The management of a patient with psoriasis involves much more than selecting and prescribing the recommended drug. Effective chronic disease management demands a holistic and proactive approach. Management incorporates patient education, screening for comorbidity and adjusting therapy depending on changes in clinical presentation.

Patient education improves patients' understanding of psoriasis and imbues a sense of control (94) in addition to improving adherence and coping. Screening for comorbidity is included in some national guidelines for managing psoriasis (2). This is particularly important for psoriatic arthritis because early diagnosis and commencement of appropriate treatment goes some way to prevent irreversible joint damage (95). It is also important for the detection of risk factors for cardiovascular disease and mood disorders, both of which are highly prevalent amongst this group and contribute to the multi-morbidity complexity of psoriasis (96, 97).

Alcohol excess, smoking and obesity are more prevalent amongst patients with psoriasis and are predictors of poor outcome to systemic therapies. Pharmacovigilance registry data demonstrate that being either a current or ex-smoker, and high body mass index are associated with a reduced odds of achieving PASI90 at 6 months when treated with biologic therapy. This underscores the need for lifestyle management as such factors are modifiable (98). A recent systematic review indicated that weight loss can improve pre-existing psoriasis and psoriatic arthritis, and prevent the onset of psoriasis in obese individuals, highlighting the importance of this intervention as an adjunct in psoriasis management (99). Further investigation into the role of lifestyle management has been identified as a key research priority by the Psoriasis Association in their recently published priority setting exercise (100). Management of these lifestyle factors using motivational interviewing techniques as espoused by the Psoriasis Wellbeing (PsoWell™) (94, 101) programme is likely to play an increasingly prominent role as part of a more integrated approach to psoriasis management going forward.

Never before have there been so many treatment options for psoriasis. However, clinicians are often faced with a challenge when selecting which systemic or biologic drug to commence for their patient as it is not possible to predict which patient will respond to a given therapy. The resultant primary and secondary treatment failures are costly from a patient and socio-economic point of view. With this in mind, the PSORT (Psoriasis Stratification to Optimise Relevant Therapy) (102) consortium was established to develop predictors of clinical response to biologic therapies. This involves analysis of genomic and other biological data in well-phenotyped patients who are commencing a new biologic therapy. It is now clear that due to the complex and multifactorial nature of the disease, multi-omic data is the key to effectively stratify patients and guide systemic therapy accordingly. Another limiting factor is the great expense associated with biologics. Biosimilar drugs which are similar but not identical to established biologics, have now become available as the originator drugs have come off patent. These should reduce the cost of therapy, and so hopefully make biologics more accessible for more patients. It is important to consider the true burden of psoriasis in any health economic evaluation. Direct costs such as medications and hospital appointments are well characterised. Indirect costs such as lost productivity can be more difficult to assess accurately. It has been estimated that indirect costs account for 43% of the mean annual cost of psoriasis amongst those with moderate-

severe disease (103). Some of this could be offset by timely and effective treatment. Psoriasis patients with comorbidities use more healthcare resources and generate higher costs compared to those without comorbidities (104). Screening for and more aggressive treatment of such comorbidities may lead to better patient outcomes. Further research is needed in this field to establish the true burden of disease and relative cost effectiveness of therapy.

Although there are lots of therapies licensed for psoriasis, access to appropriate care remains a problem for many patients around the world. These inequalities are highlighted by the World Health Organisation in their Global Report on Psoriasis (105). The Global Psoriasis Atlas (GPA) aims to address this problem, firstly by establishing the true incidence and prevalence of disease, and then investigating the true burden of disease internationally. This in turn will enable any person with psoriasis, wherever they live in the world, access to the best available care locally.

The biologic revolution has transformed the standard of care for patients with severe disease. However, the majority of patients with psoriasis have mild–moderate disease in terms of cutaneous extent. Unfortunately, there have not been many new therapeutic developments for this group. Topical therapies remain the most commonly prescribed class of drug for psoriasis (106). It is hoped that small molecule therapies which are currently in the pipeline may be accessible for patients with moderate disease.

Randomised controlled trials (RCTs) are the gold standard when it comes to investigating the efficacy and safety of new therapies and most of the evidence which informs clinical guidelines is based on this principle. However, rigorous inclusion and exclusion criteria often mean that the study population is not representative of the usual, real world clinic population. For instance patients with psoriasis identified as being ineligible for RCTs of biologics are at least twice as likely as eligible patients to suffer serious adverse events (107, 108) and reduced efficacy. Prospective longitudinal data collection through pharmacovigilance registers such as The British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) provides an invaluable service to patients and clinicians by providing real-world safety and efficacy data.

Patients with psoriasis accumulate excess physical, psychological and socioeconomic morbidity throughout their lives (4). The reason for this is multifactorial and due to a combination of genetic, behavioural and environmental factors which are unique to an individual. Unfortunately, it is not yet possible to predict which newly diagnosed patient with psoriasis will go on to develop severe disease and associated co-morbidity. The natural history of psoriasis remains poorly understood. It has been suggested that systemic inflammation in psoriasis, perhaps emanating from adipose tissue, contributes to the increased risk of comorbidity (109) and provides further rationale for managing psoriasis with systemic therapies. It has been hypothesised that early intervention with systemic therapy could modify the course of disease and, as a result, reduce the potential for this cumulative impairment which can severely limit a patient from reaching their full potential. Identifying patients at an early stage in their disease course would also provide an opportunity to proactively screen for comorbidities and unhealthy lifestyle behaviours associated with psoriasis, providing an integrated systems approach to management. The collection of multi-omic (genomic, biochemical, demographic, phenotypical, clinical) data from patients with recent-onset disease could provide novel insight into subclinical predictors of disease progression and multi-morbidity (110). Ideally, longitudinal follow up could help determine the characteristics of patients who develop specific disease and comorbidity patterns. Stratification using algrithms based on these multi-omic data is likely to play a key role in guiding the management of immune mediated inflammatory diseases, such as psoriasis, in the future.

CONCLUSION

The evolution of psoriasis treatment over the past 100 years is a celebration of the advances which have been made in understanding and improving care for patients with this disease. A collaborative approach between clinicians, patients, academics and the pharmaceutical industry has been instrumental in enabling this progress. Whilst a cure for psoriasis is unlikely anytime soon, complete clearance of the disease with the newest biologic therapies is now a realistic goal for some. A whole person approach to disease management that embraces the P4 medicine principles of prediction, prevention, personalised therapy and patient participation is the logical extension of our realisation that psoriasis is a "systemic disease" with important physical and psychosocial consequences. Although systemic therapy of psoriasis has advanced considerably there is still an unmet need for more effective topical therapies and a more widespread use of biosimilars.

Future research will focus on the use of integrated multi-omic data to stratify patients and guide therapy. Improved access to care and early intervention with systemic therapy are concepts which are being discussed increasingly. This is where service development overlaps with research, calling for innovative approaches and research methodologies to achieve this goal.

