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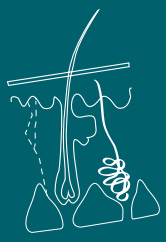

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Contents

Pathogenesis of Psoriatic Arthritis

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Abstract

Psoriatic arthritis is an inflammatory arthritis that occurs in about a quarter of patients with cutaneous psoriasis and most often begins after the onset of skin disease. PsA is highly heritable, but a greater contribution to disease susceptibility is attributable to psoriasis-associated gene variants. Class I HLA B alleles are most strongly associated with PsA. Several environmental factors, particularly trauma, have been identified as potential triggers of PsA. Recent pathogenetic studies using samples from the synovial fluid, synovium, skin and enthesis indicate the importance of tissue resident memory cells as well as CD8 T cells in disease pathogenesis. γδT-cells play an important role in the enthesis. Anti-cytokine therapies also indicate tissue cytokine hierarchy with IL-23 and IL-17 being important for skin psoriasis, TNF, IL-17and IL-23 for peripheral synovitis, TNF and IL-17 for axial arthritis, IL-17 and IL-12/23 for enthesitis and TNF and IL-12/23 for inflammatory bowel disease. The pathogenesis of PsA is complex with an interplay between genetic and environmental factors leading to aberrant immune activation possibly in the skin, gut or enthesis leading to sustained inflammation in the synovium and periarticular structures, leading to bone loss as well as new-bone formation.

1. Introduction

Psoriatic Arthritis (PsA) is defined as an inflammatory arthritis associated with cutaneous psoriasis, and is classified according to the Classification of PsA criteria (CASPAR) [1]. PsA is a heterogeneous disease: manifestations include synovitis, enthesitis, dactylitis, axial arthritis in addition to skin and nail psoriasis. These manifestations may not be present in all patients and can vary with time[2]. There is also heterogeneity in joint damage progression as well as treatment response. PsA is present in about a quarter of patients with psoriasis [3].

Most patients develop PsA after the onset of skin psoriasis [2]. Thus, a model of studying pathogenesis of PsA is to study the mechanisms that lead to the onset and progression of inflammation at the musculoskeletal structures in patients with psoriasis [4]. In this model, some patients with psoriasis develop a phase of aberrant immune response in the skin, gut or enthesis that subsequently leads to subclinical inflammation where sensitive imaging methods demonstrate musculoskeletal inflammation but the patient is asymptomatic. This is followed by the prodromal phase whereby patients experience symptoms of joint pain and fatigue with no overt signs of arthritis. Finally, patients develop signs and symptoms of overt PsA and may now be diagnosed with PsA and satisfy CASPAR [4].

2. Genetic factors

Genetic factors play a significant role in psoriatic disease susceptibility. Psoriasis and psoriatic arthritis are highly heritable [5]. In a study in the Icelandic population, the recurrence of risk ratio (λ) for PsA in first-degree relatives was found to be 39.2 [6]. This ratio declines rapidly when going down the degree of relatedness becoming non-significant with 5th-degree relatives. Since the λ in the first-degree relatives was much higher in patients with PsA than that for psoriasis alone, it was assumed that the genetic burden for PsA is higher than that for psoriasis. However, subsequent studies have not found many PsA-specific genes. Using data from genome-wide association studies (GWAS), Li et al demonstrated that both cutaneous psoriasis and PsA exhibit considerable heritability, but a greater contribution comes from cutaneous psoriasis [7]. Thus, there might not be many 'PsA-specific' gene variants. The SNPs located within the major histocompatibility region (MHC) on chromosome 6p explained a significant proportion of the heritability [7].

There have been few GWAS that have compared patients with PsA to those with psoriasis without PsA (PsC). These studies have demonstrated that only variants on the MHC are significantly different between PsA and PsC at genome-wide significance[8]. A variant near *IL23R* and another near *TNFAIP3* were more strongly associated with PsA than PsC [8]. Further interrogation of the MHC region indicated that the risk heterogeneity between PsA and PsC was driven by HLA-B amino acid position 45, where the presence of glutamine (instead of methionine, lysine or threonine) increased the risk for PsA (odds ratio: 1.46, p= 2.9×10^{-12}) [9]. This association was stronger than individual HLA C and B alleles. Interestingly, HLA alleles associated with PsA including HLA-B*27, -B*38, -B*39, as well as a number of other alleles, carries glutamine at position 45 [9]. In a similar study, Bowes et al showed that amino acid position 97 of HLA-B differentiates PsA from PsC [10].

There is a wide range in the time interval between the onset of psoriasis and PsA [11]. HLA alleles influence this relationship; patients with HLA-B*27 have a much shorter interval compared to those with HLA C*06 [12].

3. Environmental factors

Complex genetic diseases such as PsA are likely triggered by environmental factors. Overt physical trauma (deep Koebner phenomenon), microtrauma, stress, infections (requiring antibiotics), smoking and drugs such as retinoids have been associated with PsA [13]. Obesity and metabolic syndrome and associated manifestations, uveitis, depression, and thyroid disease may also provide second hits. The mechanisms by which these lead to PsA is not known; the microbiome may play a significant role [14].

4. Pathogenetic insights from target tissues

4.1 Synovium

There are no human studies evaluating immune activation prior to the onset of overt PsA. Recent studies have evaluated target tissues to describe immune activation in order to obtain clues to pathogenesis. Penkava et al studied the cellular landscape of blood, synovial fluid, and synovial tissue at single-cell resolution from a small number of PsA patients [15]. They identified significant expansions of synovial memory CD8 and memory CD4 T cells in all patients compared to blood. Plasmacytoid and conventional dendritic cells were also expanded in the synovial fluid. B cells and basophils were depleted, and monocytes, γδT, MAIT and NK cells were unchanged. When comparing gene expression between synovial fluid and blood T cells, an increased expression of activation and effector markers in synovial fluid in the HLA-DR-low CD8, HLA-DR- high CD8 and ZNF683+ CD8 clusters were observed. There was synovial clonal expansion within the ZNF683+ CD8 cluster indicating expansion of tissue resident memory T cells. Interestingly, CXCR3 was the most strongly expressed chemokine receptor gene in synovial-enriched T-cell clones. The CXCR3 ligands CXCL10, previously identified as a biomarker of progression from psoriasis to PsA, and CXCL9 were highly enriched in the synovial fluid compared to blood [15,16]. Clonal expansion of CD8 T cells indicate that arthritogenic antigen(s) may be driving immune response in the synovium. Another single cell sequencing study in PsA SF identified 12 different cell populations, with the most dominant being monocytes/macrophages. The monocytes/macrophages were comprised of four subpopulations, three of which were large representing classical, non-classical and intermediate cells. The classical monocytes/macrophages were reduced in PsA compared to other arthritides (osteoarthritis, rheumatoid arthritis), whilst the intermediate population was increased [17].

Importantly, histopathological and gene expression studies have emphasized the significant histopathological and molecular heterogeneity of the synovitis in PsA. Nerviani et al performed gene expression analysis on 14 matched synovial tissue, lesional and adjacent non-lesional skin[18]. They showed that the synovium clusters away from the skin, with a partial overlapping of lesional and non-lesional skin. Principal component analyses showed that *IL17A/F, IL23R* and *IL21* were the major contributors of variation in lesional skin, whereas in the synovium, genes related to ectopic lymphoid structure formation (*CXCL13, CXCR5*) and the IL-23 axis (*IL23A, IL12B, IL23R*) together strongly contributed to the variation. Synovial IL-23p40/p19 and IL-23R protein expression correlates with the histological inflammatory status. There was also a positive correlation between IL-23p40/IL-23p19/IL-23R-positive cells and synovitis scores, and lower IL-23 cytokines/receptor tissue-expression in the pauci-immune compared with macrophage-rich histological pathotypes [18].

4.2 Skin

Mediators originating in the inflamed skin could trigger musculoskeletal inflammation. This theory is supported by a recent study that demonstrated increased circulatory skin derived tissue resident memory CCR10+ CD8+ T cells in the peripheral circulation of PsA patients compared to patients with psoriasis [19]. However, these cells were not enriched in the synovial fluid. CD8+CCR10+ T cells co-expressed DNAM-1. DNAM-1 is an activating receptor, and TIGIT is an inhibitory receptor on T cells. CD8+CCR10+ T cells were typically DNAM-1high but had less TIGIT co-expression in PsA. Interestingly, CD8+CCR10+ T cells produced significantly more IL-17A and IL-22 compared to bulk CD8+ T cells on ex vivo restimulation and may be initiating synovial inflammation [19].

4.3 Enthesis

The entheses are important target tissues and may be the initial site of inflammation in PsA and other spondyloarthritides [20]. However, it is difficult to obtain biopsies of inflamed enthesis to study pathogenesis. Therefore, studies have used cadaveric tissues as well as spinous processes entheseal soft tissue (EST) and peri-entheseal bone (PEB) obtained during elective orthopaedic procedures. Cuthbert et al showed that γδT-cells are present in the EST and PEB and adjacent haematopoietic bone marrow and in the soft tissue of the ligaments [21]. γδT-cells were also observed in inflammatory infiltrate in ruptured Achilles' tissue, indicating their presence at the sites of injury. The Vδ1 subset of γδT-cells had a far greater proportion of cells with a naïve phenotype compared with the Vδ2 subset. Vδ1 subset from peri-entheseal bone contained a greater proportion of the tissue resident memory phenotype compared to those from blood. Following stimulation with a combination of anti-CD3/CD28, IL-17A, IL-17F and IL-22 transcripts was detected in Vδ1 and Vδ2 subsets. However, IL-23 stimulation had almost no effect in the Vδ1 subset but caused a marked increase in the Vδ2 subset. This study demonstrated that spinal entheseal Vδ1 and Vδ2 subsets are tissue resident cells with inducible IL-17A production and that the Vδ1 subset does so independently of IL-23R expression [21]. These studies indicate the possible role

of tissue resident Vδ1 γδT-cells in the entheses. The production of IL-17 independent of IL-23R expression might be the reason behind the lack of efficacy of IL-23 inhibitors in axial spondyloarthritis.

5. Insights from clinical trials

Anti-cytokine therapies have also provided us with insights into the importance of cytokines that drive inflammation in the different of PsA. Evidence from randomised clinical trials indicate tissue cytokine hierarchy with IL-23 and IL-17 being important for skin psoriasis, TNF, IL-17and IL-23 for peripheral synovitis, TNF and IL-17 for axial arthritis, IL-17 and IL-12/23 for enthesitis and TNF and IL-12/23 for inflammatory bowel disease [22].

6. Relatinship between skin and musculoskelatal inflammation

The intimate relationship between skin and musculoskeletal inflammation begets the question whether the relationship between inflammation at the two sites is successive (changes in the skin triggering musculoskeletal inflammation) or synchronous (a common trigger leading to skin and musculoskeletal inflammation). Both mechanisms may be operative (figure).

7. Summary and conclusion

Thus, the pathogenesis of PsA is complex with an interplay between genetic and environmental factors leading to aberrant immune activation possibly in the skin, gut or enthesis leading to sustained inflammation in the synovium and periarticular structures, leading to bone loss as well as new-bone formation. Taking into account the disease phenotypes and genetic (HLA) associations, Jadon et al proposed model of pathobiology of psoriatic disease [23]. They propose that amplification of the IL-23–IL-17 axis is initiated by activation of innate cells in the skin, entheses and gastrointestinal tract, ultimately resulting in the expansion of CD4+ and CD8+ Th1 and Th17 cells, which are expanded by IL-23 and IL-12 and produce TNF and IL-17. Different HLA alleles and/or haplotypes, T cell subsets and treatment response profiles are associated with different phenotypes. Synovial-predominant disease is associated with HLA-B*08:01:01, HLA-C*07:01:01, CD8+ engagement with Th1 cells and is responsive to TNF inhibition. Cutaneous-predominant disease is associated with HLA-B*57:01 and HLA-C*06:02, Th1 cell-driven and is responsive to IL-17 and IL-23 inhibition. Entheseal-predominant with or without axial disease is associated with the HLA-B*27:05:02 allele, involves engagement of both Th1 and Th17 cells that produce both TNF and IL-17, and is responsive to TNF and IL-17 inhibition. Arthritis mutilans likely represents a combination of these host genetic factors and T cell interactions [23].

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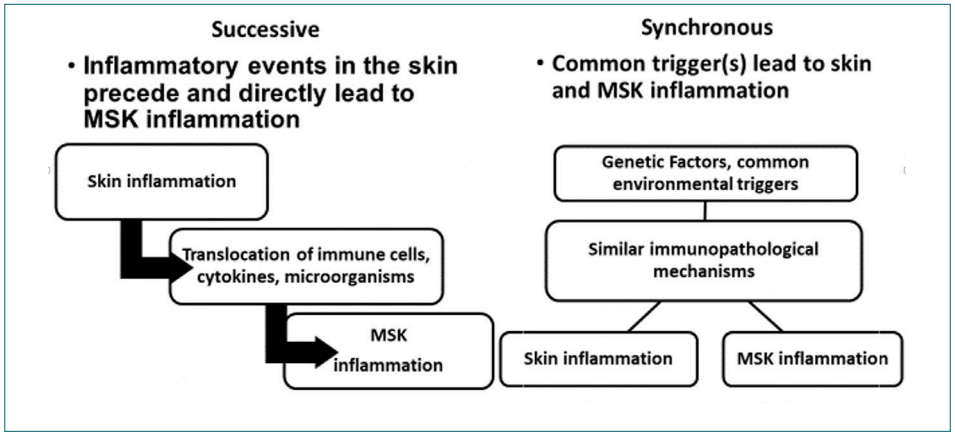
Figure 1. The relationship between skin and musculoskeletal inflammation in psoriatic arthritis. MSK- musculoskeletal.



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Inflammatory diseases – a new way of thinking

Lessons from 30 years of psoriasis management

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Abstract

Psoriasis, psoriatic arthritis, ankylosing spondylitis and the inflammatory bowel diseases form a group of pathogenetically related and possibly co-occurring diseases. After its onset, psoriasis is usually a chronic disease that often requires lifelong treatment. Today, several groups of drugs are available for the treatment of psoriasis, with different characteristics, efficacy and safety. To use these drugs appropriately, we need to develop rational criteria and strategies. Decision making in psoriasis treatment should be tailored to the individual condition and needs of the patient, considering the life phase, associated diseases and co-morbidities. In addition to the acute improvement of the disease, psoriasis therapy should generate long-term perspectives that must be developed between the patient and the treating dermatologist and implemented in management concepts.

1. Introduction

The treatment of psoriasis has made tremendous progress over the last two decades and has become seemingly simple. A number of therapeutic biologics have been developed that causally intervene by blocking certain cytokines in the immunological cascade of the T-cell mediated autoimmune response of psoriasis. Thus, depending on the drug, an injection given at intervals of 2 to 12 weeks can significantly improve the course of psoriasis and psoriatic arthritis and in a substantial percentage of patients even completely clear the psoriatic symptoms. Recent drug developments include JAK/STAT and Tyk2 inhibitors of the Janus kinase pathway, small molecules that inhibit intracellular cytokine signalling. The mechanism of action of the drugs corresponds to several genetic associations of psoriasis, which, with common gene variants such as of TNFAIP3 (TNF alpha induced protein 3), TNIP1 (TNFAIP3 interacting protein 1), TRAF3IP2 (TRAF3 interacting protein 2), IL23R (IL-23 receptor), IL12B (p40 chain of IL-12 and IL-23), IL23A (p19 subunit of IL-23), TYK2 and STAT2, define central sites in the pathogenetic cascade of psoriasis. Several of these gene variants are pleiotropic and shared between different immune-mediated diseases, which are associated with each other as a complex of psoriasis, peripheral arthritis, ankylosing spondylitis

and inflammatory bowel disease. They point to specific disease pathways and possible therapeutic approaches, which are reflected in the common response of psoriasis, psoriatic arthritis, ankylosing spondylitis and IBD to, for example, IL-23 or TNF-α blockade [1].

The presentation made at 6th WPPACongress focused on individual aspects that may play a role in the decision for the respective drug from my own clinical experience. This presentation was not intended to constitute a review of psoriasis therapy as a whole. The congress took place in 2021. The content therefore reflects the state of affairs in 2021. At that time, no JAK/STAT inhibitors were approved for plaque psoriasis. Currently, there are comprehensive reviews available to fully address the current state of the art.

2. Rational use of psoriasis drugs

Overall, this conveys the view: give an injection and the skin is clear. However, rational use of the appropriate medications should take into account that psoriasis is a lifelong disease after its onset, which usually occurs in adolescence or early adulthood. As a chronic inflammatory disease, psoriasis requires potentially life-long treatment. Consequently, psoriasis establishes long-term relationship between the patient and the treating dermatologist. The treating physician must adapt the treatment decisions to the current and future phases of life and to various and often unforeseen events. These aspects are not covered by clinical trials that select patients according to strict criteria that may not reflect life reality. They document the well-controlled exposure to treatment in rigorously selected patient populations that usually exclude real life aspects such as certain concomitant diseases, risk of associated disease, pregnancies and breast feeding, chronic or latent infections, history of malignancies and other life events. Therefore, common therapy concepts are much based on the question how fast and to what extent an improvement can be achieved. This may not always correspond to the actual patient situation and miss relevant necessities. Treatment concepts must take into account very different aspects such as the different prognoses of the diseases of the psoriasis complex. While in psoriasis a complete full reconstitution into a normal skin condition is clinically possible, arthritis and ankylosing spondylitis with the damage to the joints as well as inflammatory bowel disease (IBD) with scarring, stenoses, perforations and fistulas produce permanent impairment. The presence of arthritis and IBD with psoriasis therefore justify a more rapid access with early intensive intervention, while psoriasis of the skin allows for a slower and more restrained approach. For all these special circumstances, experience-based therapeutic decisions must be developed together with the patient.

Psoriasis management today means: Develop concepts, respond to circumstances and deliver solutions in accordance with the age, life circumstances and possible concomitant diseases of the respective patients. In addition to the direct improvement of symptoms, psoriasis treatment should create long-term perspectives. The lifelong need for treatment and exposure to medications should furthermore consider the principles of medical practice that were established by the physician Scribonius Largus at the court of Emperor Tiberius Claudius and have been valid since antiquity: Primum non nocere, secundum cavere, tertium sanare: First don't harm, second be careful and third cure the disease.