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REVIEW ARTICLE

Psoriasis and Co-morbidity

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Psoriasis is associated with multiple co-morbid medical conditions. The purpose of this study is to evaluate the relationships between psoriasis and cardiovascular disease, psoriatic arthritis, mental health conditions, and immune-mediated diseases, respectively. A literature search was performed during the study period January 1, 2015 to December 18, 2018. Of 2,499 records identified, 28 met our criteria selection and were included in this review. The relationships between psoriasis and these multiple comorbid disease conditions are discussed and are important to consider when developing the treatment plan and overall management of patients with psoriasis. Early recognition and treatment of comorbid disease conditions is important to help improve the quality of life for these patients.

Key words: psoriasis; cardiovascular disease; psoriatic arthritis; mental health conditions; depression; immune-mediated disease.

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SIGNIFICANCE

Psoriasis is associated with many different medical conditions. In this study, the relationships between psoriasis and cardiovascular disease, psoriatic arthritis, mental health conditions, and immune-mediated diseases, respectively, are assessed. A literature search was performed during the study period January 1, 2015 to December 18, 2018. Based on these findings, the relationships between psoriasis and these multiple comorbid disease conditions are identified and discussed. The treatment of comorbid conditions can promote an enhanced quality of life for patients with psoriasis. Therefore, the recognition and treatment of co-morbid medical conditions is important to consider when taking care of patients with psoriasis.

Psoriasis is a chronic inflammatory skin disease that affects approximately 125 million individuals worldwide (1). Cardiovascular disease, psoriatic arthritis, and mood disorders are common comorbid disease conditions associated with psoriasis (2). Moreover, autoimmune diseases have been reported to be associated with psoriasis, which may suggest that the pathogenesis of psoriasis may involve autoimmune mechanisms. In this review, the relationships between psoriasis and cardiovascular disease, psoriatic arthritis, mental health conditions, and autoimmune diseases, respectively, will be evaluated.

METHODS

A literature search was performed to identify comorbid disease conditions associated with psoriasis. Psoriasis and the associated comorbid conditions of cardiovascular disease, psoriatic arthritis, psychiatric conditions, and autoimmune disorders were examined. Articles from the past 3 years, specifically January 1, 2015 to December 18, 2018, were searched via PubMed and Google Scholar with the following keywords: psoriasis, comorbid, cardiovascular, psoriatic arthritis, psychiatric disease, and autoimmune disorders. The available abstracts and literature that investigated the relationship between psoriasis and cardiovascular disease, major adverse cardiovascular events (MACE), psoriatic arthritis, depression, suicidal ideation, suicidal attempts, and immune-mediated disorders, respectively, were evaluated. We restricted the search results to English-only records. Case reports, case series, and studies including pediatric patients were excluded. A manual inspection of reference lists and relevant studies was also performed to identify any additional relevant studies.

RESULTS

A total of 2,499 records were identified. After application of criteria selection and removal of duplicates, 28 of these records were included in the review (**Fig. 1**). Citations within identified articles and relevant studies were also reviewed, and 18 articles that were not originally detected in database searches were also included.

PSORIASIS AND CARDIOVASCULAR DISEASE

Psoriasis and cardiovascular risk factors

Patients with psoriasis have a higher prevalence of traditional cardiovascular risk factors, including diabetes mellitus type 2, hypertension, dyslipidemia, and obesity (1, 3). Studies have shown that obesity is an independent risk factor for psoriasis (2). Specifically, studies have demonstrated a dose-dependent relationship between psoriasis severity and obesity (2). Moreover, independent of traditional risk factors, psoriasis is associated with a greater risk of diabetes. Recent evidence has suggested

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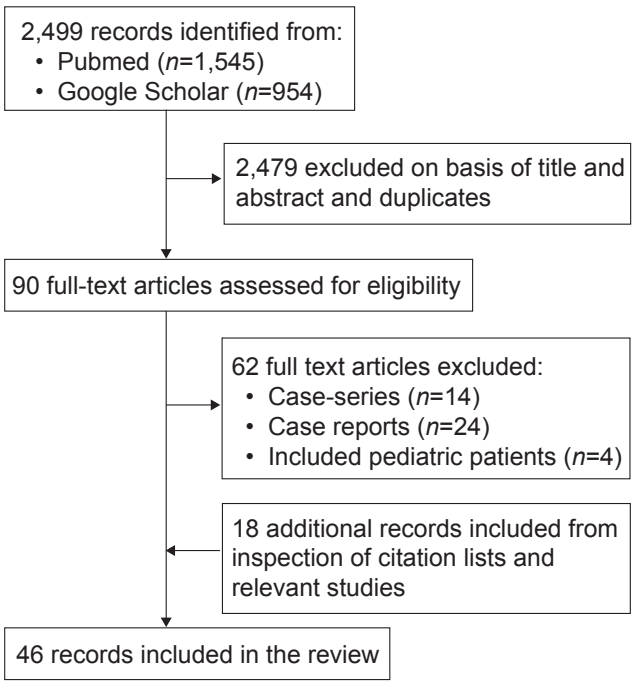

Fig. 1. Study-flow diagram of the included studies.

that the risk of diabetes, likelihood of insulin resistance, and diabetic complications increases with greater psoriasis severity, as defined by treatment patterns or BSA body surface area involved, independent of traditional risk factors (2). Studies have also demonstrated a higher prevalence of metabolic syndrome among patients with psoriasis compared to patients without psoriasis in adult and pediatric populations (2). The underlying mechanism of the association with psoriasis and these cardiovascular risk factors is not yet known, yet common inflammatory pathways, cellular mediators, and genetic susceptibility may contribute to these findings.

Association of psoriasis with vascular inflammation and cardiovascular events

Fluorodeoxyglucose F-18 positron emission tomography computed tomography (FDG PET/CT) is commonly used to measure aortic vascular inflammation and has been used as an indicator of cardiovascular risk and vascular disease (4, 5). Joshi et al. (5) demonstrated that patients with psoriasis with increased aortic vascular inflammation as evidenced by FDG PET/CT had significantly increased coronary artery disease indices, including total plaque burden, luminal stenosis, and high-risk plaques (5). Additionally, after adjustment for traditional cardiovascular risk factors, patients with severe psoriasis were at a higher risk for MACE compared to the general population (6). A prospective cohort study evaluated 115 psoriasis patients to determine the association between psoriasis disease severity and vascular inflammation as measured by FDG-PET/CT (7). At baseline, psoriasis severity was significantly associated with vascular inflammation. At one-year follow-up, improvement in psoriasis severity was associated with improvement in vascular inflammation, which maintained significance after accounting for traditional cardiovascular risk factors. Moreover, a significant 11% reduction in aortic vascular inflammation was observed for patients with greater than 75% reduction in psoriasis severity (7).

A study by Egeberg et al. (8) evaluated the impact of psoriasis duration on vascular disease and cardiovascular events. Among young patients with low cardiovascular risk by traditional risk scores and a high prevalence of cardiometabolic diseases, vascular inflammation as measured by FDG-PET/CT was significantly associated with disease duration. Moreover, duration of psoriasis demonstrated a strong association with MACE risk. Therefore, cumulative exposure to chronic inflammation among psoriasis patients may facilitate the development of vascular disease and MACE (8).

Patients with non-severe psoriasis also appear to be at an increased risk of developing cardiovascular events. Vascular indices of early arterial atherosclerosis (carotid intima-media thickness), endothelial dysfunction (flow-mediated dilation), and bioserum markers of oxidative stress (serum levels of advanced oxidation protein products) were assessed among patients with non-severe psoriasis. Compared to controls, patients with mild-to-moderate psoriasis without a history of any cardiovascular disease had significantly increased carotid intimamedia thickness, impaired flow-mediated dilation, and increased serum levels of advanced oxidation protein products (9). Additionally, a study utilizing echocardiographic evaluation demonstrated that left ventricular diastolic dysfunction was present among a greater number of young healthy patients with psoriasis compared with controls (10). Thus, patients with psoriasis appear to be at an increased risk of cardiovascular disease irrespective of underlying cardiovascular risk factors.

Impact of family history of cardiovascular disease

Family history of cardiovascular disease may help explain the increased risk of cardiovascular disease and MACE among patients with psoriasis. Egeberg et al. (11) compared the risk of incident MACE among patients with psoriasis with or without a family history of cardiovascular disease. Among patients with psoriasis and a family history of cardiovascular disease, the incidence ratios of MACE were 1.28 for mild and 1.62 for severe disease. No increased risk of MACE was detected among patients with psoriasis without a family history of cardiovascular disease (11). Therefore, it is important to determine the presence or absence of a family history of cardiovascular disease, as family history is likely a main contributor to MACE risk among patients with psoriasis.

Tumor necrosis factor inhibitor therapy and biomarkers of inflammation

C-reactive protein (CRP) is a biomarker of inflammation that has been utilized as a marker of cardiovascular risk (12). A retrospective cohort study evaluated the relationship between tumor necrosis factor (TNF) inhibitor therapy and changes in CRP among patients with psoriasis, psoriatic arthritis, or rheumatoid arthritis (13). At time of follow-up, mean change in CRP was lower among patients exposed to both a TNF inhibitor and methotrexate compared to methotrexate alone. For patients exposed to both a TNF inhibitor and methotrexate, the difference in mean CRP change was significantly lower compared to the methotrexate group after accounting for baseline CRP. Given that inflammation is a key contributing factor to the pathogenesis of cardiovascular disease (13), the results from this study suggest that exposure to TNF inhibitor therapy potentially reduces the risk of MACE among patients with chronic inflammatory conditions, including psoriasis. Thus, the results from this study further support the notion that TNF inhibitor therapy may offer a protective effect against developing MACE for patients with psoriasis.

Impact of biologic therapy on cardiovascular risk for patients with psoriasis

Treatment of psoriasis with TNF inhibitor therapy has been linked with a reduced risk of MACE among patients with psoriasis (14–16). A retrospective cohort study assessed MACE risk among patients with psoriasis receiving TNF inhibitor therapy compared to oral/phototherapy and topical therapy, respectively (14). After adjustment for cardiovascular risk factors, patients with psoriasis on TNF inhibitor therapy experienced significantly lower MACE hazard rate (HR) compared with patients on topical therapy. The MACE HR for patients in the oral/phototherapy group was similar to the topical group (14). The results from this study suggest that TNF inhibitor therapy may offer a protective effect against risk of MACE for patients with psoriasis.

Cumulative exposure to TNF inhibitor therapy may help further lower the risk of MACE for patients with psoriasis. A retrospective study by Wu et al. (15) compared the risk of MACE among patients with psoriasis receiving methotrexate versus TNF inhibitor therapy. After 12 months, patients receiving TNF inhibitor therapy developed fewer MACE and had lower cardiovascular event hazards compared to patients receiving methotrexate. Specifically, the MACE HR was 45% lower for patients receiving TNF inhibitor therapy compared to methotrexate. By 24 months median follow-up, every additional 6 months of TNF inhibitor exposure was associated with an 11% reduction in MACE risk (15). Therefore, cumulative exposure to TNF inhibitor therapy may help lower the risk of MACE for patients with psoriasis (15). A retrospective cohort study assessed the risk of MACE in patients with psoriasis receiving a TNF inhibitor versus phototherapy (16). Compared to patients receiving phototherapy, patients on TNF inhibitor therapy had a reduced MACE HR. Furthermore, every 6-month incremental cumulative exposure to TNF inhibitors was associated with a statistically significant reduction in MACE risk over a median observation period of 15.4 months. Furthermore, the risk reduction in MACE with 6 months of cumulative exposure was 11.2% greater among patients receiving TNF inhibitor therapy compared to phototherapy (16). Thus, the results of this study further suggests that cumulative TNF inhibitor exposure may lower the risk of MACE for patients with psoriasis (16).

Biologic therapy may attenuate coronary artery disease progression in patients with severe psoriasis. A prospective, controlled clinical study by Hjuler et al. (17) evaluated the association of biologic therapy with changes in coronary artery disease progression. The study evaluated coronary CT angiography among patients with severe psoriasis without symptomatic coronary artery disease at baseline and after 13 months of receiving biologic therapy (adalimumab, etanercept, infliximab, and ustekinumab) compared to control group. Among the control group, the severity of luminal narrowing in diseased segments was increased at 13-month follow-up, yet in the intervention group this was unchanged. In addition, the non-contrast coronary artery calcium scores were stable in the intervention group and progressed in the control group. A likely explanation for this finding is that biologic therapy helps decrease systemic inflammation, thus preventing cardiovascular disease progression. A limitation of this study is the small sample size of 28, which should be taken into consideration when interpreting these results. Nevertheless, biologic therapy appears to be associated with reduced coronary artery disease progression in patients with severe psoriasis.

On the other hand, there are also studies with opposing data regarding the effect of TNF inhibitory therapy on vascular inflammation. A randomized multicenter study by Bissonnette et al. (18) evaluated the impact of the TNF inhibitor adalimumab on vascular inflammation in patients with psoriasis. Utilizing PET/CT, no difference in vascular inflammation was appreciated over 16 weeks in the adalimumab group compared to placebo. Moreover, a randomized clinical trial by Mehta et al. (19) compared vascular inflammation and levels of cardiovascular biomarkers among patients with moderate-to-severe psoriasis treated with adalimumab, phototherapy, or placebo. At week 12, there was no difference in change in vascular inflammation as measured by FDG PET/CT among the adalimumab group (change compared with placebo, 0.64%) or the phototherapy group (−1.60%). Biomarkers of inflammation, serum CRP and IL-6, were decreased in both the adalimumab and phototherapy

groups. Therefore, while studies have demonstrated that TNF inhibitor therapy may lower the risk of vascular inflammation for patients with psoriasis, studies have also revealed evidence that is contradictory to these findings. For this reason, the exact impact of TNF inhibitor therapy on cardiovascular risk is currently still debated.