3. Development of life phase-adapted therapy and management concepts that consider future aspects

Psoriasis treatment concepts must consider many aspects. Treatment should be tailored to the patient's age, career developments, need for vaccinations, diseases associated with the psoriasis complex, concomitant diseases, and other aspects. In the family planning phase, drugs should be chosen that do not pose a later risk of malformation or teratogenicity. Overall, this requires early development of long-term treatment concepts that take into account the patient's needs and the particular characteristics of the available drugs.

National regulatory requirements may affect the treatment decisions. In different health care systems, such as in Germany, the less expensive, low-cost forms of treatment, such as phototherapy, fumaric acid esters, methotrexate, acitretin and ciclosporin, must be used first. Only when these drugs were not effective, could not be given because of contraindications or had to be discontinued because of side effects, the therapy may be escalated and biologics may be used. Then it is necessary to decide which cytokine should be blocked.

4. Choosing the right drugs

4.1. Biologics

Multiple aspects affect the choice of a particular biologic for psoriasis treatment [2,3]. With the exception of infliximab, blockade of TNF-α is associated with a comparatively lower efficacy in psoriasis than the blockade of other cytokines, but generally has a higher risk of severe infections and exacerbations of latent tuberculosis. Especially in regions with a high tuberculosis prevalence, this may be problematic. A family history of multiple sclerosis is a contraindication. Nevertheless, TNF-α antagonists also have considerable advantages. With the exception of congestive heart failure, TNF-α antagonists are cardio-protective, reducing the incidence of cardiovascular events. They show well-established efficacy in concomitant psoriatic arthritis, ankylosing spondylitis and Crohn's disease, which particularly justify their use when these diseases occur together with psoriasis. Furthermore, there are two representatives of the TNF-α antagonists that differ in structure from the cytokine antibodies. In etanercept, the extracellular domain of the TNF-α receptor is fused with an IgG-Fc part. This causes a short serum half-life and high application frequency of approximately three days, which, in comparison to the antibodies, allows a short-term discontinuation of therapy in the case of infections and is thus easily controllable. Furthermore,

etanercept is not contraindicated in patients with hepatitis C virus infection and can even reduce the viral load. In certolizumab pegol, a humanized antigen-binding fragment (Fab') of a TNF-α antibody has been conjugated to a polyethylene glycol residue. The absence of the Fc region prevents transplacental transfer or transfer into breast milk, thereby avoiding drug exposure of the fetus or newborn. Accordingly, certolizumab is the most preferred agent for the treatment of pregnant or lactating women and should be kept in reserve for this indication in female patients of childbearing age.

The IL-17 antagonist bimekizumab shows the highest efficacy and the fastest onset of therapeutic efficacy in psoriasis [4-7]. The IL-17 antibodies are also approved for psoriatic arthritis and ankylosing spondylitis. However, the high efficacy is accompanied by an increased risk of candida infections. Especially in patients with concomitant diabetes mellitus, who per se have an increased risk of candidiasis, or in patients with a history of urogenital candidiasis, IL-17 antibodies should be used cautiously. Furthermore, IL-17 blockade can trigger inflammatory bowel disease. Before prescribing IL-17 antibodies, the presence of IBD in the patient and in the family history should be excluded.

Blockade of interleukin (IL-) 23 or of IL-12/IL23 allows long application intervals. Compared to the somewhat faster-acting IL-17 antibodies [8], they have a better safety profile lacking *Candida* infections [9]. They are also effective in peripheral psoriatic arthritis and especially in enthesitis and dactylitis, but are not sufficiently effective in ankylosing spondylitis. Instead, they show superior efficacy in IBD accompanying psoriasis

The efficacy of fixed-dose biologics decreases with increasing body weight. The weight-based dosing of infliximab and ustekinumab makes the two biologics particularly suitable for the treatment of obese patients.

The risk of developing anti-drug antibodies when biologic therapy is interrupted is highest for TNF-α antibodies and secukinumab. Therefore, a biologic treatment should always be conducted as a continuous therapy, since an interruption of the application can cause a loss of efficacy and thus of the drug for the patient [10, 11].

4.2. Conventional anti-psoriatics

Despite the high efficacy and documented safety of biologics, conventional anti-psoriatics still have a role of their own [12]. Non-biological drugs have the advantage that their effectiveness can be better controlled by a rapid termination in the event of adverse events or other unforeseen occasions such as the need for vaccination, infections or trauma. Unlike biologics, they do not induce the formation of anti-drug antibodies that would prevent a response to retreatment.

Methotrexate has cardioprotective effects. It is therefore particularly suitable for elderly patients with a high cardiovascular risk. Ciclosporin can produce rapid remissions of psoriasis as an acute intervention for short treatment periods of several months without much risk of adverse events, as may be required presurgically or for other life events. It may induce remission in patients with refractory Crohn's disease, and it may be used in pregnant women. However, nephrotoxicity limits the duration of ciclosporin use to a few months, so it doesn't offer a longer-term perspective. Acitretin is particularly suited in patients with a history of malignancy, although the expected efficacy is much lower than with other drugs. Fumaric acid esters are a first-line therapy when available (approved in the European Union). If tolerated and effective, they can control psoriasis with a long-term perspective. However, their use should be discontinued if lymphopenia occurs, which can be prolonged and is then a contraindication to other medications, such as methotrexate or ciclosporin. The use of conventional anti-psoriatics is in turn limited in the presence of other diseases of the psoriasis complex. In psoriatic arthritis, only methotrexate offers a certain perspective, as it improves inflammation but not radiographic progression of joint damage. This makes it a basic treatment in psoriatic arthritis that usually has to be supplemented by suitable biologics. Inflammatory bowel disease is not adequately controlled by any of the conventional drugs in the long term; in this case, the immediate use of TNF-α antagonists or IL-12/IL-23 or IL-23 antibodies is justified.

4.3. Novel small molecules

The phosphodiesterase-4 inhibitor apremilast is active in psoriasis and psoriatic arthritis, although the expected effectiveness is quite low. Due to the lack of drug-drug interactions, apremilast is particularly suited for the treatment of patients with multiple concomitant medications. As with acitretin, a history of malignancy is not a contraindication, while depression limits the use of both drugs. For the inhibitors of the JAK/STAT cascade [13] and of Tyk2 [14], there is still too little experience from the long-term exposure of psoriasis patients yet. They are at least a reserve strategy for psoriasis and psoriatic arthritis when other drugs have failed. Effects beyond immunomodulation generally implicate a lower specificity for the pathogenic immunological cascade of psoriasis and thus entail a new spectrum of adverse events, including the (rare) occurrence of thrombosis and thromboembolism.

4.4. Childhood psoriasis

Most biologics are now approved for childhood psoriasis from a certain age on. Here, efficacy and safety correspond to the use in adults [2,3]. The conventional anti-psoriatic drugs methotrexate, ciclosporin and acitretin are considered safe and effective for short-term administration. While premature closure of epiphysis by acitretin cannot be ruled out, no effects on the skeleton have been observed and the administration of acitretin in this age group is considered largely safe [15].

5. Decision making - a permanent challenge in psoriasis treatment

The different properties of psoriasis medications imply different decision criteria. This includes trying to adapt drugs to

patient age and, if possible, avoiding drugs that may have a unique benefit in later stages of life. In women of childbearing age, keep certolizumab in reserve for later pregnancy. Consider methotrexate in elderly patients with cardiovascular diseases. Consider medicines with a short half-life and the possibility of flexible dosing in infectious conditions or when surgery is required. Consider weight-based medications for overweight patients. Avoid IL-17 blockade and acitretin in patients with a family history of inflammatory bowel disease. Avoid TNF blockers in patients with a family history of multiple sclerosis. Avoid acitretin or apremilast in patients suffering from depression. Use ciclosporin for short-term remission if rapid clearance is required. Don't interrupt biologic therapy unless required to avoid formation of anti-drug antibodies. Use phototherapy, acitretin or potentially apremilast in patients with a history of malignancy.

6. Inflammatory disease – a new way of thinking: some conclusions from 30 years of psoriasis management

Psoriasis belongs to a group of pathogenetically related diseases and has comorbidities, all of which must be considered in the treatment decision. Today, there are numerous treatment modalities available with different characteristics. Efficacy must not be the sole criterion for a particular drug or treatment. To use these drugs appropriately, we need to develop better criteria and strategies that are adapted to the actual patient condition, take into account the current and later phases of life, consider family history and other aspects. Accordingly, decision-making in psoriasis treatment should be tailored Case by Case and Phase by Phase (of life).

Authors' contributions

J.C.P. wrote the manuscript.

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Recent innovations in psoriasis

Cardiovascular disease, COVID-9, Teledermatology and psoriasis in 2022

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Abstract

In a global webinar on psoriasis, organised by IFPA on 18 February 2021, I presented a selection of new insights into psoriasis and its management. Our knowledge of (1) cardiovascular comorbidities of psoriasis, (2) the relationship between the immunology of COVID-19 and targeted treatments of psoriasis, and (3) practical skills in teledermatology have advanced markedly during those years that the COVID-19 pandemic was a major threat to humanity. In these areas, compelling new findings and experiences are reported. Some of these steps forward are the direct result of the COVID-19 pandemic and many innovations are the result of continuations of clinical research, although COVID-19 impacted us.

Introduction

It is a well-established fact that patients with psoriasis have an increased cardiovascular risk. In a study by Gelfand et al. on a large collective of patients in the UK with a total of 556,995 control patients and patients with mild (n=127,139) and severe psoriasis (n=3,837), a total of 11,194 myocardial infarctions (MIs) were found in the control group (2%) against 2,319 (1.8%) and 112 (2.9%) MIs in the patients with mild and severe psoriasis groups [1]. An important observation was that the risk was higher in patients below the age of 50. In various regions of the world, similar results were found [2–5]. In a German health insurance database (n=1,344,071), metabolic syndrome and related conditions are more prevalent in those with psoriasis than those without psoriasis [6]. Therefore, it is of major importance that screening for cardiovascular risk factors is established in all national guidelines on the management of psoriasis. The joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities provide practical guidance for screening for vascular risk factors for psoriasis consultations (Table 1) [7].

The question arises at what age we should start with screening for cardiovascular risk factors in patients with psoriasis. In a study on paediatric psoriasis by the International Psoriasis Council (IPC), cardiovascular risk factors were observed in increased frequency in children with psoriasis as compared with children without psoriasis: waist circumference above the 90th percentile occurred in 9.3% of the control (n=19), 14.0% of the mild psoriatic patients (n=27), and 21.2% of the severe.

Insight into the pathogenetic relation between cardiovascular disease and psoriasis has revealed important shared pathways between psoriasis and the formation of atherosclerotic plaque. IL-17 has been suggested to be a potential mechanistic link between psoriasis and cardiovascular disease [9,10]. A 52-week, randomised, double-blind, placebo-controlled trial on secukinumab was carried out in patients with moderate-to-severe plaque psoriasis without clinical CV disease [11]. The primary outcome was endothelial function measured by flow-mediated dilation (FMD). Baseline FMD was significantly lower in psoriasis patients than in healthy volunteers (4.4 ± 3.9% vs 6.1 ± 3.3%; P<0.01). At week 52, FMD increased across groups. FMD was significantly higher than baseline in patients receiving the label dose of 300 mg secukinumab for 52 weeks (2.1%; P<0.0022).

More recently, insights into the genetics of psoriasis and obesity and cardiovascular disease have been gained from Mendelian randomisation studies [12,13]. From these studies, it appeared that the genetic risk for obesity and cardiovascular disease

Table 1. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities [7]

CV risk assessment (screening for hypertension, diabetes, and hyperlipidemia) with national guidelines is recommended for all patients with psoriasis.
Clinicians should consider early and more frequent screening for hypertension, diabetes, and hyperlipidemia in psoriasis patients who are candidates for systemic or phototherapy or who have psoriasis involving >10% of the BSA.
Risk score models should be adapted for patients with psoriasis by introducing a 1.5 multiplication factor when the patient with psoriasis meets either criteria: disease severity of BSA >10% or candidate for systemic or phototherapy.
CV risk management in psoriasis for hypertension and dyslipidemia should be carried out according to national guidelines. The target for blood pressure and lipid levels are based on risk calculated for psoriasis. Antihypertensives and statins may be used as in the general population. CV risk management should be performed by either a primary care physician or other healthcare provider experienced in CV risk management or the dermatologist.

causes psoriasis, but the reverse could not be shown: the genetic risk for psoriasis does not induce obesity or cardiovascular disease, which implies that psoriasis in itself might not be causal for cardiovascular disease. However, psoriasis is an indicator disease for cardiovascular disease, which is compatible with the observation that cardiovascular risk factors can be present in patients with psoriasis at an early age. Furthermore, weight reduction and other lifestyle improvements should be advised early on. In line with the causal relationship between obesity in the direction of psoriasis is the observation that weight reduction may improve psoriasis involvement of the skin considerably [14].

Anti-inflammatory treatments for psoriasis have been suggested to reduce cardiovascular risk. In particular, intensive treatment of psoriasis with anti-TNF, anti-IL-12/23, and anti-IL-17 have been claimed to have positive effects on cardiovascular comorbidity. A prospective observational study with biologic therapy versus non-biologics therapy revealed a significant improvement in coronary artery parameters after one year follow-up: total plaque burden and non-calcified plaque burden improved significantly [15].

Various biologics used to treat psoriasis influence vascular inflammation and cardiometabolic parameters, thereby reducing cardiovascular risk [16–19]. Furthermore, methotrexate, cyclosporine, and tofacitinib have been suggested to impact vascular inflammation and biomarkers of cardiometabolic disease in psoriatic patients [20]. Also, the small molecule apremilast proved to induce beneficial changes in blood cardiometabolic biomarkers [21]. However, further prospective controlled studies are needed before we can conclude whether anti-inflammatory treatments of psoriasis improve cardiovascular comorbidities in patients with psoriasis.

In studies on big data, substantial reductions of cardiovascular risk have been shown by anti-TNF; 3-year exposure to TNF antagonists resulted in a 51% reduction of the hazard for cardiovascular disease [22]. On the other hand, data from patient registries have been less convincing so far [23]. In a large prospective cohort study, the risk reduction of cardiovascular disease between three different biologic therapies and methotrexate could not be shown to be different [23]. Further well-designed prospective controlled long-term studies are needed before we can conclude whether anti-inflammatory treatments of psoriasis improve cardiovascular comorbidities in patients with psoriasis.

So far, our knowledge of the impact of various anti-psoriatic treatments on cardiovascular disease and cardiovascular disease risk factors is fragmentary. But, should we wait for evidence from long-term controlled studies before taking advantage of the daily practice of these new compelling insights revealed by surrogate markers for cardiovascular disease? In a learning healthcare environment, we can treat our patients while capturing real-world evidence on the effect of the anti-psoriatic treatments on cardiometabolic risk factors and cardiovascular disease in patient registries, not only from the point of view of pharmacovigilance but from the point of view of a more holistic disease severity assessment, which is more than skin deep, considering cardiovascular risk and comorbidity.

Lessons from COVID-19

The pandemic COVID-19 has had its impact on patients with psoriasis. The virus SARS-CoV-2, responsible for COVID-19, invades host cells in the lung [24]. Binding of the spikes of the virus with angiotensin-converting enzyme (ACE)2 receptors is the first step. Viral replication follows and an immune response is induced which comprises a T-cell response and a differentiation of B cells into plasma cells, producing neutralising antibodies. Type I interferon is a critical cytokine in the first week of the COVID-19 infection. Crucial in the course of COVID-19 is whether a cytokine storm will complicate the immune response. It has been shown that TNF, IL-17, and IL-4 are key cytokines in the cytokine storm. The cytokine storm is responsible for the life-threatening course COVID-19 may have.

It is intriguing that anti-TNF and anti-IL-17 are important treatment classes for psoriasis. In the first months of the COVID-19 pandemic, dermatologists felt unsure about the impact of systemic non-biologics and biologics on the course of COVID-19 and later on the course of the COVID-19 vaccination process. In particular, the fear that patients on these drugs might have a more severe course of the disease as these drugs are contraindicated in active infections, but also the fear that these treatments may facilitate contracting COVID-19. Similar questions arose when vaccinations became available. Are vaccinations safe in patients who are on systemic treatments for psoriasis? Are vaccinations effective when patients are on these treatments?

At first, decisions were based on the best insights into modes of action of anti-psoriatic drugs and the pathomechanism in COVID-19. Early in the pandemic, a registry was constructed and international organisations motivated dermatologists to collect information on patients with psoriasis, the treatments they received for psoriasis, and the course of COVID-19.

To build evidence for the decision to continue or discontinue immunosuppressive medication in patients with psoriasis during the COVID-19 pandemic, another international patient registry was established: PsoProtect. This registry also collected detailed information on patients with psoriasis, who contracted COVID-19. The information collected in the registries provided evidence relevant to clinical practice on the treatment of psoriasis in COVID-19. COVID-19-related hospitalisation in patients on biologics proved to be lower than in patients on non-biologic systemic therapies [25]; however, it is remotely possible that patients on biologics had more rigorous isolation, which might be a confounding factor. In the population of patients with psoriasis, the well-known risk factors (older, male, non-white ethnicity, and comorbidities) caused higher hospitalisation rates. Similar trends were seen in other immune-mediated inflammatory diseases (IMIDs). Data from 3 international COVID-19 registries (including patients with rheumatic diseases, inflammatory bowel disease,

and psoriasis collected from 12 March 2020 to 1 February 2021) were merged [26]. TNF inhibitor monotherapy implied a lower risk of a bad COVID-19 outcome compared with other immunomodulatory treatments in patients with IMIDs.

This rapid development of partially harmonised, international patient registries was an important international achievement [27]. Real-world data have helped to formulate the lessons of this pandemic. One of those lessons is that biologics are safe in children with psoriasis and COVID-19 [28]. In 15% of the children, an aggravation of psoriasis was seen during the pandemic. Greater shielding among people with IMIDs receiving targeted therapies may contribute to the reported lower risk of adverse COVID-19 outcomes.