PSORIASIS AND PSORIATIC ARTHRITIS

Psoriatic arthritis is an inflammatory disease that involves the peripheral and axial joints, skin, nails, and entheses (20, 21). Psoriatic arthritis has been reported to affect approximately 6–42% of patients with psoriasis (2). The prevalence of psoriatic arthritis appears to increase with greater severity of skin disease and duration of psoriasis (2). Clinically, patients experience joint pain and swelling secondary to chronic joint inflammation that, if left untreated, can lead to long-term irreversible joint damage and disability (20, 21). Cutaneous lesions tend to precede joint involvement, which can develop years after being diagnosed with psoriasis (18, 19). Yet, according to a meta-analysis by Villani et al. (22), the prevalence of undiagnosed psoriatic arthritis in patients with psoriasis at time of seeking medical care is approximately 15.5%. Thus, all patients with psoriasis should be screened for psoriatic arthritis at every stage of their disease.

Screening for psoriatic arthritis

Multiple questionnaires are available to help diagnose psoriatic arthritis (21). These questionnaires include the Toronto Psoriatic Arthritis Screening Questionnaire (TOPAS), Psoriasis Epidemiology Screening Tool (PEST), Psoriatic Arthritis Screening and Evaluation (PASE), and the Psoriasis and Arthritis Screening Questionnaire (PASQ) (21). Despite the development of these screening questionnaires, the ability to differentiate psoriatic arthritis from other forms of arthritis remains difficult and the diagnosis of psoriatic arthritis is often delayed (23). In a large population-based survey (24), 37.6% of dermatologists indicated that their greatest challenge in managing patients with psoriatic arthritis is discerning psoriatic arthritis from other arthritic diseases, while 25% of rheumatologists indicated that delayed referral is one of their greatest challenges. Moreover, joint pain was reported among 51.8% of psoriasis patients without a diagnosis of psoriatic arthritis, however only 18.6% of dermatologists reported that their patients had joint pain (24). Based on these results, there could be a discrepancy in the interpretations of joint involvement between physicians and patients with psoriasis. Additionally, there may be a need for enhanced communication between dermatologists and rheumatologists as well as within rheumatologists using enhanced tools to differentiate psoriatic arthritis from other arthritic diseases (25, 26). Cohen et al. (23) offered a simple, concise screening tool that encompasses key characteristics of psoriatic arthritis. The tool consists of the mnemonic "PSA," for which P stands for pain (joint pain), S stands for both stiffness (>30 min after a period if inactivity) and sausage digit (dactylitis), and A stands for axial (axial joint involvement/back pain referring to stiffness that improves with activity) (23). Moreover, the Classification Criteria for Psoriatic Arthritis (CASPAR) incorporates clinical findings specific to psoriatic arthritis, including presence of psoriatic nail dystrophy, a negative rheumatoid factor test, dactylitis, and radiographic evidence of juxta-articular bone formation) (21). CASPAR is highly specific (99.1%), however has lower sensitivity for detecting early psoriatic arthritis (87.4%) (21). Thus, it serves better as a confirmatory test rather than a screening tool, and can help physicians differentiate psoriatic arthritis from other forms of arthritis.

Symptom and complications of psoriatic arthritis

Patients with psoriasis and comorbid psoriatic arthritis tend to experience more symptoms and complications with respect to physical functioning compared to psoriasis patients without psoriatic arthritis (27). Compared to psoriasis patients without psoriatic arthritis, patients with psoriasis and psoriatic arthritis appear to have significantly more comorbid conditions, including hypertension, diabetes mellitus, and hyperlipidemia (20). In addition, patients with psoriasis and psoriatic arthritis have higher health care utilization and costs compared to patients without comorbid psoriatic arthritis (20). A study by Edson-Heredia et al. (28) demonstrated that patients with moderate-to-severe psoriasis and comorbid psoriatic arthritis experienced a greater impact on quality of life and symptoms of itching, physical irritation, and pain compared to patients with moderate-to-severe psoriasis alone. Among psoriasis patients with comorbid psoriatic arthritis, a greater frequency of comorbid diseases was reported, including type 2 diabetes mellitus and hypertension, compared to patients with psoriasis alone (28). Thus, psoriasis patients with psoriatic arthritis may experience greater psoriasis-related disease burden compared to patients with psoriasis alone.

Importance of recognition and treatment of psoriatic arthritis

Early recognition of psoriatic arthritis is imperative because improved control of inflammation can prevent joint destruction and improve quality of life. According to a study by Haroon et al. (29), a diagnostic delay of over 6 months from time of symptom onset to visit with a rheumatologist contributed to the development of joint erosions and worse functional disability as evidenced by Health Assessment Questionnaire (HAQ) scores for patients with psoriatic arthritis. Yet, a delayed diagnosis of psoriatic arthritis over one year was not associated with a significant difference in HAQ scores. A large

United Kingdom multicenter study that evaluated factors contributing to work disability among patients with psoriatic arthritis found that worse physical function was associated with unemployment (30). Moreover, among participants that were employed, greater disease activity and worse physical function were associated with higher levels of productivity loss. Thus, among patients with psoriatic arthritis, productivity loss could potentially be prevented with treatment of psoriatic arthritis (30). Rahman et al. (31) also found that treatment of psoriatic arthritis was associated with improvements in physical function and health-related quality of life. Additionally, a study by Kirkham et al. (32) demonstrated that treatment of psoriatic arthritis was associated with improved quality of life as measured by patient reported outcomes (specifically, EuroQol-5D scores). Moreover, patients with shorter disease duration exhibited significantly greater improvements in disease activity and patient reported outcomes of joint pain and quality of life (32). The results from this study suggest that early intervention may have a more prominent impact on patient-reported outcomes of disease activity and quality of life. Moreover, treatment options for psoriasis, including biologics, can have different efficacy on cutaneous disease versus joint disease, which is important to consider when choosing appropriate therapy, which should ultimately be tailored for the individual patient (33).

PSORIASIS AND MENTAL HEALTH CONDITIONS

Patients with psoriasis are at an increased risk of depression compared to the general population (34). Moreover, depression in psoriasis patients may increase risk of other comorbidities. In a prospective cohort study, patients with psoriasis and major depressive disorder (MDD) were found to be at a significantly increased risk of developing psoriatic arthritis compared to psoriasis patients without MDD (35). Additionally, a study by Egeberg et al. (36) found patients with psoriasis and comorbid depression to be at an increased risk of myocardial infarction, stroke, and cardiovascular death. Moreover, Aberra et al. (37) demonstrated that vascular inflammation (as measured by FDG PET/CT) and total and non-calcified coronary plaque burden (as measured by coronary CT angiography) were significantly higher among patients with psoriasis and self-reported depression versus patients with psoriasis alone. After adjustment for traditional cardiovascular disease risk factors, vascular inflammation, total plaque burden, and non-calcified burden were significantly associated with self-reported depression (37). The reported findings may be due to the chronic inflammation present in psoriasis, which potentially increases the risk of developing cardiovascular events. Furthermore, psoriasis patients with comorbid depression are at an even greater cardiovascular risk due to the reported association between depression and cardiovascular events, subclinical atherosclerosis, and all-cause mortality, independent of traditional cardiovascular risk factors (37). Therefore, patients with psoriasis and comorbid depression appear to be at a greater risk of inflammation-induced atherosclerotic plaque development, ultimately increasing the risk of developing cardiovascular events. Comorbid depression could also result in reduced adherence to treatment for psoriasis as well as utilization of healthcare resources, consequently interfering with cardiovascular risk factor management (36, 38). Thus, detecting and treating comorbid depression may prevent the development of complications for these patients.

Psoriasis is also associated with anxiety and suicidal ideation (39, 40). A systematic review and meta-analysis by Singh et al. (41) assessed the relationship between psoriasis and suicidality. Compared to patients without psoriasis, patients with psoriasis were twice as likely to exhibit suicidal ideation and suicidal behaviors (combined attempted and completed suicides; pooled (41). Thus, it is important to detect and treat comorbid mental health conditions in patients with psoriasis.

PSORIASIS AND IMMUNE-MEDIATED DISORDERS

An increased frequency of immune-mediated disorders has been reported among patients with psoriasis (42–46). However, a definite relationship between psoriasis and immune-mediated diseases remains unclear (42). Compared to patients with mild psoriasis, patients with severe psoriasis demonstrated significantly higher diagnosis rates of rheumatoid arthritis, lupus, and Crohn's disease (43). In addition, the presence of autoreactive T cells have been demonstrated in the pathogenesis of psoriasis, which suggests that psoriasis may be autoimmune in nature (44–46). A nationwide, population-based, cross-sectional study evaluated the association between psoriasis and various immune-mediated rheumatic diseases among 267,230 patients with psoriasis and 267,230 controls without psoriasis (47). Psoriasis was significantly associated with ankylosing spondylitis (AS), rheumatoid arthritis (RA), Behçet disease, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and dermatomyositis/polymyositis (DM/PM). Moreover, male patients with psoriasis exhibited higher associations with AS, RA, SLE, SSc, and DM/PM compared to female patients with psoriasis (47).

A case-control study evaluating 287 patients with bullous pemphigoid (BP) and 1,373 matched controls found that the prevalence rate of psoriasis was greater among patients with BP versus controls (48). Moreover, psoriasis preceded the diagnosis of BP, by a mean duration of 25.2 years (48). Additionally, a cross-sectional study detected a significant association between psoriasis and Hashimoto's thyroiditis that sustained after adjusting for confounding variables, including sex, age, psoriatic

arthritis, and use of systemic anti-psoriasis agents (odds ratio 2.49) (49). Chronic inflammation and subsequent damage to the basement membrane has been suggested as a possible mechanism for the reported association between BP and psoriasis (42). Another theory is that treatment for psoriasis may worsen subclinical bullous pemphigoid (42). Further studies would help determine the exact association between psoriasis and BP, as well as other autoimmune disorders.

CONCLUSION

The association between psoriasis and comorbid disease conditions is important to consider when developing the treatment plan and overall management of patients with psoriasis. Psoriasis is associated with cardiovascular disease, and chronic inflammation likely plays a major role in this relationship. Treatment of psoriasis improves underlying inflammation and TNF inhibitor therapy may provide a protective effect against risk of MACE for patients with psoriasis, which would ultimately promote better health outcomes for these patients. Moreover, psoriatic arthritis is a common comorbid condition associated with psoriasis that can lead to permanent disability. Early treatment is imperative to help prevent complications of psoriatic arthritis and improve quality of life for these patients. Furthermore, it is important to address and treat comorbid psychiatric conditions among patients with psoriasis, including depression, suicidal behavior, and suicidal ideation. Future clinical trials would help better assess the role of biologic therapy on improving health outcomes, wellness, and quality-of-life for patients with psoriasis. Certain immune-mediated disorders have been reported to be associated with psoriasis. Further research will help better assess these associations as well as the autoimmune aspects of the underlying pathogenesis of psoriasis.

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REVIEW ARTICLE

Pustular Psoriasis: The Dawn of a New Era

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Pustular psoriasis is a clinically heterogeneous entity of different, orphan disease subtypes, among which the most clearly defined are generalized pustular psoriasis, palmoplantar psoriasis, and acrodermatitis continua of Hallopeau. Although phenotypically and genetically distinct from psoriasis vulgaris, these subtypes may be associated with plaque psoriasis lesions, establishing the rationale for their inclusion in the psoriasis spectrum. Unlike psoriasis, however, their genetic background is thought to be mainly monogenic, as shown by the recent identification of mutations in 3 different genes of the skin innate immune system; *IL36RN*, *CARD14* and *AP1S3*. These major advances in the understanding of the disease pathogenesis have led to the design and ongoing development of tailored therapeutic approaches, which are highly necessary given the refractory nature of pustular psoriasis in response to most available antipsoriatic drugs.

Key words: pustular psoriasis; pustulosis; generalized pustular psoriasis; palmoplantar pustulosis; interleukin-36.

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SIGNIFICANCE

Pustular psoriasis defines a heterogeneous group of skin inflammatory diseases, which have in common the presence of aseptic pustules. Genetically distinct from psoriasis vulgaris, they have been shown to be related to mutations in any of 3 genes of the skin immune system, respectively called *IL36RN*, *CARD14* and *AP1S3*. These recent advances have initiated the design of biological drugs specifically targeting key actors of inflammation in pustular psoriasis, with interleukin-36 inhibitors as the most advanced example of therapeutic development.