The question arises to what extent shielding causes the lower occurrence of severe COVID-19 development in those patients using targeted treatments [29]. In an international patient survey, 2,262 of 3, 720 participants (60.8%) reported risk-mitigating behaviour or 'shielding'. Patients receiving targeted therapies (biologics and Janus kinase inhibitors) reported shielding more frequently compared with those receiving no systemic therapy. Shielding was also associated with risk factors for severe COVID-19 comorbidity, indication for drugs for rheumatic musculoskeletal diseases and anxiety or depression.

Anxiety and non-adherence regarding antipsoriatic treatments have impeded the treatment of psoriasis during COVID-19 [30]. In patients with worsening psoriasis, anxiety to take the medication might be the reason for aggravation. Fears, anxieties, and confusion have to be addressed by an optimal doctor-patient relationship and, if needed, psychotherapy.

Only 8% of individuals with psoriasis reported vaccine hesitancy [31]. This is reassuring for the efficacy of COVID-19 vaccine uptake. Identifying individuals with concerns regarding COVID-19 vaccination and providing personalised information will help to reduce the risk of patients with psoriasis in the ongoing pandemic.

Teledermatology and psoriasis

Teledermatology has been practised by dermatologists for years. During the COVID-19 pandemic, we had to learn how to work more and more in the virtual environment. There is, however, a large variation between dermatologists in enthusiasm and actual use of teledermatology for psoriasis. Some dermatologists are reluctant with respect to making the diagnosis and starting and maintaining treatment of psoriasis using teledermatology. Other colleagues are enthusiastic about the opportunities teledermatology is providing with respect to psoriasis care.

During the COVID-19 pandemic, we had to make far more intense use of teledermatology for the treatment of psoriasis and interestingly, the popularity of teledermatology has increased. Teledermatology may be restricted to the dermatologist and the patient or it may be the consultation of both the general practitioner, the dermatologist, and the patient. Storing and forwarding pictures is a highly efficient form of teledermatology, where the consultation by the patient and the reply by the dermatologist do not have to be synchronous. Live video conferencing is a more dynamic form of consultation, which is of course synchronous.

The International Psoriasis Council (IPC) installed a working group of experts in telemedicine [32]. Statements on opportunities and limitations of telemedicine in the diagnosis and treatment of psoriasis were formulated by this group. Thirty-six statements were agreed upon. Overall, the value and necessity for the implementation of teledermatology in dermatologic healthcare practices for psoriasis was regarded to be crucial by the group. Best practices on personalised care in psoriasis have to be developed and shared. Especially for early diagnosis of psoriasis, teledermatology provides opportunities but also limitations; in particular, in case the diagnosis is not so apparent.

According to the working group, initiation and maintenance of topical treatments can be managed by teledermatology. Also, for maintenance treatments of patients with biologics, teledermatology provides an excellent approach with a low threshold approach contact possibility. For remote areas in the world, different forms of teledermatology can be successful. For some situations teledermatology may have limitations; for example, when whole skin inspection is needed and in case of functional tests (psoriatic arthritis).

In a learning healthcare environment, we have to take advantage of the opportunities of telemedicine and in-person consultations, reconciling the individuality of the patient and his/her psoriasis. Everyone has his own psoriasis and every person is unique, so, we have to personalise the treatment, making use of the classical in-person consultations where needed and possible and teledermatology where appropriate.

The impact of the innovations described above for patients living with psoriasis and their dermatologist are clear:

1. Cardiovascular comorbidities and psoriasis are associated. Screening for cardiovascular risk factors is also important in patients with a short history of psoriasis. Adequate treatment of these risk factors is important.
2. Lessons from COVID-19 comprise the insight that COVID-19-related hospitalisation in patients on biologics was lower than in patients on non-biologic systemic therapies, and regarding vaccination: there is no reason to avoid vaccination in patients with psoriasis. For an up to date advice on COVID-19 and psoriasis, consult the IPC webpage: www.psoriasiscouncil.org/covid-19/ipc-statements-on-covid-19-psoriasis
3. Practical skills in teledermatology have advanced markedly during the COVID-19 pandemic. Compelling new findings and experiences have emerged that enrich treatment opportunities and improve access to care worldwide.

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Comorbidity in adult psoriasis

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Abstract

Psoriasis is a chronic systemic immune-mediated disease associated with an extensive list of comorbidities [1]. In this proceeding paper, we have focused on two comorbidities with high clinical impact: cardiovascular disease and liver disease. Patients with psoriasis have an increased risk of cardiovascular disease, with reduced life expectancy as a consequence. The reason for this is still not fully understood; however, it is most likely caused by a combination of common systemic low-grade inflammation, shared genetics, and co-existing cardiovascular risk factors. Screening for cardiovascular risk factors and cardiovascular disease, enabling early detection and treatment is crucial. If anti-psoriatic treatment reduces risk of cardiovascular disease is still not clear. Patients with psoriasis also have an increased risk of liver disease, historically attributed to the use of methotrexate. However, recently several studies have reported increased frequency of metabolic dysfunction-associated steatotic liver disease (MASLD), and subsequently, the focus has shifted towards metabolic risk factors, such as obesity and diabetes. The relationship between psoriasis and the liver is complicated and not fully understood; however, presumably a result of the large total burden of risk factors for developing liver disease including low-grade systemic inflammation, obesity, alcohol consumption, and use of methotrexate.

Comorbidity in adult psoriasis

Psoriasis was once thought to only involve the skin, but today the disease is recognised as a chronic systemic disease associated with a high burden of comorbidities [1]. Psoriatic arthritis is the most well-known comorbidity, which is considered as a disease entity with psoriasis, affecting ~20% of the patients [2]. There is an extensive list of other disorders that occur more frequently in patients with psoriasis such as cardiovascular disease (CVD), liver disease, the metabolic syndrome, inflammatory bowel disease, pulmonary disease, chronic kidney disease, mental disorders, and malignancies [3].In this proceeding paper we will focus on two comorbidities with high clinical impact; cardiovascular disease and liver disease. Additionally, causal associations will be discussed.

Cardiovascular disease

CVD, such as myocardial infarction and stroke, is a leading cause of death globally [4] highlighting the importance of sufficient treatment and prevention of the disease. Patients with psoriasis have an increased risk of CVD, and reduced life expectancy as a consequence [5,6]. In the early 1970s, the association between psoriasis and CVD was first suggested by a small retrospective study [7]. Approximately 30 years later, a landmark study confirmed this link [8] and since then, several epidemiological studies have showed similar findings [9–12] Some of these studies indicate that the risk of CVD is highest among young patients with severe psoriasis and that the risk increases with the severity of the disease [8,10]. Further, the risk of CVD is observed to be equal to patients with diabetes, which is already a well-known risk factor of CVD [10]. Additionally, subclinical atherosclerotic disease, detected by cardiovascular imaging studies including e.g., positron emission tomography/computed tomography (PET/CT) and ultrasound imaging, is increased in patients with psoriasis [13–15]. Indeed, multiple studies have been published the last three decades, providing strong evidence that patients with psoriasis have an increased risk of CVD and subclinical CVD [16–20].

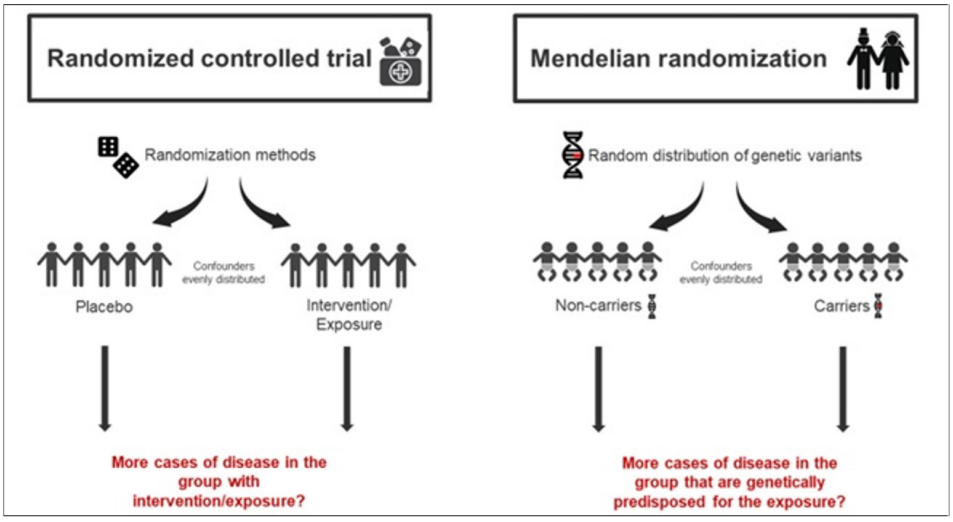
Let´s begin with the cardiovascular risk factors.

Patients with psoriasis have a higher frequency of established CVD risk factors such as hypertension, obesity, diabetes, hyperlipidaemia, the metabolic syndrome and they tend to smoke more [21–24]. The reason for this high frequency of CVD risk factors in patients with psoriasis is not fully understood. Are traditional CVD risk factors actually risk factors for both psoriasis and CVD? Or could it be a matter of *reverse causation*, meaning that psoriasis, due to its large negative impact on the quality of life, could lead to use of unhealthy stimuli? Shared genetics could also be part of the explanation.

Most findings regarding psoriasis and CVD risk factors are results from observational studies. Inherent limitations of observational studies are confounding and reverse causation [25], even though matching and statistical adjustments try to compensate for these limitations. Thus, associations and correlations can be found in observational studies; however, causal relationships are more difficult to prove. Recently, the causal relationships between psoriasis, the many CVD risk factors and comorbidities have been explored in Mendelian randomization (MR) studies [26–31]. The MR approach is based on Mendel´s law of inheritance and uses the fact that genetic variants are randomly distributed during conception[25,32–34], and in this way imitating the randomized controlled trial (Figure 1). By using genetic variants as a surrogate (instrumental variable) for a modifiable exposure, e.g., lifestyle factors, to examine the effect on a specific disease (e.g., psoriasis), confounding and reverse causation are less likely to occur. In situations where the randomized controlled trial cannot be conducted, the MR-study can be a valuable tool. For instance, several MR-studies have shown a causal relationship between obesity and psoriasis [26,29]. These results support previous observational findings, e.g., that weight loss reduces the severity of psoriasis [35,36]. There are possible limitations in MR-studies [33], and findings from MR-studies should be interpreted in the context of other observational studies. In addition, findings should also be confirmed by more MR-studies. For example, one MR study have found that smoking is a causal risk factor for psoriasis [29]; however, these findings could not be confirmed in another MR study [37].

The Mendelian randomization (MR) design uses the fact that genetic variants are randomly distributed during conception. Confounders are therefore equally

Figure 1. Randomized controlled trial vs. Mendelian randomization



disseminated in the group without the genetic variant (non-carriers) versus the group with the genetic variant (carriers). The MR study therefore imitates the randomized controlled trials.

So why do patients with psoriasis have increased risk of cardiovascular disease?

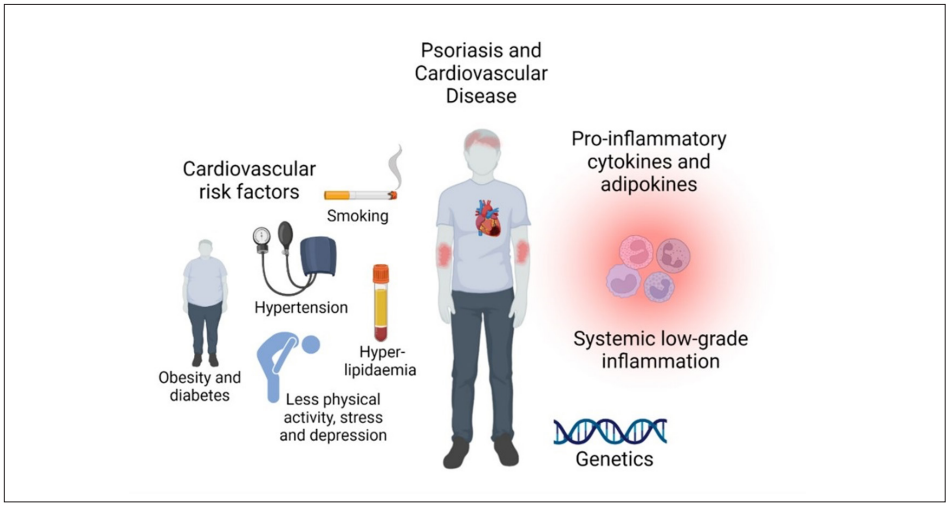
The possible mechanisms of the increased risk of CVD in patients with psoriasis are still discussed and the exact mechanisms are not fully understood. Several studies suggest that psoriasis itself is an independent risk factor of CVD after adjusting for other potential risk factors [8,38,39]. This has recently been confirmed by MR-studies [29,40]. Inflammation is not only restricted to the skin in patients with psoriasis, and a state of chronic systemic low-grade inflammation occurs in these patients which may in part contribute to the increased risk of CVD.41 This is supported by increased levels of blood inflammatory markers such as C-reactive protein [42]. In addition, T-helper (Th)-1 and Th-17 cells are both activated in psoriasis and atherosclerosis, and important immunologic mediators including e.g., tumor necrosis factor (TNF), interleukin (IL)-23, IL-17 and interferon (IFN)-γ are involved in the process of atherosclerotic and psoriatic plaques [43,44]. Furthermore, many of these important cytokines as well as adipokines enhance insulin resistance and can thereby cause endothelial dysfunction [45]. Indeed, many studies have suggested common immunologic pathways between the two diseases, but the potential shared genetics between psoriasis and CVD are less explored [46,47]. Interestingly, a recent MR-study found shared genetic risk factors between psoriasis and coronary artery disease, and that coronary artery disease may have a causal effect on developing psoriasis, indicating that atherosclerotic disease could also be a trigger for developing psoriasis [48]. In conclusion, the increased risk of CVD is most likely caused by a combination of a psoriasis-induced activated immune system, shared genetics, and co-existing CVD risk factors (Figure 2) [5].

The increased risk of cardiovascuæar disease is most likely caused by a combination of systemic low-grade inflammation, shared genetics, and co-existing cardiovascular risk factors.

How can we help our patients?

There are different considerations when screening and treating CVD risk factors in patients with psoriasis. Guidelines with the intention to identify these factors, in order to prevent CVD, vary and do not necessarily guide the physician sufficiently when facing patients with psoriasis. Additionally, it seems as there is no definite agreement whether psoriasis itself should be considered a risk factor. The joint guidelines provided by the American Academy of Dermatology (AAD) and the National Psoriasis Foundation (NPF) highlight the importance to integrate psoriasis in CVD risk management and the American College of Cardiology/American Heart Association indicate that psoriasis should be considered as a risk-enhancing factor [49,50]. Moreover, the AAD/NPF guidelines suggest that we use a 1.5 multiplication factor when the risk of CVD is calculated in these patients [49]. The European League Against Rheumatism (EULAR) guidelines also describe the principles and recommendations of how to handle the increased risk of CVD in patients with inflammatory joint diseases such as rheumatoid arthritis (RA) and psoriatic arthritis [51]. But in guidelines to prevent CVD by the European Society of Cardiology, psoriasis is only briefly mentioned as a disease that may have potential to increase the risk of CVD and seemingly

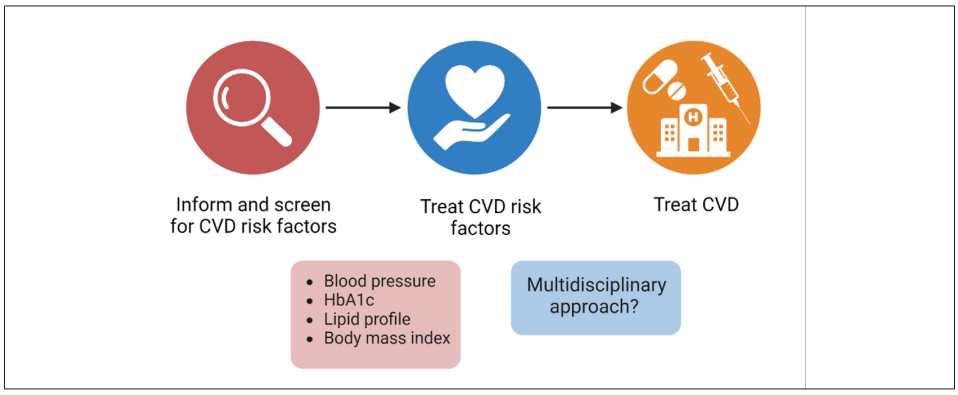
Figure 2. Why do patients with psoriasis have increased risk of cardiovascular disease?



with no further guidance [52]. Therefore, it depends on which guidelines different physicians (e.g., dermatologists, rheumatologists, or general practitioner) follow, and this will affect the results of potential CVD prevention and treatment for these patients. Notably, to reduce the risk of CVD in patients with psoriasis, a multidisciplinary approach is recommended and the physicians are suggested to screen these patients on a regular basis at least for lipid profile, glycated haemoglobin (HbA1c), blood pressure and anthropometrics such as body mass index (BMI) (Figure 3) [53]. Although previous studies have indicated that patients with psoriasis are undertreated for their CVD risk factors, a recent Danish study show that patients with psoriasis do not receive less pharmacological treatment for CVD risk factors compare to the general population [53–55].

Data on the effect of anti-psoriatic treatment on the risk of CVD in patients with psoriasis are inconsistent. Hypothetically, reduced inflammation in the psoriatic lesions could lead to a reduced systemic inflammatory response and thereby reducing the risk of CVD, especially considering the results from the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS). This study found that Canakinumab, an anti-inflammatory drug targeting interleukin-1β, reduced the rate of recurrent cardiovascular events in patients with previous myocardial infarction [56]. In patients with psoriasis, epidemiological studies indicate that TNF-α inhibitors and methotrexate (MTX) reduce the risk of CVD compared to other anti-psoriatic treatments. In line with this, TNF-α inhibitors have also been linked with reduced coronary artery inflammation in psoriatic patients [57–59]. However, meta-analyses based on imaging studies that examine the effect of biologic treatment on vascular inflammation detected by PET/CT do not confirm these results [60,61]. Currently, we lack well-designed randomized clinical trials designed for the purpose to better evaluate the effect of anti-psoriatic treatments on the risk of CVD in patients with psoriasis, especially with clinical endpoints.

Figure 3. How can we help our patients to avoid cardiovascular disease?



Clinical considerations regarding identification and screening for cardiovascular disease (CVD) risk factors in patients with psoriasis. Hba1c, glycated haemoglobin.

Psoriasis and liver disease

It all began with methotrexate…

Historically, the interest of liver disease in patients with psoriasis began in the 60´s when MTX was introduced in the treatment of psoriasis. MTX was first approved for the treatment of psoriasis by the US Food and Drug Administration (FDA) in 1972; however, it has been used off-label in the form of aminopterin since 1951 [62]. The rare complication of liver fibrosis during treatment with MTX was previously described from patients with leukaemia; however, these patients received a much larger dosage of MTX and were evidently suffering from a more generalized severe disease [63]. Early case reports and case series from patients with psoriasis treated with MTX showed abnormal serum transaminases [63], and smaller retrospective studies reported permanent liver damages [64]. Since then, many studies have addressed this issue because MTX has been first-line therapy for patients with inadequate response to topical treatment [49,65]. Most of the studies have found an reversible increase in serum transaminases, but the risk of liver fibrosis has been difficult to quantify [49,66,67].

… but now everyone is talking about metabolic dysfunction-associated steatotic liver disease

During the last 15 years, metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease [68], has been suggested as an important reason for the increased risk of liver fibrosis in patients with psoriasis. MASLD is currently the most common form of liver disease worldwide, affecting approximately 25% of the general population [69]. Risk factors for developing MASLD includes e.g., obesity, type 2 diabetes, hypertension, the metabolic syndrome, and insulin resistance [70]. MASLD is associated with both cardiovascular [71] and liver-specific morbidity and mortality. MASLD is a continuum ranging from simple steatosis, which is harmless, to steatohepatitis (MASH)with steatosis, inflammation, and ballooning [72]. MASH can lead to liver fibrosis, and eventually cirrhosis and hepatocellular carcinoma. In the early stages of MASLD the disease is reversible; however, in the later stages with advanced fibrosis and cirrhosis, treatment is merely symptomatic [72]. Treatment in early stages of MASLD include weight loss, physical activity, optimal treatment of other cardiovascular risk factors such as hypertension, dyslipidaemia, and type 2 diabetes. No pharmacological agents are approved for treatment of MASLD but vitamin E and pioglitazone are used off-label for patients with significant fibrosis [72]. Several randomized controlled trials testing new pharmacological agents are currently ongoing, with promising results for glucagon-like peptid-1 receptor agonists, which reduces steatosis by inducing weight loss [72].

Because the disease is reversible in the beginning, early detection is crucial but difficult.

Serum transaminases can be affected but are actually normal in 80% of patients with steatosis [72]. Clinical symptoms will often first appear in the very late stages with advanced fibrosis or cirrhosis.

Gold standard to diagnose MASLD is a liver biopsy [74].; however, this is an invasive procedure with potential serious side effects. In addition, the procedure requires hospitalization, which means it is time-consuming for the patient and the healthcare system. Because simple steatosis and MASH without fibrosis are rather harmless, non-invasive methods to find patients with sign of liver fibrosis have a great clinical significance. Several non-invasive alternatives exist; biomarkers such as Fibrosis-4 (FIB-4) or NAFLD fibrosis score (NFS), and imagine techniques such as MR-elastography and controlled-vibration transient elastography (often assed by a Fibroscan®) [74]. These non-invasive techniques enable exclusion of patients without sign of liver fibrosis, saving the liver biopsy only for patients with sign of liver fibrosis in the non-invasive techniques.

Psoriasis and the liver – it´s complicated

The first case series of three patients with concurrent psoriasis and steatohepatitis was published in 2001 [75]. In 2009, larger case-control studies were published [76,77]. Gisondi and colleagues [77] compared 130 patients with psoriasis with 260 healthy controls matched on sex, age, and BMI. They found MASLD (simple steatosis) in 47% of the patients with psoriasis and in 28% of the healthy controls. Some years later, larger population-based studies were published, confirming the association between psoriasis and MASLD, also after adjusting for potential confounders e.g., obesity and metabolic syndrome [78,79]. Bellinato and colleagues summarized existing literature in a systemic review and meta-analysis including 15 studies, concluding that MASLD was more prevalent in patients with psoriasis compared to non-psoriatic controls, and patients with MASLD and psoriasis had a more severe form of psoriasis than patients with psoriasis without MASLD [80]. Furthermore, they reported that patients with psoriasis and psoriatic arthritis had the greatest risk for MASLD. However, most of these studies were cross-sectional and therefore merely reporting a correlation and not necessarily a causal relationship. In addition, the diagnosis of MASLD was for most of these studies based on simple steatosis. More interesting would be to examine the prevalence of MASLD with fibrosis, as described earlier.

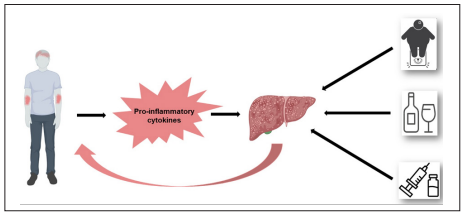
Some studies have also estimated the risk of incident liver disease (including MASLD) [81], including subgroups of patients receiving systemic therapy [82,83], supporting the results from above-mentioned studies. However, future large prospective studies are needed to understand the causal relationship between psoriasis and MASLD better.

Theoretically, a causal relationship could be possible. The pro-inflammatory cytokines (such as IL-6, IL-17, TNF-α) driving the inflammation in psoriasis could aggravate the development of MASLD, also suggested as the hepato-dermal axis [84]. Similarly, pro-inflammatory cytokines produced by the liver could subsequently worsen the skin symptoms, potentially explaining why patients with both MASLD and psoriasis have a more severe disease than patients with psoriasis without MASLD.

Recently, two MR-studies could not find evidence for a causal relationship between psoriasis and NAFLD [29,31]. These results indicate that the observational association between psoriasis and MASLD is a result of shared confounding factors, such as e.g., obesity. Obesity is the strongest risk factor for MASLD, and have also been established as a causal risk factor for psoriasis [26,29]. Moreover, another important potential confounder is alcohol consumption. A diagnosis of MASLD requires that the patient do not have an excessive alcohol consumption [72]. However, alcohol consumption is always self-ported and there may be overlap and misclassifications between patients with MASLD and with alcoholic liver disease. Patients with psoriasis have a higher alcohol consumption than the general population, so this could indeed be an important confounder [85]. Interestingly, among MTX users, patients with psoriasis have a higher risk of developing liver disease compared to patients with RA [83]. This could be due to the higher BMI found in patients with psoriasis [86], a possible difference in how the inflammation in psoriasis vs. RA affects the liver/interacts with MTX, or a combination [83].

In conclusion, the total burden of risk factors for developing liver fibrosis is larger in patients with psoriasis compared to individuals without psoriasis, including systemic inflammation, obesity, alcohol consumption, and the use of MTX (Figure 4).

Figure 4. Psoriasis and liver disease - a complicated association



The total burden of risk factors for developing liver fibrosis is large in patients with psoriasis.
The pro-inflammatory cytokines (such as IL-6, IL-17, TNF-α) driving the inflammation in psoriasis could aggravate the development of metabolic dysfunction-associated steatotic liver disease. Similarly, pro-inflammatory cytokines produced by the liver could subsequently worsen the skin symptoms (the *hepato-dermal axis*). Furthermore, patients with psoriasis are often more obese than the general population, drink more alcohol, and many patients with moderate to severe psoriasis receive methotrexate (which can be hepatotoxic).

What can we do to help our patients with psoriasis?

Dermatologists still focus on the risk of liver disease due to the use of MTX; however, there are no international consensus on how to monitor these patients. AAD suggests an algorithm including non-invasive serologic tests at baseline (e.g., FIB-4), liver function tests every 3-6 months, and if necessary, assessing the liver stiffness with for example Fibroscan® [49]. In Europe, some countries measure procollagen type III N-terminal peptide (P3NP) at baseline and every 6 months to detect patients with potential hepatotoxic side effects [87]. Furthermore, there is increasing evidence

suggesting that the clinical focus should be on metabolic risk factors (e.g. obesity, type 2 diabetes) instead because these confer a much larger risk of developing liver disease than MTX. International consensus of how to detect and monitor patients with psoriasis, and not only patients using MTX, are needed. More studies examining non-invasive biomarkers and assessment of liver stiffness are required to reach a consensus on how to detect and monitor different subgroups of these patients. In the meantime, we should consider the metabolic risk factors just as important, or even more, than MTX when assessing the risk of developing liver disease. Prevention and treatment of metabolic lifestyle factors have never been more important, aiming to reduce both the severity of the skin symptoms and the risk of comorbidities.

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Psychodermatology and Psoriasis

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Abstract

Psoriasis is an immune-mediated chronic inflammatory skin disease affecting 2-3% of the adult population globally. It is associated with several co-morbidities linked to low-grade inflammation including cardiovascular disease, inflammatory bowel disease and psoriatic arthritis. It is strongly associated with psychosocial co-morbidities including depression, anxiety, suicidality, and substance use regardless of severity. This can negatively impact adherence to and efficacy of treatment leading to a complex negative cycle between skin and mental health which is often under-recognised rendering psoriasis increasingly challenging to treat. It is imperative that a holistic approach to treatment is taken through multi-disciplinary psychodermatology services to maximise treatment outcomes and quality of life.

1. Introduction

Psoriasis is an immune-mediated chronic inflammatory skin disease affecting 2-3% of the adult population globally [1-3]. Chronic plaque psoriasis is characterised by pruritic, well-demarcated, pink plaques (in lighter skin) or grey plaques (in darker skin) covered in silvery scale [1]. There is a strong genetic susceptibility to developing psoriasis; over 80 risk loci have been identified by genome-wide association studies, resulting in a 30% disease heritability [1]. Environmental triggers such as stress, weight gain, smoking, and alcohol consumption play a huge role in disease onset [1]. Lesions can occur anywhere on the body, with common sites including the extensor surfaces of the knees, elbows, trunk, and scalp [1]. Currently, there is no complete cure. Treatment aims to induce remission through topical therapy, phototherapy, oral systemic treatments, and biologics, depending on severity [1,4].

Immunological studies have suggested that pathogenesis is driven by immune-mediated inflammation primarily through helper T cells type 17 (Th17) and the subsequent production of pro-inflammatory cytokines. This results in the activation of keratinocytes leading to epidermal hyperproliferation and the production of several chemokines, growth factors and other inflammatory molecules setting up a cycle of systemic inflammation [1]. Consequently, psoriasis is well-recognised as a multi-system disease with several co-morbidities such as depression, cardiovascular disease, and inflammatory bowel disease. Involvement of the joints in psoriatic arthritis and nail psoriasis is very common (up to 40% and 90% of patients, respectively) [5,6]. Both exacerbate the painful and disabling nature of the disease with a significant impact on quality of life. There is a significantly reduced functional status in patients with psoriatic arthritis compared to those with psoriasis alone [7].

Severity of disease, measured by the Psoriasis Area and Severity Index scale (PASI), does not directly correlate with quality of life impairment [8]. There is correlation between mental health and presence of lesions in more visible areas such as the scalp and upper limbs [8]. Severe psoriasis with greater body surface involvement significantly impairs work productivity and daily activities [9]. This can be attributed to the psycho-social burden of the visibility of the disease through low self-esteem, avoidance of social activities, and isolation [10].

The All-Party Parliamentary Group on Skin (APPGS) published a report recognising the increasing burden on mental health from skin disease [11]. 98% of patients felt their skin disease impacted their emotional wellbeing [11]. The report further highlighted the lack of recognition of the emotional wellbeing of patients with 54% of patients being unaware that they could seek help [11]. The available mental health services are limited. However, there is an increasing awareness for the need for expanding psychodermatology services [12].

Given the high impact of psoriasis on patient's quality of life, it is imperative that research is led by, and addresses, unmet needs reported by both patients and healthcare professionals [13,14]. The James Lind Alliance (JLA) identified potential misalignment between the priorities of academics, patients, and clinicians [13,14]. The JLA provides a methodology to establish these research priorities through Priority Setting Partnerships (PSPs) [13,14], led by steering groups with organisations representing both patients and clinicians that provide collaboration between both stakeholders to outline the most essential questions for future research. PSPs in the United Kingdom for psoriasis and psoriatic arthritis have identified the top 20 and 10 research priorities respectively for these diseases [13,14,15]. This narrative review has focused on several key research priorities identified by these PSPs including: the psychological impact of disease, the impact of lifestyle on both treating and causing disease, and the development and management of co-morbidities seen with psoriasis [13,14,15].

2. Psychiatric co-morbidities

Anxiety and Depression

Epidemiological studies have shown the prevalence of depression and anxiety in up to 55% and 48% of patients respectively [16, 17]. Psoriasis patients have a significantly higher rate of depression and suicidal ideations compared to other chronic skin conditions, such as acne, alopecia areata, and atopic dermatitis [18]. All psoriasis patients (regardless of severity) are at a higher risk of depression [19]. There are multiple factors that contribute to this, including pruritus, stigmatisation, and psoriatic arthritis, and there is a higher prevalence of depression and anxiety in patients with psoriatic arthritis compared to those with psoriasis alone [20,21]. This higher depressive burden can be explained through a higher functional disability from severe joint pain [7].

Consideration of the negative impact on treatment outcomes for patients with depression and anxiety is imperative. Depression in psoriasis is a strong risk factor for poor adherence to treatment. Appropriate management of depression is essential for clinical outcomes of psoriasis treatment [20]. Similarly, anxiety in the form of pathological worrying is a significant factor impairing the clearance of psoriasis through treatment with phototherapy [22]. This can be explained from an increasing body of evidence, from animal and human studies, suggesting that the pro-inflammatory pathways of psoriasis, anxiety, and depression overlap [4]. This creates a bidirectional association and vicious cycle between skin and mental health [23].

Brain-Skin Axis

It is well established that both acute and chronic stress activate the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the production of corticotrophin-releasing hormone (CRH) and further downstream increase in adrenocorticotrophin hormone (ACTH), glucocorticoids, and neuropeptide mediators [24,25]. CRH itself induces a pro-inflammatory systemic response and is a key mediator between the brain-skin axis; hence it provides a link between psoriasis, depression, and anxiety [24]. Cutaneous corticotrophin-releasing hormone (CRH) peptide and corticotrophin-releasing hormone receptor (CRH receptor hormone) provide CRH binding sites in the skin. This creates a peripheral HPA axis known as the corticotrophin-releasing hormone-proopiomelanocortin (CRH-POMC) system [26]. Through interaction with CRH receptor hormone type 1, CRH stimulates pro-inflammatory cytokines in the skin such as IL-6, IL-8, IL-22, and vascular endothelial growth factor (VEGF) which are also involved in psoriatic plaque formation [24,27]. Psoriatic skin lesions have a reduced expression of CRH-receptor 1 mRNA compared to healthy controls, which can be explained by over-stimulation through local or systemic CRH [28]. Gene expression analysis studies report an up-regulation of POMC mRNA in both lesional and non-lesional skin in psoriasis patients when compared with controls [26].

Regarding treatment, both the cumulative inflammatory effect from psoriasis itself and the negative psychosocial impact from the lesions render it more difficult to treat. Biologics in psoriasis patients improve depressive symptoms along with clinical severity [29,30]. A recent cross-sectional study comparing oral agents to biologics found significantly higher rates of depression in patients taking oral systemic drugs compared to biologics [31]. Studies do not adjust for obesity or provide sub-group analyses by weight. There is established research that psoriasis patients with a higher BMI struggle to achieve remission with systemic treatment and biologics [32]. Obesity, like depression, induces an additional pro-inflammatory effect through the dysregulation of inflammatory cytokines and adipokines [33, 34]. Further research is required to elucidate the dominant inflammatory components which exacerbate psoriasis in patients with overlapping pro-inflammatory conditions.

Brain Changes

Functional magnetic resonance imaging (MRI) studies have reported that, when shown images of disgusted faces, psoriasis patients have lower levels of activity in the bilateral insular cortex compared to controls [35]. This is attributed to coping mechanisms developed to manage negative social responses to their body. A recent study reported an increased praecuneus thickening using MRI in psoriasis patients with depression [36]. Praecuneus thickening was linked to recurrent lifetime suicidality. However, the study found no significant correlation of praecuneus thickening with systemic inflammation [36]. Positron emission tomography scanning studies have demonstrated no significant increase in neuroinflammatory signals psoriasis between patients and controls suggesting the blood-brain barrier provides a protective role against peripheral inflammation [37].

Suicide

A multi-centre cross-sectional study reported that, among chronic skin conditions, only psoriasis had a significant association with suicidal ideation [38]. In both younger patients and female patients, there is a significantly higher risk of suicidality regardless of psoriasis severity [39]. Suicidal ideation rates are reported to be from 1-27% [40].

Systematic reviews about the risk of suicide in psoriasis report conflicting results due to a lack of subgroup analyses, high heterogeneity within cross-sectional studies, and variation within suicidal ideation measurement [40-43]. Singh et al. [40] reported that psoriasis doubles the risk of suicidality and Wu et al. [42] reported a higher risk for younger patients but no significant association with gender.

There is limited data on suicidality specific to psoriatic arthritis [20]. A cross-sectional study reported a higher prevalence of anxiety and anhedonia in patients with psoriatic arthritis compared to those with only psoriasis, however, found no difference in lifetime suicidality [44]. Given that an estimated 350 diagnoses of suicidality per year are the result of psoriasis in the United Kingdom, further research with subgroup analyses is required [45].

There is an emerging concern regarding biologic treatment and a potentially

increased risk of suicidality specifically for brodalumab and apremilast [46,47]. There is no established mechanism. Nonetheless, patients are recommended to be counselled on this risk [46-50].