Psoriasis is a chronic inflammatory disease entity that includes different clinical phenotypes, of which the so-called psoriasis vulgaris (PV) or plaque psoriasis variant is by far the most prevalent, representing approximately 80% of cases, and resulting from the combination of a multigenic, complex genetic background with environmental triggers (1, 2). Aside from this most frequent clinical form of psoriasis, much rarer clinical phenotypes, all characterized by the presence of neutrophilic skin inflammation with macroscopically visible, non-infectious or aseptic pustules, have been termed pustular psoriasis and, in some cases, psoriasis-related subphenotypes (2). Long-neglected, these phenotypes have attracted a lot of interest over the last 10 years due to major advances in the understanding of their pathogenic mechanisms, involving a major deregulation of skin innate immune responses, reflected at the histological level by an intense afflux of neutrophils and monocytes in the lesional dermis and epidermis (2). The current review integrates long-established clinical features with the more recently re-defined disease subtypes classification and, more importantly, advances in physiopathological scenarios, which have already driven therapeutic innovations.

Pustular psoriasis consists of several clinical entities, of which the best defined are: (*i*) localized pustular psoriasis dominated by palmoplantar pustular psoriasis (PPPP), also called palmoplantar pustulosis (PPP); (*ii*) acrodermatitis continua of Hallopeau (ACH), which predominantly involves acral areas of the hands and/or feet; and (*iii*) generalized pustular psoriasis (GPP), a disseminated, severe and potentially life-threatening form of psoriasis. The question of whether these pustular skin disorders belong to the psoriasis spectrum has been debated for a long time. Their intersection and overlap with PV is reflected by their frequent coexistence in a given patient, and by some commonalities in their respective mechanistic models. In this sense, studies of pustular psoriasis have also been insightful regarding mechanisms of skin inflammation, both in physiology and for other skin-inflammatory diseases.

GENERALIZED PUSTULAR PSORIASIS

Clinical characteristics and diagnostic procedures

GPP, the most severe of all the psoriatic disease variants, is an orphan skin and multisystemic inflammatory disease characterized, in its typical forms, by intermittent flares or attacks with partial or complete remission in between (**Fig. 1**). Estimated prevalences of GPP are 0.0002% and 0.0007%, in France and Japan, respectively (3, 4). Each flare consists of the acute onset of a rapidly disseminating cutaneous eruption an extensive skin rash covered with aseptic pustules at an early stage, combined at some point

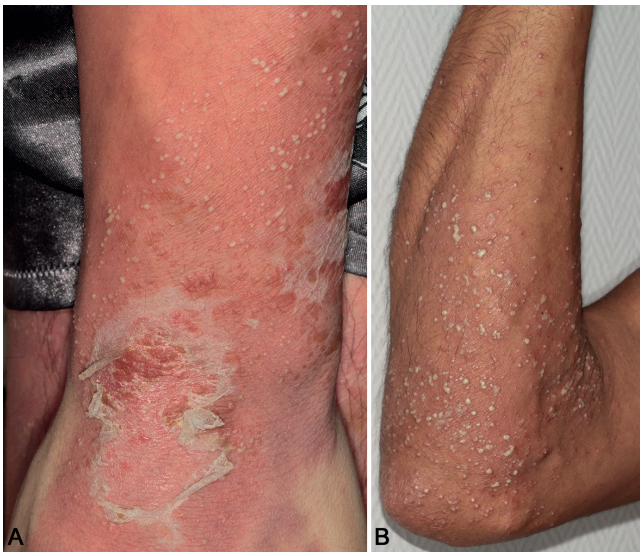

Fig. 1. Skin lesions in patients with generalized pustular psoriasis. (A) A diffuse erythema is covered with confluent pustules, leading to formation of pustular lake, with superficial scaling at a later stage, in a patient free of *IL36RN* or *CARD14* mutation. (B) Disseminated, separated pustules on an erythematous basis of the forearm of an adult patient with identified deficiency of IL36 receptor antagonist.

with systemic symptoms, such as a variable degree of fever up to 40°C, and general malaise with fatigue. Other extracutaneous manifestations, such as polymyalgia and polyarthralgia, are common, and arthritis may occur (5, 6). Several subtypes of GPP have been defined depending both on disease course and clinical presentation: (*i*) the acute von Zumbusch type; (*ii*) GPP in pregnancy, previously named impetigo herpetiformis; (*iii*) the annular GPP clinical subphenotype; and (*iv*) GPP associated with PV. GPP is an unpredictable disease; the spectrum of severity of attacks varies widely between patients and in any given patient, ranging from the absence of any systemic symptoms, which does not rule out diagnosis, to the presence of high fever or even life-threatening complications requiring admission to the intensive care unit (6). Biological test abnormalities typically consist of raised serum concentrations of inflammatory proteins, mainly C-reactive protein (CRP), peripheral blood hyperleukocytosis with neutrophilia, and a high prevalence of liver test abnormalities, sometimes delayed with respect to the onset of ongoing GPP flare (7, 8). Extracutaneous manifestations of GPP, such as osteoarthritis, uveitis, acute respiratory distress syndrome, and cardiovascular aseptic shock (the last related to the massive release of inflammatory cytokines), may occur at any stage during the disease course (7, 9–11). The reported high prevalence of liver test abnormalities during GPP attacks, mainly mild to moderate cholestasis and/or cytolysis, raised the hypothesis of aspecific liver/biliary involvement by the inflammatory process. This hypothesis was reinforced by results from magnetic resonance imaging (MRI) of the liver and biliary ducts, showing, in some patients, strictures alternating with dilatations of the principal and/or accessory biliary ducts, and was definitively ascertained by histopathological analysis of liver biopsies showing innate immune cells, mainly neutrophils, infiltrating the epithelium of biliary ducts and the portal and periportal spaces (6). This last entity, which shares features of other types of inflammatory cholangitis, was further termed neutrophilic cholangitis, and seems to have a benign short- and medium-term evolutive profile, although additional follow-up studies are needed to investigate its long-term prognosis (8). More recently, cases of neutrophilic cholangitis have been reported in patients with localized pustular psoriasis, and in those with PV with or without psoriatic arthritis, raising the hypothesis that deregulation of the extracutaneous innate immune system is not exclusive to GPP, but may also be observed in more frequent psoriatic variants (12).

One very specific evolutive feature of GPP is the spontaneously self-remitting pattern of disease flares, at least in classical intermittent forms. Typically, this spontaneous remission of attacks happens in a matter of weeks following the onset of attacks, but there are cases in which chronic skin lesions persist in between attacks of GPP (9). Whatever the genetic background, the intermittent, acutely flaring course of GPP allowed triggering factors to be identified, the best known being infections, stress, corticosteroid treatment withdrawal, and pregnancy (5, 6, 13). Cases of GPP with onset during pregnancy, usually early during the third trimester, have been also termed impetigo herpetiformis, but they are now acknowledged as part of the GPP entity. Their prognosis may be severe both for the mother and the foetus, potentially leading to intrauterine growth restriction, miscarriage, or foetal death (14, 15). Therefore, GPP in pregnancy requires close monitoring of foetal viability. GPP in pregnancy should be considered as a serious, potentially life-threatening situation for both mother and foetus.