An exploratory analysis of initial phase three trials reports no evidence of causality between suicidality and brodalumab, with Kaplan-Meier curves of time-to-event analyses reporting no relationship between the initiation of brodalumab and suicide [48]. Apremliast is licensed for both psoriasis and psoriatic arthritis [47]. The evidence for a potential causal association between apremilast and suicidality is limited and largely based on the initial phase three trials on apremilast [47,51]. At week 16 of the placebo-controlled phase, patient reported depression with apremilast was 1.4% compared to 0.5% with placebo [51]. A recent 5-year cohort study found no evidence of increased risk of suicidality with apremilast [52].

Substance Use and Addictive Behaviours

Rates of alcoholism and smoking are higher in psoriasis patients compared to the general population [53-55]. This can be attributed to their use as maladaptive coping mechanism for managing the psychological distress of this chronic skin condition [9]. Both smoking and alcohol use are considered potential risk factors for the onset of psoriasis [1].

The association between smoking and a higher severity of psoriasis is well established through observational studies. These may be biased through confounders such as depression [55-58]. A higher intensity of smoking (over 20 cigarettes per day) is associated with a two-fold increase in psoriasis severity [59]. Smoking has also been reported to be a major risk factor for lack of response to anti-TNF treatment [60].

The evidence suggesting alcohol as a risk factor is conflicting. A prospective cohort study of female nurses found that alcohol use increases risk of psoriasis compared to controls [61]. Conversely, Wolk et al. [62] found a significant association between alcohol consumption and psoriasis only in male participants. Conflicting results may be explained by difference in measurement of alcohol intake and bias through retrospective patient-reported alcohol intake [54]. A recent Mendelian randomization study found no causal relationship between alcohol intake and psoriasis [58].

Both smoking and alcohol use are associated with a lack of adherence to treatment leading to poor clinical outcomes and further driving substance misuse as a coping strategy [58,63,64]. Further research on the relationship between alcohol consumption and psoriasis is required.

It is imperative to take into consideration that addiction can take many forms beyond smoking and alcohol use [66]. Research on other forms such as gambling, illicit drug use, and food addiction have not been as extensive and is mainly based on questionnaires in cross-sectional studies, heavily susceptible to recall bias and potential under-reporting of illegal substances [67,68].

In the US, a cross-sectional study of 392 patients and 14,572 controls investigated the prevalence of illicit drug use in psoriasis patients and found associations between psoriasis and cocaine, heroin, and regular cannabis use [68]. Two cross-sectional studies in Germany investigated the prevalence of the 6 most common forms of addiction: smoking, alcohol, gambling, illicit drugs, and food [66,67]. Both studies demonstrated that, compared to controls, there are significant higher rates of alcohol ($p<0.005$), smoking ($p<0.001$) and illicit drug use ($p<0.001$) [66]. Despite a higher BMI, food addiction was less prevalent in the psoriasis population [67]. However, logistic regression analysis revealed a positive relationship between food and BMI. Patients of a younger age were found to have a higher chance of developing any addiction [67]. Gambling was assessed using the 'Gamblers Anonymous Twenty Questions (GA-20) which is limited to casinos or gambling halls. The exclusion of online gambling may lead to under-reporting and may not fully capture the extent of gambling addiction, especially in younger populations [66].

Of all addictions, only alcohol use and illicit drug use were associated with disease severity measured by PASI [66]. These results may be limited by the fact that the PASI score was only being assessed on the day of the questionnaire. Previous or pre-treatment PASI scores were not considered. Co-morbidities, especially addictions, are developed over a longer period as a mechanism of coping – not only over the time of a flare-up period. Hence, further studies should utilise the 'PeakPASI', which is the highest documented PASI score in a patient, to fully understand and provide valuable insights into the development of addiction-based co-morbidities as a coping mechanism in psoriasis [66].

Overall, more research is needed to fully understand the relationship between psoriasis and different forms of addiction and to identify effective prevention and treatment strategies for these comorbidities.

3. Quality of life

Patients with psoriasis report a significant impact on their quality of life. The World Health Organisation (WHO) describes the quality of life as "an individual's perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a concept affected by the person's physical health, psychological state, personal beliefs, social relationships and relationship to salient features in their environment" [68].

Objective measures of quality of life (QOL) are important when assessing psoriasis patients, as the high prevalence of alexithymia may impair clinicians' ability to ascertain the extent of the psychological impact of the disease. As results are not uncommonly higher than projected, and not always comparable to the severity of patient's skin disease, measuring the extent of skin disease is not an accurate marker for assessment of quality of life [4]. High scores on quality-of-life assessments should prompt the assessing clinician to consider whether the patient may benefit from psychological intervention.

Importantly, for patients on systemic and biologic therapy, QOL represents important endpoints in assessing treatment response and the results of certain therapies.

QOL questionnaires in dermatology are generally categorised as general health, dermatology-specific and disease-specific questionnaires. General health questionnaires aim to assess the overall physical and psychosocial factors. Skin-specific questionnaires can be more helpful, and efforts have been made to devise psoriasis-specific questionnaires to generate more relevant and meaningful information. These can be used in combination with general health questionnaires to provide a better understanding of the disease impact.

Examples of some of the most used questionnaires in psoriasis are listed below
QOL questionnaires

- Salford Psoriasis Index
- Dermatology Life Quality Index (DLQI)
- Hospital Anxiety and Depression Scale (HADS)

Other questionnaires that can be used include those psoriasis patients with joint disease include:

- Psoriasis Epidemiology Screening Tool (PEST)

Alexythmia

Alexithymia is the difficulty in identifying, expressing, and describing one's feelings. An observational study measuring alexithymia using the validated Toronto Alexithymia Scale [69] in a large cohort of psoriasis patients showed a 24.8% prevalence in this group (compared to approximately 5–10% in the general population) [70]. These patients had more severe disease, significantly reduced quality of life, greater prevalence of anxiety and depression, a higher rate of alcohol dependence, and reduced work productivity. This means, alexithymia can make it problematic for clinicians to determine the true effect of the patient's psoriasis on their life.

4. Physical factors

The physical factors (table 7.1) in psoriasis can have a severely harmful effect on quality of life, with studies reporting that two-thirds of patients feel the negative physical impact of psoriasis in their day to day lives. This increases to up to 80% in those with severe disease. The physical symptoms of their skin are a significant factor in the negative effects on quality of life, and these include itching, pain, irritation, and the functional inability of various joints. In addition, the physical impact of co-existing psoriatic arthritis has the potential to cause devastating effects on quality of life. Other associated comorbidities such as obesity, metabolic syndrome, and autoimmune conditions such as inflammatory bowel disease, may all result in physical and consequent psychosocial morbidity [4].

Pruritus

Pruritus remains an under-recognised symptom in psoriasis, yet its prevalence and effect are substantial. Studies report that between 67% and 77% of patients with psoriasis have symptoms of pruritus which are significant and arise daily [71]. The magnitude of pruritus does not appear to always correlate to clinical severity. It is exacerbated by heat, skin dryness, sweating and importantly, stress. There is a known association between pruritus in psoriasis and the risk of depression, again leading to a deleterious cycle of worsening psoriasis and mental health. In a survey of 104 patients with psoriasis, 30% of patients reported pruritus to be the worst physical factor, a symptom that is often under-estimated in this condition [4].

Table 7.1 Physical symptoms of psoriasis [4]

Skin symptoms	Functional impairment
• Itching	Self-care
• Skin shedding	• Activities of daily living
• Tightness	• Occupational factors
• Redness	
• Dryness	Sexual dysfunction
• Bleeding	Sleep disturbance
• Pain	

5. Functional impairment

Functional impairment in psoriasis is common, especially in patients with psoriatic arthritis and particularly seen when it affects the palms and soles; the consequent physical disability from pain results in higher levels of functional impairment. This, in addition, to nail involvement has been shown to limit the ability to self-care and perform basic activities of daily living. These restrictions result in psychological distress and isolation [72].

These physical factors can have significant sequelae, ranging from the inability to carry out simple activities of daily living, through to occupational difficulties which can be so severe as to render patients unable to work. These effects can exacerbate the condition and can lead to social isolation and a downward spiral of psychological distress and worsening of the skin manifestations of psoriasis [72].

Sexual Dysfunction

Psoriasis is reported to interfere with sexual relations in 35–50% patients. This appears to be more prevalent in female patients and can present in a variety of ways. The physical involvement of the genital skin can make sexual intercourse painful or uncomfortable. A large study of 354 patients revealed that 39% patients experienced pain, 42% dyspareunia and 32% worsening of genital psoriasis after intercourse [73]. The psychological effect of skin involvement can make it difficult for patients to enter relationships, due to self-consciousness or fear of stigma. Additionally, psoriasis causes a decrease in libido in a large proportion of patients. Those who report sexual dysfunction from psoriasis have more symptoms of depression [4]. It is apparent that psoriasis has a profoundly negative impact on sexual health and satisfaction.

Sleep Disturbance

Sleep disturbance is common and variable in psoriasis, with reports ranging from 5.9% to 44.8% prevalence. The skin has an important role in mediating core body temperature and acts as a primary circadian mediator to reduce this temperature at night as part of normal sleep initiation. The normal and physiological reduction in core body temperature occurs due to a drop in metabolic heat generation, increase in blood flow to the skin, and distal vascular dilatation;

these result in the dissipation of heat and an increase in trans-epidermal water loss. In psoriasis, thermoregulation via the skin is impaired, and therefore sleep initiation may be compromised as a result [74].

Cutaneous symptoms including pruritus and pain are well recognised in psoriasis (see section 4 "Physical Factors"). Pruritus is often said to be worse towards the end of the day. This symptom is also regulated by circadian mechanisms and the threshold for symptoms is lower in the evening due in part to a reduction in cortisol levels, increase in temperature, and reduced epidermal barrier function. This therefore manifests as an exacerbation of cutaneous symptoms at night, which causes disturbed sleep.

Many of the associated comorbid conditions can also result in sleep disturbance; for example, there is a higher prevalence of obstructive sleep apnoea in psoriasis [74] with studies reporting 36%–81.8% in psoriasis, compared with 2%–4% in the general population. There is also a known increased prevalence of restless leg syndrome (15%–18% in psoriasis patients compared with 5%–10% in the unaffected population). The increased prevalence of psychiatric comorbidity (see section 2 "Psychiatric Comorbidities") is also a significant contributor to problems with sleep.

6. Psychosocial factors

The psychosocial aspect of psoriasis has been reported by patients to be one of the worst aspects of their condition, resulting in a severely negative impact on the quality of life [75]. The extent to which this occurs differs widely and does not always correlate with the extent of disease. The psychosocial implications are varied and include negative emotional effects on the self, as well as impacting their interactions with their close and wider social network.

Psychosocial Factors and Schemas

The profound psychological impact of psoriasis and the role of distress in the onset, exacerbation and persistence of the condition is well-recognised. The common and recurrent patient reported themes in studies include negative effects on self-confidence, feelings of shame, embarrassment, and a lack of self-esteem. In a large study of 217 patients, over 50% reported feeling self-conscious around strangers [76]. Research has shown that patients with psoriasis use anticipatory and avoidance behaviours as a coping mechanism. Schemas are engrained cognitive and emotional patterns which influence the individual's approach to life; they are now recognised as an important part of the psychological sequelae of psoriasis (table 9.1). The early maladaptive schemas (EMS) are those which originate in childhood and develop in adulthood [77]. Schemas are particularly difficult to challenge as they are deeply held beliefs that are consolidated through repeated and often self-fulfilling experiences.

Table 9.1 Schema in psoriasis [4]

Early maladaptive schemas in psoriasis (Mizara et al.2012)
• Emotional deprivation
• Social isolation
• Defectiveness
• Failure
• Vulnerability to harm
• Subjugation
• Emotional inhibition

Social Factors

Psoriasis affects many patients' ability to function to their best potential in social environments (table 9.2). The fear of stigma plays a large part in this (see section 6.1). Numerous studies have shown that patients with psoriasis try to hide their skin symptoms, and many report avoiding social activities that involve showing their skin, such as swimming, with one study quoting that 83% of patients would 'often' or 'always' avoid these situations [78]. Social functioning appears to be more severely affected in psoriasis than in other chronic conditions such as hypertension and arthritis, reflecting the visible nature and stigma associated with this skin condition.

The ability to work and study can also be severely impacted by psoriasis; in a large survey of 369 patients with psoriasis in the UK, one-third attributed 'not working' to their psoriasis [79]. Over 17% of 18–54-year-old patients with psoriasis report a psychological impact of psoriasis on their work, and 23% reported that their psoriasis had an impact on the choice of their career [79]. Of those who do work, over half report that the quality of their work life is negatively impacted due to their psoriasis [79].

Table 9.2 Psychosocial impact of psoriasis on quality of life [4]

Negative psychological effects on the patient:
• Self-image
• Self-esteem
• Self-wellbeing
• Early maladaptive schemas
Negative effects on social functioning:
• Relationships with friends and family
• Sexual relations
• Day to day encounters with the general public
• Occupational effects

Stigma

Stigma is defined as 'a mark of disgrace which sets people apart from each other'. Many patients with psoriasis report experiencing stigma from their skin, which can have a profound effect on their social interactions and general quality of life. This effect is most pronounced in the 18–45-year-old age category, correlating with the age in which people are most likely to be socially and professionally active [80].

The visible nature of psoriasis renders patients exposed and vulnerable to external perceptions and misconceptions. Many patients report experiences of being publicly rejected due to a public belief that the condition is contagious, or simply due to fear or lack of knowledge. This results in feelings of shame and lack of self-worth, with consequent avoidance, isolation, and social withdrawal. In a large study of patients with moderate-to-severe psoriasis, 25% reported an episode where someone 'had made a conscious effort not to touch them'. Those with visible affected skin perceive their condition to be more disabling and have higher levels of self-reported physical morbidity [80].

Ginsburg et al. identified six dimensions to stigmatisation (table 9.3) [81]. There appears to be a significant variation in the frequency with which these feelings are experienced,

and contradictory feelings could be experienced simultaneously. The group also investigated predictors for the components of stigma experienced. They found that age of onset, bleeding, employment, duration of experience, and rejection were the strongest predictors of stigma. Of these, bleeding was the most strongly predicting factor and correlated highly with stigma. Stigma was also associated with poor adherence to treatment and worsening of their skin condition.

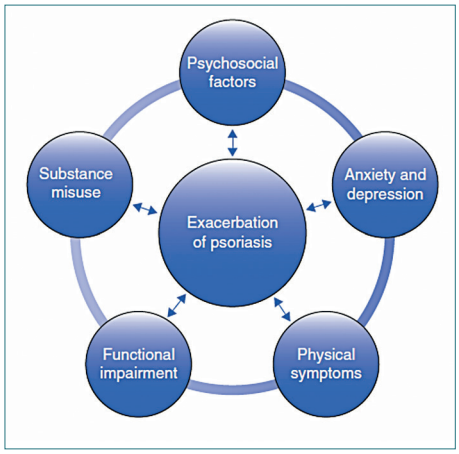
Table 9.3 Components of stigmatisation (Ginsburg and Link 1989) [82]

- Anticipation of rejection
- Feelings of being flawed
- Sensitivity to others' attitudes
- Guilt and shame
- Secretiveness
- Positive attitudes

7. Treatment

Psoriasis is a complex condition with a significant psychological overlay (Fig 10.1). Therefore, just simply treating the skin and joint symptoms is not always sufficient; often a more holistic approach, including a focus on psychological health, is required to successfully manage these patients. Due to the chronic and relapsing nature of the condition, and the fact that many patients have been undertreated for years, it can be difficult for clinicians to encourage patient adherence and positivity to treatment [4].

Fig 10.1 Factors leading to exacerbation of psoriasis [4]



Treatment of the Skin and Joints

Treatment of the skin is generally instigated in a stepwise approach and should be tailored to the individual patient depending on the extent of disease, severity, and effect on the quality of life. This involves topical treatments, phototherapy, systemic and biologics [4]. Further details are outside the scope of this paper. There is plenty of evidence from every day clinical practice that when the skin is treated, patients are generally more satisfied and have an improved quality of life. However as mentioned previously, this is not always a predictable response and sometimes quality of life measures reveal that the patient may still be suffering from significant psychological morbidity despite an improvement in their physical health. Joint disease can be treated simultaneously with systemic and biologic agents and requires close collaboration with rheumatologists.

Cognitive Behavioural Therapy

Cognitive Behavioural Therapy (CBT) is a psychological intervention that involves identifying and challenging unhelpful thoughts and behaviours and learning competing coping mechanisms in order to break the negative cycle [82]. It is well established that stress and distress are frequent exacerbators of psoriasis, but this recognition can also cause patient anxiety which can perpetuate a worsening of their physiological and psychological state. CBT aims to break this cycle. There is evidence that just 6 weeks of weekly CBT sessions combined with standard treatment, versus standard treatment alone, carries a significant improvement in the clinical severity of the skin, and ameliorates symptoms of anxiety, depression, stress, and disability [83]. In one study, these results persisted at the 6-month follow-up, with 64% of patients achieving a greater than 75% improvement in the clinical extent of their psoriasis, compared with 23% in the control group [84]. Other evidence suggests that CBT is effective at improving anxiety levels but less effective at treating depression. Another study has shown that just seven psychotherapy sessions delivered over 12-weeks resulted in clinical improvement although the perception of stress remained similar. Promising results have also been demonstrated using an internet-based electronic CBT intervention, with an improvement in anxiety and quality of life.

Psychotropic Medication

Psychotropic medication includes any medication which affects the mind, emotions, or behaviour. There is limited high-level evidence for the use of psychotropic medication in psoriasis; however, identifying and treating comorbid psychiatric diagnoses is anecdotally known to be beneficial [4]. In one double-blind placebo-controlled study of 60 patients with psoriasis, patients were randomised to moclobemide (a monoamine oxidase inhibitor antidepressant) plus topical corticosteroids, or to topical corticosteroids alone [78]. Those treated with the antidepressant and topical corticosteroids showed improvements in the clinical severity of psoriasis as well as in depression and anxiety. Another small observational study of 38 patients with psoriasis treated with anti-TNFα treatment compared concurrent treatment with escitalopram (a selective serotonin reuptake inhibitor antidepressant) and psychotherapeutic treatment, compared with psychotherapeutic treatment alone [78]; those treated with escitalopram plus psychotherapeutic treatment had greater improvements in the clinical severity of their skin, as well as greater reduction in symptoms of anxiety and depression.

Clinicians should however be aware that there are reports of psychotropic medication resulting in flaring or inducing psoriasis, and these include but are not limited to lithium (a well-recognised culprit), fluoxetine (several case reports), beta-blockers, and bupropion [4].

8. Conclusion

Psoriasis is a complex to treat condition due to the multitude of co-morbidities (both physical and psychosocial) which have a profound impact on quality of life and treatment outcomes. Effective treatment

requires a holistic approach. Psychological co-morbidities have a large impact on treatment adherence and efficacy. Patients at risk of psychological distress should be identified and supported through simultaneous management of both skin disease and mental health, disrupting the negative cycle between the two.

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How to improve people-centred healthcare in dermatology?

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Abstract

People with chronic skin diseases, such as psoriasis, experience multifaceted impairments that include physical symptoms, such as pain, psychological symptoms, such as anxiety, and social impairments, such as stigmatisation. To address this broad spectrum of impairments, a holistic healthcare approach is needed. The World Health Organization has established the people-centred model of care, in which health services adopt the perspective of people affected and their environment. The needs of patients are respected, and patients are put at the centre of care. This model was also adopted by the global report on psoriasis, which aims to improve the wellbeing of the affected people. This paper gives a brief overview of the status quo and an outline of how to improve people-centred care and patient orientation in dermatology, specifically for people with psoriasis. This includes the application of shared decision-making. Although only a few patient decision aids for psoriasis have been published, promising results regarding the reimbursement of shared decision-making applications in the hospital setting by health insurances are available, which also refer to dermatology departments.

1. Background

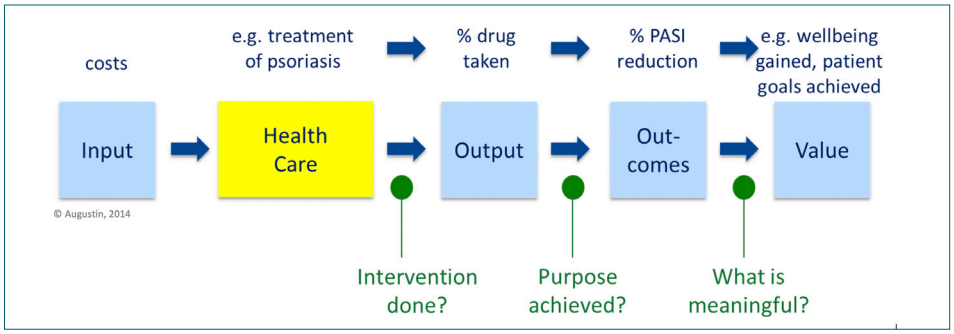
Psoriasis is a chronic inflammatory skin disease characterised by extensive redness and thick scales on the skin, usually accompanied by a painful and itchy skin, leading to a high level of suffering and a decades to life-long course impairment. Its prevalence varies in different geographic areas from 0.14% to 2.5% [1]. Relevant cardiovascular and metabolic comorbidities have been shown in adults [2] and children [3]. The quality of life of patients is not only negatively affected by the physical symptoms and comorbidities of psoriasis but also by psychosocial factors. A study among dermatological outpatients in 13 European countries reported the presence of clinical depression in 10.1%, clinical anxiety in 17.2%, and suicidal ideation in 12.7% of all patients [4]. Studies have shown a considerable psychosocial effect with a major impact on social life, altering interpersonal relationships and feelings of stigmatisation, as well as impairments in sexuality [5]. In addition to physical and social consequences, affected people perceive a high psychological burden and have to deal with psychiatric comorbidities [6]. There is extensive research demonstrating high levels of external and self-stigmatisation [7, 8] and a higher risk of having body dysmorphic disorder symptoms [9]. Moreover, patients are significantly more likely to consider, attempt, and complete suicide [10]. These multifaceted impairments interact and may lead to cumulative long-term burden in the course of life, with non-reversible damage [11]. Cumulative life course impairment (CLCI) is a theoretical construct referring to persisting disease burden over time leading to non-reversible damage in the worst case. In a recent systematic literature review, risk factors for the development of CLCI were assessed [12]. Subsequently, measurement tools were developed to identify patients at risk for CLCI in routine care [13]. These new tools are currently undergoing psychometric validation. Their use in clinical practice and research may facilitate identifying patients at risk for CLCI, thus support preventing people affected from non-reversible damage in their disease course.

To adequately address the multiple impairments associated with a dermatological disease such as psoriasis, a holistic view and a people-centred perspective are needed. In its resolution of 2014, the World Health Assembly (WHA) stressed the importance of a holistic approach to healthcare, including efforts against stigmatisation of patients with psoriasis. The WHA identified psoriasis as one of the five major non-communicable diseases (NCDs) and called on its member states to take measures to improve healthcare for people with psoriasis [14].

In order to address such holistic and people-centred care, as claimed by the World Health Organization (WHO) [15], it is necessary to define the objective of healthcare. According to the (social) law, the main objective of healthcare is the promotion and prevention of health problems, as well as the maintenance or restoration of patients' health. Health is defined as "a state of complete physical, mental, and social wellbeing and not merely the absence of disease." Thus, the WHO defines health in terms of people's wellbeing. There are clear examples in different countries that postulate that patients are jointly responsible for their health and, consequently, for their wellbeing, and physicians should support patients' self-responsibility in terms of patient empowerment. Shared decision-making is an

example of patient empowerment [16–19]. Summarising, restoring the wellbeing of patients is part of the legal mandate of healthcare. This is linked to individual therapy goals regarding wellbeing and the assessment of these goals. Therefore, valid measurements for the assessment of wellbeing and comparable patient reported outcomes (PROs) are needed. Shared decision-making (SDM) may facilitate achieving these goals.

Figure 1. Concept of values in medicine

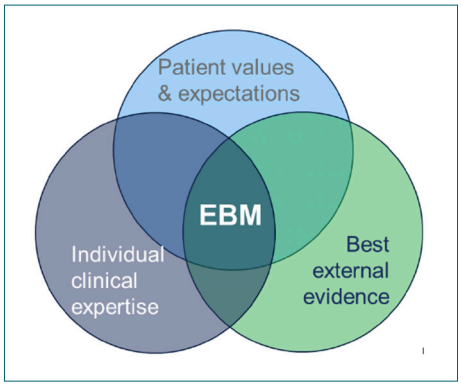


2. Value-based healthcare in psoriasis

Value-based medicine is an approach to healthcare that prioritises the delivery of high-quality care that is aligned with patient values and preferences while minimising unnecessary costs. This approach focuses on achieving the best possible outcomes for patients and ensuring that the resources used to provide care are used in the most effective way possible. It takes the patient's perspective and their individual preferences into account, as well as the best available evidence and clinical expertise. Value-based medicine emphasises the importance of measuring outcomes that matter most to patients and incorporating these measures into clinical decision-making. Ultimately, value-based medicine aims to improve patient outcomes and the overall quality of care while ensuring that resources are used efficiently and effectively. Considering the example of psoriasis, this means that to evaluate healthcare interventions, it is important to consider both input and output. However, in the case of psoriasis treatment, the output is not limited to just the percentage of drugs taken. More information is needed beyond just determining if the intervention has been completed. It is also essential to verify if the intended treatment goal has been achieved, such as a percentage reduction like PASI90 in psoriasis. Furthermore, it is of great importance to assess what is meaningful for the patient. The question "what is meaningful?" subsequently leads to what is called "value." Value refers to the importance of outcomes from the patient's perspective, such as gained wellbeing and achieved patient goals. Large-scale studies have shown that people with psoriasis can have a wide variety of relevant treatment goals. [2,20]. It is notable that patient reported outcomes (PROs) translate the outcomes of our treatment decisions into values (figure 1).

Remarkably, evidence-based medicine (EBM), which is considered the core element of medical healthcare, has expanded its self-definition from being simply a combination of clinical experience and the best external evidence to include a third component: patient values [21,22]. The current EBM concept, therefore, includes all three elements, forming what is called the EBM triad: the best external evidence, individual clinical expertise, and patient values and expectations. As a result, value-based care has become extremely important in healthcare from the perspective of evidence-based medicine, demonstrating that shared decision-making (SDM) is an essential dimension of EBM. [23] (figure 2).

Figure 2. Concept of evidence-based medicine



Adapted from: Armstrong, E.C. (2003) Harnessing new technologies while preserving basic values. Fam Sys & Health, (21)4, 351-355.

3. People-centered healthcare in psoriasis

This concept has been up taken in the global report on psoriasis by the WHO [14] and in the European White Paper for psoriasis [25] and psoriatic arthritis [24]. The people-centered health care approach from the WHO is an approach to healthcare that focuses on the needs and preferences of individuals and communities. This approach recognises that healthcare is not just about treating diseases or conditions, but also about addressing the broader physical, social, and emotional needs of patients. The WHO's people-centered approach to healthcare emphasises the importance of ensuring that health services are accessible, affordable, and of high quality. It also emphasises the importance of involving patients in their own care, as well as their families and communities.
Key principles of the people-centered approach include:

1. Respect for the dignity and autonomy of individuals and communities.
2. Recognition of the importance of social and environmental factors in health and wellbeing.
3. Empowerment of individuals and communities to participate in their own care and decision-making.
4. Collaboration and partnership between healthcare providers, patients, families, and communities.
5. Equity and fairness in the distribution of healthcare resources and services. The people-centered health care approach from the WHO is a way to ensure that healthcare is patient-focused and responsive to the needs of individuals and communities. It is an important step towards achieving better health outcomes for all [15].

3.1 Shared decision-making in psoriasis management

Shared decision making (SDM) is an important dimension of patient orientation in healthcare. It is a process that involves healthcare providers and patients to work together to make informed decisions about healthcare options, based on the best available evidence and the patient's preferences, values, and goals. The shared decision-making (SDM) model was defined in contrast to the paternalistic model, in which the clinician decides on treatment without patient involvement, and the informed model, in which clinicians provide information and the patient is the sole decision-maker [26]. In SDM, patients are considered experts in their illness and clinicians are considered experts in management of disease, allowing for an egalitarian partnership that supports patient autonomy. SDM is based on the idea that patients have the right to be fully informed about their healthcare options, and to be involved in making decisions about their care. It recognises that healthcare decisions can be complex and involve a range of options with different risks and benefits, and that patients may have different priorities and preferences that need to be taken into account. SDM involves a structured conversation between the healthcare provider and the patient, in which the options, risks, benefits, and uncertainties of different therapies or management options are discussed. The patient is encouraged to ask questions, express their preferences and concerns, and work with the healthcare provider to make a decision that is right for them. SDM has been shown to improve patient satisfaction, increase adherence to treatment plans, and lead to better health outcomes. It is particularly important for patients with chronic conditions, such as psoriasis, who may need to make ongoing decisions about their care over time. Overall, SDM is an important dimension of patient orientation in healthcare, as it helps to ensure that patients are involved in decisions about their care, and that those decisions are based on their individual needs and preferences.

Regarding psoriasis and psoriatic arthritis, there is a huge number of systemic drugs available for use in healthcare at the moment. For example, if dermatologists want to prescribe a systemic drug for psoriasis in Germany, there are more than 20 different choices of active substances. All together, including psoriatic arthritis, more than 30 single drugs are available that dermatologists need to consider and discuss with the patient to make the best personalised treatment choice. Therefore, the next few years with such a large plurality of treatment options in psoriasis will be about choices and values, making shared decision-making crucial.

To facilitate SDM for physicians and patients, patient decision aids provide detailed, balanced, and evidence-based information about varying treatment options. These aids can be used before, during, or after a patient visit. However, a recent literature review found only five publications introducing SDM tools specifically for dermatologic conditions. In total, four of these tools referred to psoriasis. Time and a lack of training for clinicians were mentioned as barriers for implementation. However, all studies emphasised the value of SDM for both patients and physicians [27]. To address these barriers, it is important to train SDM skills from the early stages of medical education. There is encouraging progress in implementing SDM into the curricula of medical education [31]. In addition, there is promising progress regarding the reimbursement of applying SDM in the hospital setting by health insurances [32].

Besides the implementation of SDM in clinical practice, the use of PROs to assess patient preferences, values, goals, and treatment outcomes is an important step in order to improve patient orientation in psoriasis care. However, there are many PROs available, and they need to be selected carefully to assess topics that truly matter to patients and their lives, in accordance with a holistic, people-centered approach.

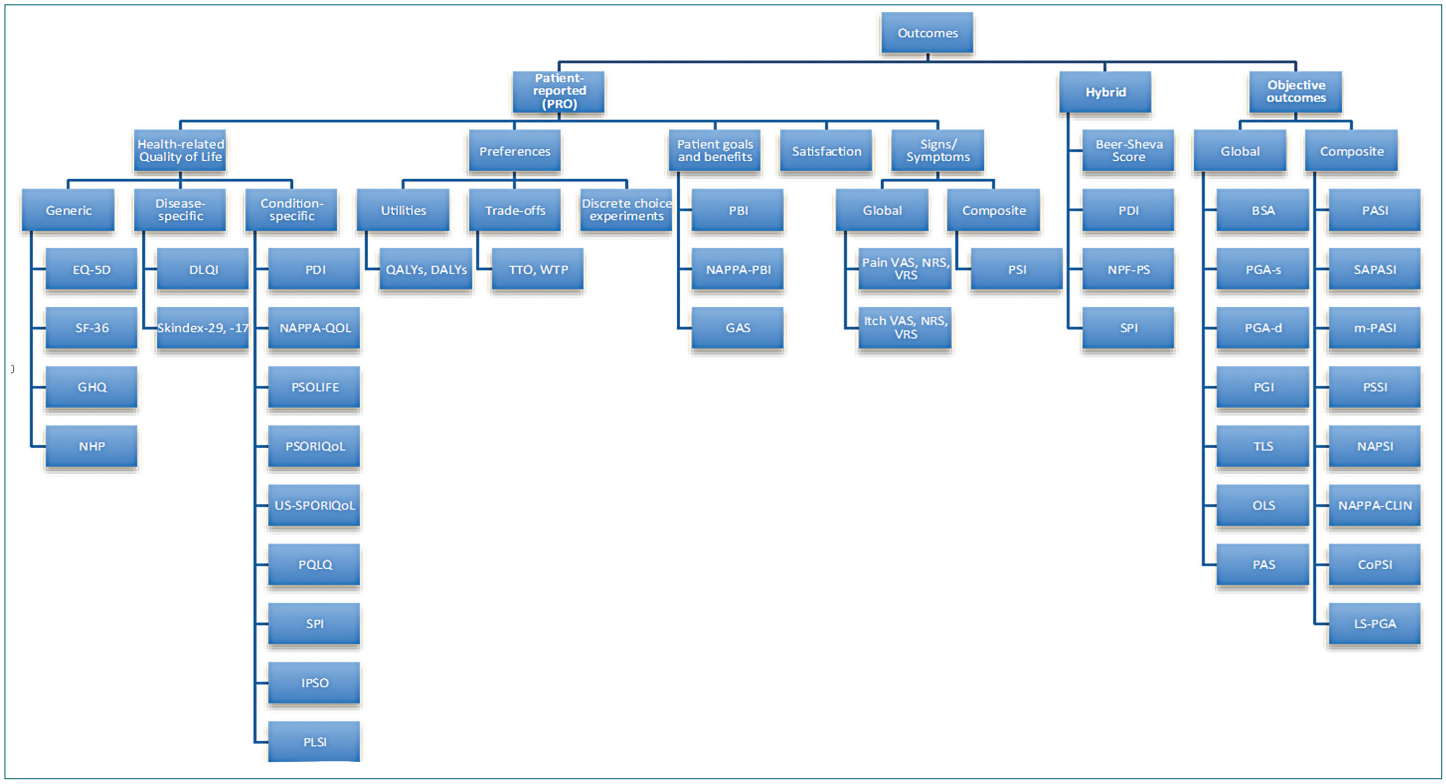
3.2. Patient-reported outcomes measures in psoriasis

Patient-reported outcomes (PROs) are an important dimension of patient orientation in healthcare. They provide a direct measure of the patient's perception of their own health, quality of life, and treatment outcomes. PROs are collected through questionnaires or interviews that ask patients to report on their symptoms, physical functioning, emotional wellbeing, and overall quality of life. By incorporating PROs into clinical practice and research, healthcare providers can gain valuable insights into the patient's experience of their illness and treatment. This information can help to identify areas of unmet need, inform treatment decisions, and improve communication and shared decision-making between the patient and healthcare provider. Moreover, PROs can be used to evaluate the effectiveness of healthcare interventions and to compare the outcomes of different treatments or healthcare providers. This can help to identify best practices and improve the overall quality of healthcare. In summary, PROs are a key component of patient-centred care and can play a vital role in improving the health outcomes and quality of life of patients.

Figure 3 provides a brief overview of the most commonly used clinician-observed outcomes, such as the Psoriasis Area and Severity Index (PASI) [28], which measures disease severity in psoriasis, and patient-reported outcome measures, such as the Dermatology Quality of Life Index (DLQI) [29]. However, other instruments have also emerged, such as the Patient Benefit Index (PBI) for identifying patient needs and treatment benefits [30]. The PBI is available in several disease-specific versions, including psoriasis, and is often used in international practice for clinical and health services research.

There are many more generic, skin-specific, and disease-specific measurements that can be used in psoriasis. PROs can be divided into outcomes that assess clinical characteristics, such as the self-administered Psoriasis Area and Severity Index (SAPASI),

Figure 3. Psoriasis family outcomes measures



functionality-related measurements, quality of life-related instruments, instruments that assess the impact on patients' families (FamilyPso), symptoms (such as pain numeric rating scale), psychosocial impact, and the impact on economic issues such as work productivity. Given the wide range of choices, it is important to focus on selecting the most suitable outcome measures.

In order to select the most appropriate measurements, it is necessary to first clarify whether it is needed to measure both clinician-observed and patient-reported outcomes. This question is supported by data from routine care in Germany, which reveals a discrepancy between objective and subjective outcomes (see Figure 4). The X-axis displays the Psoriasis Area and Severity Index (PASI) score calculated by the physician, while the Y-axis displays the DLQI score derived from the patients. The data clearly show that there is no correlation between objective and subjective outcomes in the cross-section, which supports the conclusion that both should be measured as one cannot predict the other. However, over the course of treatment (as demonstrated by the red line in Figure 4), the deltas correlate, demonstrating that an improvement in PASI is correlated with an improvement in DLQI. This indicates that, to make sound clinical decisions, both clinician-observed and patient-reported outcomes should be measured.