Physiopathology and prognosis

Infectious respiratory viral triggers have been identified recently by multiplex PCR-based analysis of nasopharyngeal swabs in a small cohort of patients with different subtypes of psoriasis, including GPP (16). Interestingly, viral nucleic acids are potent agonists of the innate immune system, and can stimulate the release of inflammatory cytokines operating in psoriasis pathogenesis, including interleukin-36 (IL-36) (16). The role of these viral triggers has been raised in several studies, and a striking observation is the short time interval between the infection and onset of GPP flare, in keeping with a potent stimulation of the innate immune system (9, 13, 16). The role of these infectious triggers raises the challenge of immune intervention with immunosuppressants during GPP attacks with simultaneous infection, emphasizing the need for effective therapeutic strategies with appealing infectious safety profiles. The deciphering of

the pathogenesis due to identification of causal genetic abnormalities, mainly mutations of the *IL36RN* gene encoding a regulator of the IL-36 inflammatory pathway in a subset of patients with GPP, established a strong rationale for the development of targeted therapies, a crucial breakthrough which is addressed below (13).

Mortality rates for recent cohorts of GPP are not available, but its life-threatening potential is acknowledged. Likewise, some skin and systemic signs and symptoms-based attempts to score the severity of GPP flares have been launched in Japan, paving the way for more specific, reproducible scoring tools, in a disease where PV-specific Psoriasis Area Severity Index (PASI) is not suitable, notably due to the absence of any induration in GPP lesions (7).

Recent advances in the assessment of the severity of pustular psoriatic diseases are addressed below.

PALMOPLANTAR PUSTULAR PSORIASIS

PPPP, also called palmoplantar pustulosis (PPP), is the most common of pustular psoriasis variants, and the most common localized pustular variant (**Fig. 2**) (17). Prevalence estimates of 0.01% have been reported, and the disease predominates in women, with a strong link with smoking (18, 19). The disease usually presents as aseptic pustular lesions following a chronic course, going through different stages in the form of yellow scales or crusts, and at a later stage brown macular residual lesions. The onset of PPP usually occurs in adulthood, severely impairs patients' quality of life in severe cases, and may associate with extracutaneous involvement, such as nail disease, arthritis, and, rarely, with neutrophilic cholangitis (10). Occasionally PPPP may associate with autoimmune conditions, such as thyroiditis, although it is not known if the prevalence of clinical autoimmunity is higher than in the general population (20). One particular axial spondyloarthritis feature observed in patients with PPPP led to the definition of a syndrome called SAPHO (synovitis, acne, pustulosis, hyperosteosis osteomyelitis) (16). This is characterized by painful swelling of sternocostal and manubrial areas, and its diagnosis is usually established by bone scintigraphy (21).

While GPP typically follows a relapsing, intermittent course with disease-free intervals that may last for months or sometimes years, the evolutive pattern of PPPP is usually chronic and, like other pustular psoriatic subtypes, may associate with PV. It may also combine in some patients with ACH or, rarely, with GPP (13, 16).

ACRODERMATITIS CONTINUA OF HALLOPEAU

The ACH subphenotype is defined by pustular lesions involving extremities of the hands and feet, with progressive destruction of the nail apparatus, with or without underlying bone erosions (Fig. 2C) (22). Like PPPP, this rare, debilitating form has been reported in between GPP flares in patients with deficiency of IL-36 receptor antagonist (DITRA) (13). The threat of definitive nail and/or bone damage warrants early treatment of patients with ACH.

DIFFERENTIAL DIAGNOSES

Diagnosis of pustular psoriasis relies mainly on clinical features and is usually easy. Characteristic histopathological findings include the formation of intraepidermal neutrophilic abscesses, with marked dermal infiltrate composed of neutrophils, monocytes and T-lymphocytes (1, 2). One major differential diagnosis of GPP is acute

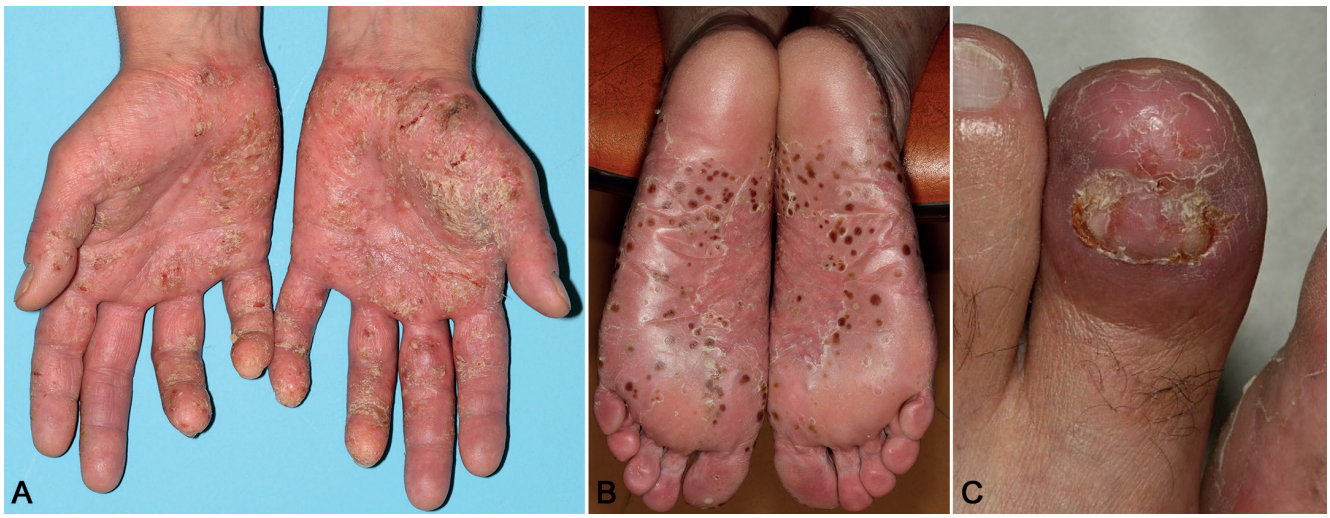

Fig. 2. Typical lesions of palmoplantar pustular psoriasis in 3 different patients free of any mutation in *IL36RN*, *CARD14* and *AP1S3* genes. (A) Pustular lesions involving palmar areas of hands, with some degree of acropustular damage, reflecting the possible association between palmoplantar pustular psoriasis and acrodermatitis continua of Hallopeau (ACH). (B) Disseminated pustules of the soles leave dark-brown macular lesions, coexisting with fresh evolutive pustules and erythemato-squamous lesions. (C) Typical lesions of ACH involving the toes, leading to destruction of the nail apparatus.

exanthematous generalized pustular eruption (AGEP), the clinical signs and symptoms of which may be impossible to differentiate from GPP, but which is caused by drugs, notably by anti-infectious chemotherapy, such as pristinamycin and amoxicillin, but also other classes, such as non-steroidal anti-inflammatory drugs, among others (23, 24). The recent detection in patients with AGEP of mutations in *IL36RN*, sometimes identical to the ones identified in patients with GPP/DITRA, challenges the current view of AGEP and GPP being separate entities (25).