Given the limitations of the DLQI, the question arises as to whether we can obtain value-based information on what matters to patients from such instruments. The DLQI is one of the most widely used PROs for assessing the impact of skin diseases, including psoriasis, on quality of life. However, it has certain biases, such as inadequate items, differential item functioning based on disease, age, and gender, disordered response thresholds, and inadequate measurement of patients with mild disease [33], which underestimate the emotional problems, psychological well-being, and overall burden experienced by people with psoriasis [34, 35]. Furthermore, a recent study investigated whether the DLQI is a sufficient indicator of wellbeing according to the WHO's holistic definition of health. The study concluded that the DLQI primarily measures physical impairment associated with negative emotions and, therefore, provides only a limited assessment of wellbeing [36].

Nevertheless, the DLQI is very easy to use in practice. However, it has some biases, such as item inadequacy.The question is how patient needs can be measured directly rather than translating this from the DLQI. The global report on psoriasis has provided guidance on how to measure those patient needs. Patient needs can be directly assessed through standardised questions, using the PBI. It was shown that patients with psoriasis largely have several needs, the most frequent being "to get better skin quickly,". Other important goals include "to be free of itching," "to experience a greater enjoyment of life," and "to feel less depressed" [37]. Remarkably, most of the goals cannot be measured by the PASI but need to be measured and asked from the patient directly. Thus, there is a large number of patient needs leading our

way to the treatment of choice and then leading to value-based care if the goals have been achieved (see Figure 1). However, how can the achievement of the goals be measured? The answer is "goal attainment scaling," which means measuring the patient needs and goals before treatment and then re-evaluating after some period of treatment to determine whether these goals have been achieved by treatment.

But how can we promote positive outcomes thinking and people-centred care beyond goal orientation and patient benefit measurement? There is a second approach that relates to the WHO definition of health. According to the WHO, "health is a state of complete physical, mental, and social wellbeing" [38]. This demonstrates that wellbeing is an essential and powerful component of health. Wellbeing as a holistic outcome, in turn, comprises several dimensions, such as psychological wellbeing and life satisfaction [42].

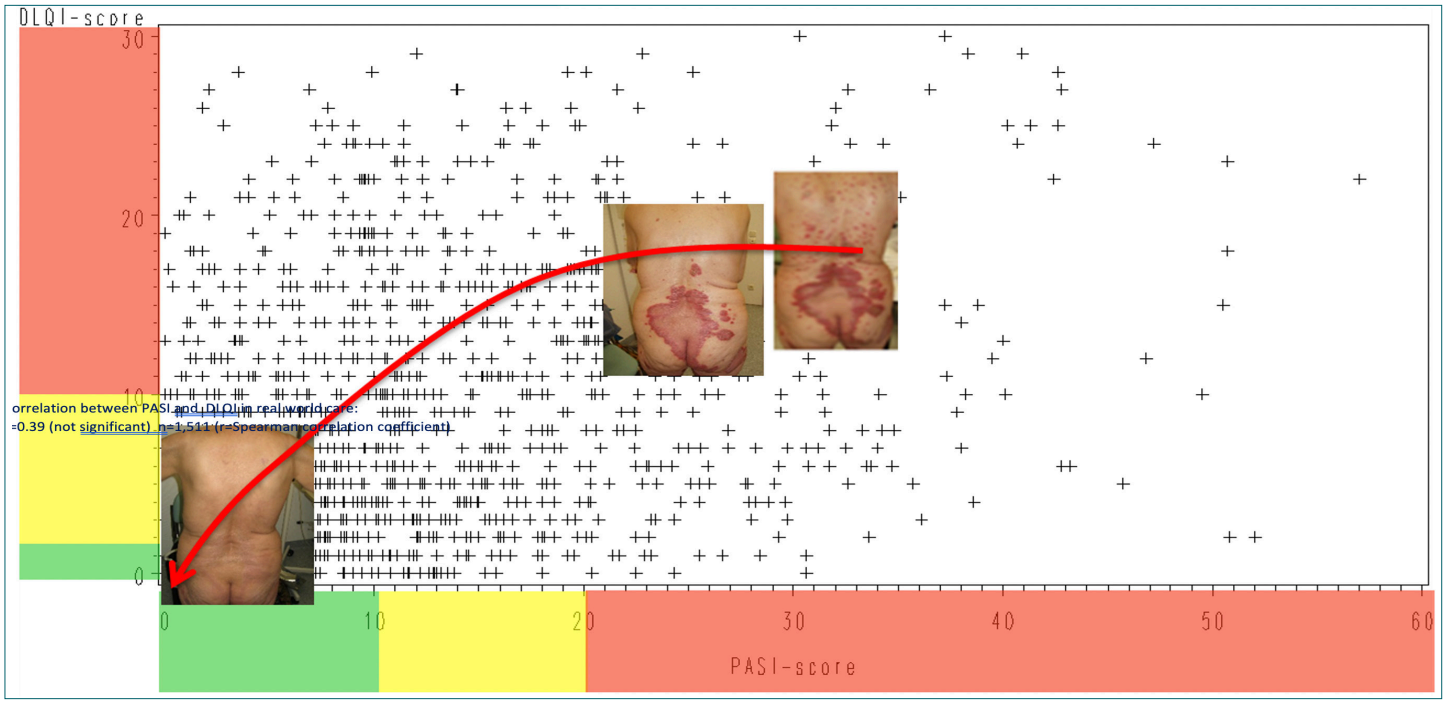
The wellbeing of patients has rarely been measured in dermatology, even though the ultimate goal of disease management should be to live a healthy life. This highlights the need for a paradigm shift away from hard clinical measures towards a more holistic approach that encompasses overall wellbeing. Considering this, a recent study has shown that positive affect, as part of emotional wellbeing and life satisfaction, can complement the information provided by the DLQI, contributing to a comprehensive evaluation of wellbeing in accordance with the WHO's holistic definition of health [36]. Furthermore, the importance of wellbeing as a treatment outcome from the patient's perspective was recently assessed. Patients were asked to reflect on the importance of wellbeing as a treatment goal and on its importance compared with other treatment outcomes. All patients confirmed that changes in wellbeing reflected treatment benefit. Wellbeing was evaluated as a central aspect of treatment benefit by the majority of participants. In addition, positive associations of wellbeing with other outcomes that were considered relevant were reported [39]. However, only a few studies have assessed disease-related wellbeing in psoriasis so far [40, 41], and none of them were therapeutic studies. This presents a particular gap in the literature since the rising number of highly effective innovative drugs [43] increases the need for differentiated choices and shared decisions based on patient-relevant outcomes. Identifying drugs with a particular positive effect on wellbeing may be a useful decision aid. Therefore, to assess wellbeing in psoriasis in research and clinical practice, valid measurements need to be available. The WHO-5 questionnaire, an internationally recommended questionnaire on health-related wellbeing, was recently psychometrically validated in a psoriasis sample [44]. The WHO-5 showed excellent reliability, with Cronbach's alpha for the WHO-5 total score at baseline and at the second measurement time point. Responsiveness was proven acceptable, demonstrating that the WHO-5 is ready for use in clinical practice in psoriasis to facilitate a holistic care in terms of treatment outcomes.

4. Conclusion

Summarising how people-centred care can be integrated into dermatological practice includes the following recommendations:

- The patient should be actively included in all steps of healthcare practice; this requires listening to the patient
- The perspective of patients through patient-reported outcomes measures should be asssesed. Supporting the

Figure 4. Discrepancy between objective and subjective outcomes



acquisition of patient-reported data by digital devices can be of great help. This first series of information, including patient needs and therapy goals, is gathered in a structured way independently from the physician.

- After this, there should be direct interaction between the patient and physician (as well as other healthcare professionals, such as nurses and psychologists), allowing for a participatory and shared decision-making process.

Altogether, in line with the SDM model, patients should be considered experts in their illness, and clinicians should be considered experts in the management of the disease. There is a clear need for a paradigm shift away from hard clinical measures towards a more holistic way of considering patient wellbeing. Thus, measuring wellbeing can contribute to a more comprehensive understanding of health. In addition, wellbeing is bidirectional and includes the patient, physician (and other healthcare professionals, such as nurses and psychologists), and the patient's environment, contributing to a people-centred healthcare environment.

One recent example of such a people-centred approach is the POSITIVE study, which is the first study assessing the effect of tildrakizumab on the wellbeing of patients with moderate to severe psoriasis. Moreover, the long-term benefit of tildrakizumab on physician satisfaction and patients' partners' lives will be evaluated [45]. For the first time, the WHO-5 will be used as a primary endpoint in patients with psoriasis to investigate the improvements that a systemic treatment can achieve on patients' wellbeing in a real-world setting. This study will provide novel insights into the dimensions of patients' perspectives and their overall state of wellbeing using a holistic patient-partner and physician-centred approach, ultimately helping to improve not only patients' wellbeing but also the wellbeing of their environment. Thus, it could serve as a best practice example of how to integrate a people-centred approach in dermatological research.

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SARS-CoV-2 vaccination management in patients with chronic plaque psoriasis

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Abstract
Since December 2020, large vaccination campaigns have been initiated all over the world, changing dramatically the course of the COVID-19 pandemic. As SARS-CoV-2 vaccines have become widely available, dermatologists need to face issues related to their safety and efficacy for patients with immune-mediated inflammatory diseases including those with psoriasis taking immunomodulatory treatments. According to different guideline including EuroGuiDerm Guideline, National Psoriasis Foundation and International Psoriasis Council recommendations, patients with psoriasis are candidate to SARS-CoV-2 vaccination whether they are on systemic drug treatment or not. Although randomized controlled trials of SARS-CoV-2 vaccines excluded such patients, current real-world data suggest that they are safe in patients with psoriasis undergoing immunomodulatory treatment. An open issue is whether patients on immunomodulatory treatments will mount a sufficient humoral and cellular immune response to the vaccine. In individuals receiving methotrexate or TNF-α inhibitors, impairment and waning in immunogenicity has been reported. Consequently, such patients might require testing to assess whether adequate immune responses are elicited after vaccination and booster vaccination are required to generate sufficient protection against SARS-CoV-2 infection.

1. Introduction
In December 2019, in Wuhan (China), SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) was described for the first time [1]. This novel type of coronavirus spread rapidly through global population in few months with raising concern among public and health authorities worldwide until the World Health Organization (WHO) declared pandemic status on 11th March 2020 [2]. SARS-CoV-2 is the etiologic agent of Coronavirus disease 2019 (COVID-19), a condition characterized by a spectrum of symptoms, from mild (e.g., headache, cough, and fever) to severe manifestations and life-threatening events, such as acute respiratory distress syndrome (ARDS) and venous thromboembolisms, with an increased risk in chronically ill and immunologically compromised patients [3,4]. After 3 years of pandemic the number of deaths related to COVID-19 is 6.88 million out of a total of more than 761 million confirmed cases [5]. From the beginning of the first outbreak, one of the most viable ways to counter this health, social and economic

burden has been to develop a vaccine using the spike (S) protein of the virus as the main activator of the immune system. With huge efforts by governments and pharmaceutical industries, numerous vaccines have been developed with the aim to prevent viral infection or, in case of infection, avoid the most severe manifestations, to reduce hospitalizations, intensive care unit admissions and, consequently, the overloading of health systems worldwide. Therefore, the largest vaccination campaign in human history was launched and only 1 year after the first vaccine was approved more than 10 billion doses had already been administered in the world [6,7].

Different categories of vaccines have been designed using different technology platforms and several of them are globally in use: (1) inactivated viral vaccines, which contain pathogens altered in a way to prevent their replication, (2) protein subunit vaccines, composed of fragments of the original virus by recombinant technology, (3) viral vector (non-replicating) vaccines, employing a carrier virus such as an adenovirus, and (4) nucleic acid-based vaccines (mRNA- or DNA-based) which code for viral proteins and induce the cells themselves to synthesize the antigen [8]. To date World Health Organization (WHO) approved 11 vaccines: Covilo (Sinopharm-Bejing), Covaxin (Bharat Biotech), CoronaVac (Sinovac) (Inactivated virus-based); Nuvaxoid (Novavax), COVOVAX (Serum Institute of India) (Protein Subunit-based); Vaxzevria (Oxford/AstraZeneca), Covishield (Serum Institute of India), Convidecia (CanSino), Jcovden (Janssen) (Non-Replicating Viral Vector-based); Spikevax (Moderna), Comirnaty (Pfizer/BioNTech) (RNA-based) [9].

Most vaccines showed a significant reduction in cases of symptomatic COVID-19 and severe or critical disease compared with placebo, and little or no difference for serious adverse events [8]. The effectiveness was also demonstrated against COVID-19-related hospitalization, intensive care unit admission and death, not only in cases of full vaccination but also in those who have received partial vaccination, although to a lesser degree [10]. Data collected by Centres of Disease Control (CDC) showed that the number of Covid-19-related deaths in the U.S. was higher in the unvaccinated than in the vaccinated with similar results across vaccine types [6]. An increase in efficiency was also observed with booster dose administration compared to primary immunization [11]. As the mass vaccination campaign progressed, increasing numbers of post-vaccination adverse reactions were reported and several studies have found that this risk is greater for mRNA vaccines [12,13]. Expected adverse events related to the body's normal reactiveness were observed in conjunction with the administration of different types of vaccine, such as local reactions at injection site, like pain, redness and swelling, or signs of systemic response, like fever, headache, chills, myalgia and fatigue, which were, however, mild and transient, [8] developing within 1 to 2 days after vaccination and lasting 1 to 2 more days [14]. It is also important to consider the relevance of the "nocebo effect", which led to significant frequency of adverse events even in placebo recipients, probably because of the many concerns in population regarding vaccines, their rapid development, and uncertain safety [15]. In addition to reactions at the injection site, other frequent patterns of skin manifestation were described, which were, however, self-limiting and not severe, mostly urticarial and morbilliform eruptions [16,17]. Other less common manifestations were pernio/chilblain, pityriasis rosea-like reactions, zoster, cosmetic filler reactions and herpes simplex exacerbations [16,17].

The most important severe adverse events described in the literature are divided into four major organ-specific groups: immune-allergic (urticaria, angioedema, anaphylactic shock, autoimmune hepatitis, vasculitis), cardiovascular (myocarditis and pericarditis, acute coronary syndrome, pulmonary thromboembolism, hypertension crisis), hematologic (vaccine-induced thrombotic thrombocytopenia, diffuse intravascular coagulation, venous thromboembolism, immune thrombocytopenia) and neurologic events (Guillain-Barré syndrome, transverse myelitis, cerebrovascular attack, cerebral venous sinus thrombosis and Bell's palsy) [18]. Episodes of myocarditis and pericarditis, which represent some of the main safety concerns in male young adults, appear to be more frequently Covid-associated than mRNA vaccine-associated, while thromboembolic events have been described particularly in young women with a pre-existing hypercoagulability state receiving adenoviral vector vaccines [18]. The link of causality is still under investigation for several of these adverse events [19]. Despite the low incidence of severe adverse events, SARS-Cov-2 vaccines are receiving careful surveillance by national and international programs, continuing to show a good safety and efficacy profile in several studies, including during pregnancy and in children [20]. Despite these few and rare risks associated with their administration, they continue to be recommended in the general population by the scientific communities because benefits still outweigh risks and remain the most effective strategy to facilitate the gradual transition from pandemic to endemic state [6].

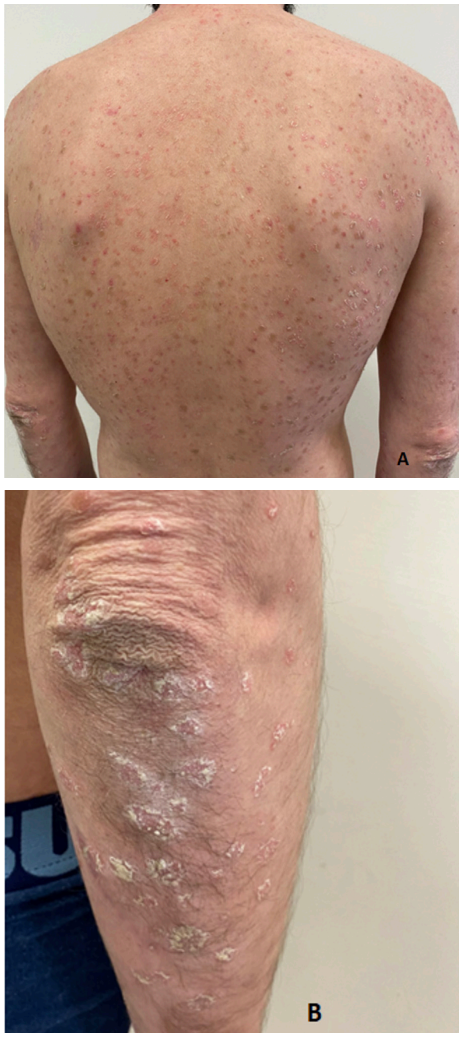
2. Safety of SARS-CoV-2 vaccines in patients with chronic plaque psoriasis

As SARS-CoV-2 vaccines have become widely available, dermatologists needed to face their safety and efficacy in patients with immune-mediated inflammatory diseases, particularly those with psoriasis who take immunosuppressive/immunomodulatory treatments [21]. Drugs such as methotrexate, cyclosporine and biologics targeting tumour necrosis factor (TNF), interleukin (IL)-17, IL-12/23, IL-23 are highly effective in blocking the immune pathways of psoriasis, but also can increase the risk of certain infections and potentially reduce vaccine immunogenicity.