GENETICS AND IMMUNOPATHOGENIC MECHANISMS

The extreme severity of these inflammatory pustular skin disorders, especially GPP, and the existence of Mendelian familial cases, raised the hypothesis of a monogenic model, unlike most cases of PV. This monogenic model has been robustly established by the identification of homozygous or composite heterozygous, loss-of-function mutations of the *IL36RN* gene, which encodes a negative regulator of the IL-36 pathway, which is involved in the limitation of the intensity of skin and systemic innate immune responses. Indeed, *IL36RN* mutations have been found in sporadic or familial cases of GPP in patients from different geographical territories worldwide (13, 26–32). These *IL36RN* mutations are more prevalent in patients with GPP without plaque psoriasis, and influence the age of disease onset (32). Mutations of *IL36RN* lead to major structural and functional impairments of its encoded protein, the IL36 receptor antagonist (IL36Ra), leading to increased inflammatory responses resulting from unrepressed interactions of the IL36 pathway agonists IL36α, IL36β and IL36γ with their receptor, and from subsequent uncontrolled activation of the transcription factor NFκB (13). This results in the massive release by keratinocytes, macrophages and dendritic cells, of several inflammatory mediators including CXCL8, TNFα, IL1 and IL23 (33). Dysregulated activation of the IL-36 pathway has also been shown to trigger the expansion and activation of TH17 cells in GPP (34). So far, different scale studies of cohorts from various geographical territories have reported various prevalences of *IL36RN* mutations, ranging from approximately 5% to 70%, while much lower prevalences have been observed in patients with PPPP, and no causal *IL36RN* mutation has been detected in patients with PV without pustular psoriasis (29–32, 34). An interesting finding has been the identification of identical *IL36RN* mutations across the different subtypes of pustular psoriasis (35). However, mutations leading to the absence of IL-36Ra protein expression are preferentially associated with the most severe entities of GPP and AGEP, while hypomorphous mutations seem to be more prevalent in PPPP and ACH (35). The major breakthrough in the identification of causal mutations of the *IL36RN* gene has been instrumental in establishing without ambiguity the autoinflammatory nature of GPP, and led to the definition of a new entity called DITRA, which differs from the previously described deficiency of IL-1 receptor antagonist (DIRA) by the presence of striking lesions of joints and bones (13, 37, 38). Finally, although causal mutations of *IL36RN* have not been found in patients with PV, several studies have shown deregulation of the IL-36 pathway in PV lesions (39).

The 2 other genes associated with pustular psoriasis so far are *CARD14* and *AP1S3*. Likewise, heterozygous gain-of-function mutations of *CARD14* (caspase activating recruitment domain, member 14), a gene expressed in keratinocytes the protein of which interacts with Bcl 10, a positive regulator of NFκB activation, has been shown to be primarily involved in autosomal dominant forms of PV and in some patients with pityriasis rubra pilaris (40–43). The Adaptor Related Protein Complex 1 subunit sigma 3 (AP1S3) gene has been also found to be heterozygously mutated in patients with different subtypes of pustular psoriasis, mainly GPP and ACH, leading to structural and functional alterations of the protein, a member of the Adaptor Protein 1 (AP1) family, contributing to deregulation of skin innate immune responses (42, 44, 45). Likewise, it is notable that some patients have "digenic" features, e.g. a pattern characterized by mutations reported to be damaging in 2 of the 3 genes identified so far (32). Further identification of other genes, especially in GPP, will undoubtedly complement the current genetic map of pustular psoriasis, and is likely to greatly contribute to personalized therapeutic approaches.

THERAPEUTICS: TOWARDS PRECISION MEDICINE

The low prevalence of pustular psoriasis and the capricious course of the disease with unpredictable flaring frequency in many cases of GPP, explain the low level of scientific evidence regarding treatment efficacy. Indeed, although topical steroids and/or vitamin D derivatives, used as single agents or combined, or phototherapies are still used in mild forms of pustular skin disease with limited involved body surface area, pustular psoriasis often requires systemic therapy. In PPPP, cyclosporine has the highest level of evidence for efficacy, while there is weak or very weak evidence, respectively, for acitretin and methotrexate (46–48). More recently, randomized, placebo-controlled phase 3 clinical trials have been conducted in PPPP with secukinumab and guselkumab, targeted inhibitors of IL17A and IL23p19, respectively (49, 50). However, neither drug showed clinically relevant superiority over placebo at the population level, suggesting that the IL23/IL17 pathway is not the major

pathogenic axis in pustular disease (49, 50). Randomized clinical trials are currently being conducted in PPPP with inhibitors of cytokines of the IL-1 family, the most advanced programme investigating the efficacy and safety of anakinra, the recombinant form of the IL-1 receptor antagonist, based on encouraging responses in isolated cases, including with ACH (51, 52).

There is even less available evidence in GPP, due to the previously exposed challenges, but also to the spontaneously self-remitting evolutive pattern of acute GPP flare. Thus positive responses reported with conventional or biological drug interventions in the setting of retrospective, or open-labelled prospective trials, should be considered with caution. Therefore, although high-dose steroids, cyclosporine, acitretin and apheresis have been promoted for severe acute flares, and although some biologics, such as IL17 inhibitors, have been approved for GPP in Japan, these interventions lack randomized controlled studies to assess the magnitude of their efficacy effect (53, 54). Furthermore, the efficacy of anakinra, the recombinant form of the IL-1 receptor antagonist, has been reported only in a case series of GPP with or without DITRA, reporting most often transient and partial responses (55, 56). These cases should be confronted with the outstanding efficacy of IL-1 inhibitors in patients with DIRA, emphasizing the fine specificity of pathogenic pathways across different monogenic autoinflammatory syndromes of the skin (36). Therefore, the emerging development of specific inhibitors of the IL-36 pathway in GPP and PPPP is not surprising. The most advanced development investigates an anti-IL-36 receptor monoclonal antibody, which, administered as a single intravenous dose, proof-of-concept study in acute GPP, showed very encouraging results in 7 patients, only 3 of whom were carrying *IL36RN* mutations (57). Ongoing phase 2 and 3 studies will provide a more accurate picture of the efficacy and safety of this new targeted strategy.

CONCLUSION

Pustular psoriasis is a very challenging spectrum of autoinflammatory skin diseases, with both clinical and genetic heterogeneity. However, the increasing collaboration between medical experts and scientists is encouraging in enabling the better nosological classification of subentities, as well as the development of specific therapeutic strategies, approximately 100 years after the pioneering description of GPP by von Zumbusch (58).

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