Case reports of psoriasis flares following SARS-CoV-2 vaccination have been reported (Figure 1) leading to hesitancy and apprehension among patients and physicians [16,17,22-30]. Such flares were frequently described after the boost dose and the mean interval between vaccination and psoriasis flare was 9.3 days [16]. The pathogenetic mechanism

behind psoriasis exacerbations has not fully understood. In mRNA vaccines, single-stranded RNA can activate toll-like receptors (TLR), the inflammasome and the production of type I interferons, which are known to flare autoimmune disease. Similarly, double stranded DNA in adenoviral vector vaccines induce type I interferons production via TLR9 [16]. However, a more recent self-controlled case series analysis reported that vaccination against SARS-CoV-2 was not statistically associated with risk for psoriasis flare. The adjusted incidence rate ratio (IRR) of psoriasis flare was 0.96 (95%CI 0.80-1.14) 21 days after vaccination [31].

Figure 1. Numerous guttate plaques of psoriasis on the back (A) and right elbow (B) of a 45-year-old atient triggered 2 weeks after administration of the booster of an mRNA vaccine



Regarding the safety of SARS-CoV-2 vaccination in psoriatic patients on biologics, current real-world data suggest that adverse effects are comparable to those observed in healthy individuals, even if prospective randomized controlled trials excluded such patients for the current available vaccines, particularly the now widely used mRNA vaccine BNT162b2 [21]. For example, a study on 436 psoriatic patients treated with biologics (78 of whom underwent SARS-CoV-2 vaccination) reported no vaccination-related adverse effects [32]. In another study on 369 patients with psoriasis receiving anti-IL-17 and 23 agents who underwent SARS-CoV-2 vaccination, no serious vaccination-related adverse events were reported, while about a third developed mild adverse events (such as injection site pain, fever, fatigue, and muscle pain) that resolved within 48 hours [33]. In a study involving 505 patients with IMID treated with methotrexate, glucocorticoids, biologics and 203 healthy controls, no significant difference in frequency of adverse events between patients with IMID and controls was found [34]. A survey involving 325 patients with IMID treated with disease modifying anti-rheumatic drugs and biologics, most reactions were local and transient like those reported in vaccine trials, no series allergic reactions were reported [35]. Conversely, in a cohort study involving 127 patients with IMID and 97 controls receiving ChAdOx1-S vaccine, those with psoriasis were more likely to experience vaccine-related adverse effects than controls (72 vs 57%) [36]. In conclusion, there is no evidence that patients with psoriasis receiving biologics are at greater risk of harm from SARS-CoV-2 vaccination.

3. Efficacy of SARS-CoV-2 vaccines in patients with chronic plaque psoriasis

An open question is whether patients with psoriasis receiving biologics or other immunomodulatory treatments can mount an adequate immune response to the SARS-CoV-2 vaccine. In vaccine-induced host protection against SARS-CoV2 a complex interaction between innate, humoral, and cellular immunity occurs. In prospective cohort studies different assessment of humoral and cellular response after SARS-CoV2 vaccination has been evaluated, including total antibody titres, neutralizing activity and T-cell mediated immunogenicity as measured by interferon-gamma releasing assay (IGRA), as summarized in Table 1. Earlier studies on vaccination against pneumococcus, meningococcus, influenza, or tetanus showed that treatment with TNF-α inhibitors, IL-12/23 inhibitors and IL-17 inhibitors is not associated with lower antibody response [37].

In contrast, a decreased humoral immune response to SARS-CoV-2 vaccines in patients with immune-mediated inflammatory diseases was reported after the first dose [38]. As an example, among 120 patients with immune-mediated inflammatory diseases (including 107 with psoriasis) who received either mRNA or viral vector-based vaccines, 15% of participants receiving immunomodulatory drugs, particularly methotrexate, did not develop detectable concentrations of antibodies [38]. In the study by Mahil et al. involving 87 patients with psoriasis (treated with methotrexate, TNF-α and IL-17 and IL-23 inhibitors) and 17 healthy controls after a single BNT162b2 vaccine dose, seroconversion rates were found to be lower in patients receiving immunosuppressants than controls (78%, 95%CI 67-87 vs 100%, 95%CI 80-100), with the lowest rate in those rtable 1 to controls. The cellular response was found numerically lowest in the anti-TNF-αgroup as well. These findings suggests that anti TNF-α agents have faster waning of immunity to mRNA-based vaccination [43]. Data from a cohort of 194 patients with axial spondylarthritis and psoriatic arthritis confirmed that TNF-α inhibitors attenuate immunogenicity to the inactivated CoronaVac vaccine. After three doses of vaccine, anti-TNF-α drugs were still associated with impaired seropositivity and neutralizing antibodies ($p<0.005$) [44].

The three-dose antibody response of COVID-19 mRNA vaccine in psoriasis patients treated with biologic drugs is a further ongoing issue. In a prospective cohort study involving forty-five psoriatic patients on biologic treatment a significant increase in antibody titres after each dose of

Table 1. Studies assessing Sars-Cov-2 vaccine immunogenicity in patients with chronic plaque psoriasis.

First author	Vaccine	Population	Therapies used at the time of vaccination	Immune response to Sars-Cov-2 vaccine
Mahil S. et al.	BNT162b2 (Pfizer-BioNTech)	84 patients with psoriasis and 17 healthy controls	Methotrexate (n=17), TNF-α inhibitors (n=27), IL-17 inhibitors (n=15), IL-23 inhibitors (n=25)	Functional humoral immunity at 28 days after a single dose was impaired by methotrexate but not by biologics, whereas cellular responses were preserved in all patients.
Mahil S. et al.	BNT162b2 (Pfizer-BioNTech)	67 patients with psoriasis and 15 healthy controls	Methotrexate (n=14), TNF-α inhibitors (n=19), IL-17 inhibitors (n=14), IL-23 inhibitors (n=20)	Neutralizing antibody responses at 14 days following a second dose was not impaired by methotrexate or targeted biologics. A proportion of patients did not have detectable T-cell responses following the second dose.
Marovt M et al.	BNT162b2 (Pfizer-BioNTech)	32 patients with psoriasis and 22 healthy control	TNF-α inhibitors (n=7), IL-12/23 inhibitors (n=11), IL-17 inhibitors (n=6), IL-23 inhibitors (n=8)	No difference in the rate of seroconversion, but significantly lower titres were observed in patients with psoriasis treated with biologic monotherapy compared to controls
Cristaudo A. et al.	BNT162b2 (Pfizer-BioNTech)	48 patients with psoriasis and 48 healthy control	TNF inhibitors (n=21), IL-12/23 inhibitors (n=8), IL-17 inhibitors (n=6), IL-23 inhibitors (n=13)	No difference in the rate of seroconversion between patients and controls
Chanprapaph K et al.	ChAdOx1-S[recombinant] (Astrazeneca)	127 patients with immune mediated dermatoses (57 with psoriasis) and 97 healthy controls	Mostly methotrexate and IL-17A inhibitors	The immunogenicity of the vaccine in patients with psoriasis was comparable to healthy controls
Kvist-Hansen A et al.	BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna)	123 patients with psoriasis versus 226 healthy controls	Adalimumab (n = 39), infliximab (n = 2), etanercept (n = 2), ustekinumab (n = 25), risankizumab (n = 2), secukinumab (n = 10), ixekizumab (n = 4), methotrexate (n = 28) or combined with a biologic (n = 3)	Treatment with TNF-α inhibitors resulted in a faster waning of humoral and cellular markers of immunity

vaccine compared with baseline was found, with no significant differences between patients and controls. Methotrexate used in combination with biologics has been shown to negatively influence the antibody response to the vaccine [45].

Conclusions

SARS-CoV-2 vaccination management in chronic plaque psoriasis is a clinically relevant issue. According to different guideline/recommendations including EuroGuiDerm, National Psoriasis Foundation and International Psoriasis Council, patients with psoriasis are candidate to SARS-CoV-2 vaccination whether they are on systemic drug treatment or not. Psoriasis is not a contraindication to vaccination [46,47]. In fact, the advantages of avoiding severe COVID-19 through vaccination is much greater than the theoretical risk of its adverse events. The American College of Rheumatology, recommended to withhold methotrexate 1 week after each dose of vaccine for patients with well-controlled disease [48]. This recommendation is based on data from influenza and pneumococcal vaccines showing that methotrexate, but not target therapies, impair humoral responses [49].

Although several studies support the safety and efficacy of SARS-CoV-2 vaccination, a considerable population still expresses vaccine hesitancy, including those affected by psoriasis. Age, gender, lack of trust in science, and concerns of safety and efficacy represent determinants for vaccine hesitancy. According to the global patient-reported PsoProtect*Me* survey, up to 8% of patients with psoriasis have vaccine hesitancy [51]. A recent systematic review recommends strategizing the campaign for booster doses by identifying and evaluating the reasons for such hesitancy and by appropriate communication [50].

In conclusion, current data suggests that SARS-CoV-2 vaccines appear safe in patients with psoriasis undergoing immunomodulatory treatment. In some individuals receiving methotrexate or TNF-α inhibitors, waning in immunogenicity of the vaccine could occur. Consequently, such patients might require testing to assess whether adequate immune responses are elicited after vaccination and whether booster vaccination is required to generate sufficient protection against SARS-CoV-2 infection. Further studies are needed to assess the long-term impact of the different classes of biologics on humoral and cellular immunogenicity [21].

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Psoriasis and COVID-19: findings from PsoProtect*Me*

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Abstract

The COVID-19 pandemic prompted the rapid mobilisation of the research community to investigate the impact on people with psoriasis. This led to the creation of the online patient-facing PsoProtect*Me* registry, developed in partnership with people with psoriasis and patient organisations. Launched in May 2020 and available in nine languages, PsoProtect*Me* was created to understand the lived experience and mental health burden of people with psoriasis during the pandemic. The registry was far reaching: it had 5479 participants from more than 30 countries worldwide. Here, we review the key findings from the PsoProtect*Me* registry, which have helped to inform clinical guidelines in psoriasis during the pandemic. We highlight the important role for online data collection from an engaged and motivated patient community in facilitating time and resource efficient research.

1. Introduction

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), heralded an unprecedented era in healthcare[1]. There was global concern amongst both the clinical and scientific communities about the immediate and longer-term health implications of COVID-19 in the general population. Risk factors for poor COVID-19 outcomes were uncovered early in the pandemic using population-level studies, including male sex, increased age and comorbidities such as cardiovascular disease and obesity [2]. There was thus heightened concern regarding poor outcomes for people with immune-mediated inflammatory disease (IMID) and specifically psoriasis, given the prevalence of multimorbidity in this group. Indeed, prior to the COVID-19 pandemic, cohort studies found a greater risk of respiratory infection related hospitalization amongst people with psoriasis compared to the general population [3–5]. Additionally, there was uncertainty regarding the risk of severe COVID–19 associated with immune-modifying therapies, especially given pre-pandemic data on serious (including respiratory) infection risk in the psoriasis population [6,7].

These knowledge gaps prompted rapid mobilisation of the research community, resulting in the development and dissemination of multiple, partially synergistic, international patient registries to investigate the impact of the pandemic[8]. In psoriasis, an international collaborative effort led to the launch of two aligned sister registries which were developed in partnership with people with psoriasis and patient organisations. These were a clinician facing registry PsoProtect (Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of COVID-19 Infection) and a patient-facing registry, PsoProtect*Me* (Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of COVID-19 Infection Me) [9,10].

PsoProtect launched globally on March 27, 2020. Its initial assessment of 374 clinician-reported patients from 25 countries was the first global case series of COVID-19 in people with psoriasis. It found that older age, male sex, and non-white ethnicity were associated with greater risk of hospitalization for COVID-19 in people with psoriasis, in addition to comorbid chronic lung disease [11]. Furthermore, in individuals with moderate-to-severe psoriasis, biologic use was associated with lower risk of COVID-19–related hospitalization compared to non-biologic systemic therapies. However, limitations to this dataset included a limited number of patients reported, the absence of a control group and potential clinician reporting bias. Differences in confounding factors across treatment groups such as risk mitigating behaviours (social isolation) and drug non-adherence could not be assessed[11]. Importantly, information on the lived experience and mental health burden of people with psoriasis during the pandemic remained unknown.

2. Study design

To address some of these limitations, PsoProtect*Me* was rapidly launched early in the pandemic in May 2020 shortly after its sister registry PsoProtect. It was designed to collect information directly from people with psoriasis, including information on medication adherence, mental health, and social isolation behaviour. It was aligned to clinician reported COVID-19 registries (e.g. PsoProtect) and patient reported registries in other IMIDs (e.g SECURE-IBD registry for inflammatory bowel disease, SECURE-AD Patient Survey for atopic dermatitis and HS COVID for hidradenitis suppurativa).

PsoProtect*Me* partnered with CORE-UK (a patient-facing self-report survey for those with rheumatic disease) so that data could be pooled across IMIDs, enabling increased statistical power for analyses. This was a valuable opportunity given the shared immune-modifying therapies across dermatology and rheumatology.

The data fields in PsoProtect*Me* were defined following multi-stakeholder input from a study group of patient representatives, clinicians, epidemiologists and health data researchers. Key variables included demographics (age, sex, ethnicity, and country), details of psoriasis (phenotype, severity and treatment), COVID-19 (symptoms, treatment, and outcome), medication adherence, social isolation behaviour, comorbidities and smoking status. Validated screening tools were embedded including the Dermatology Life Quality Index (DLQI) assessing health related quality of life, the Generalized Anxiety Disorder Scale -2 (GAD-2) and the Patient Health Questionnaire Depression Scale -2 (PHQ-2). These embedded screening tools allowed for improved quality and interpretability of the self-reported data collected. eConsent for future healthcare record linkage was collected from UK participants, to enrich and validate self-report data.

PsoProtect*Me* was freely accessible online and took around 10 minutes to complete. The eligibility criterion was any person (all ages) with a clinician-confirmed diagnosis of psoriasis, irrespective of COVID-19 status. Data were collected and managed using REDCap electronic data capture tools licensed to King's College London Division of Health and Social Care Research [12,13].

3. Engagement and recruitment

Patient-facing registries advocate citizen science, the act of involving members of the public to act as collaborators in scientific research. Citizen science can encourage support and advocacy for people with chronic diseases and empowers communities to act to support their health and wellbeing [14]. Citizen participation in data generation is likely to be crucial in pandemic management [15], and the uncertainty and urgent need for data may have contributed to the psoriasis patient community being highly motivated to submit their own data, resulting in robust recruitment in PsoProtect*Me*.

People with psoriasis were involved in all aspects of PsoProtect*Me* research, including deciding the research questions, design of data fields, beta-testing prior to launch, supporting dissemination and data interpretation. PsoProtect*Me* partnered with global patient organisations [16] and had patient representatives on the research steering committee. Following its launch, it was promoted and disseminated globally by an international cohort of patient organisations, including the International Federation of Psoriasis Associations (IFPA), and professional clinical networks to enable uptake [16]. It was available in nine languages (English, Italian, Japanese, Portuguese, Polish, Spanish, French, Chinese and Vietnamese) to improve international uptake. Research inclusivity was also promoted by sharing direct quotes via social media from a wide diversity of participants from over the world detailing why they contributed to PsoProtect*Me*.

Rapid data feedback throughout helped to keep the psoriasis community engaged as they could see the results of their participation efforts. Results were regularly published on the 'current data' page of the PsoProtect*Me* website and shared through the social media channels of PsoProtect (including Instagram, Facebook and Twitter) and partner patient organisations. Continued engagement with participants was led by a communications working group who met regularly to review the dissemination strategy. This group included representatives from IFPA, Psoriasis Association and Global Psoriasis Atlas. This resulted in robust recruitment throughout the early months of the pandemic. Successful patient-facing registry recruitment was echoed elsewhere, and a review of the seven dermatology registries initiated during the COVID–19 pandemic found that patient-facing registries reported greater recruitment than clinician facing registries[17]. However, the relative increased recruitment in the PsoProtect*Me* study could also be explained by the recruitment being independent of COVID-19 status, which differed from PsoProtect's inclusion criteria.

4. Study population

The PsoProtect*Me* registry was far-reaching, with 5479 participants from more than 30 countries worldwide. Countries with more than 200 participants included the UK, USA, Chile, Argentina and Portugal. The mean age of participants was 45 years (range 3-91 years) and 67% were female. The mean BMI of participants was 26.8kg/m^2. 4408 respondents reported plaque psoriasis, 1122 guttate psoriasis, 289 pustular psoriasis and 120 self-reported erythroderma. 2320 (36%) respondents stated that they were receiving a systemic therapy for psoriasis, and 32% reported concurrent psoriatic arthritis.

5. PsoProtect*Me* findings on the burden of the COVID–19 pandemic

Analysis of PsoProtect*Me* data facilitated an international cross-sectional assessment of the impact and burden of the pandemic in people with psoriasis, along with assessing changes in behaviour during the pandemic.

5.1 Association between worsening psoriasis and mental health

People with psoriasis have a high prevalence of anxiety and depression: a pre-pandemic single centre UK cross-sectional study of 607 people with psoriasis (81.6% of whom were receiving systemic therapy) revealed that 10% screened positive for major depressive disorder (MDD) and 13% for generalized anxiety disorder (GAD) [18]. The risk of MDD or GAD was significantly higher in those with severe psoriasis. During the pandemic, there was an increased multifactorial mental health burden in the general population [19] and in people with psoriasis[20]. Public health efforts to reduce infection risk, such as

shielding behavior and stay at home measures, were hypothesized to cause indirect morbidity including worsening psoriasis and mental health.

An analysis of PsoProtect*Me* data from 4043 individuals highlighted that worsening psoriasis was common during the pandemic, and reinforced the association with poor mental health. The association between mental health and self-reported worsening psoriasis was assessed using a multivariable logistic regression model. A score of ≥3 in GAD-2 (anxiety) or PHQ-2 (depression) screens was defined as a positive mental health screen [21]. A total of 1728 (42.7%) PsoProtect*Me* respondents reported worsening psoriasis. The multivariable logistic regression model for worsening psoriasis estimated an odds ratio (OR) 2.01 (95% confidence interval (CI), 1.72–2.34) for those with a positive screen for anxiety or depression compared to those without a positive screen. Similar associations were observed for female sex (OR 1.82, 95% CI 1.56–2.13); obesity (OR 1.22, 95% CI, 1.09–1.36) and shielding behaviour (OR 1.18, 95%CI 1.03–1.35) [22]. These results highlight the burden of the COVID-19 pandemic in people with psoriasis. Access to holistic care and psychological support for people with psoriasis is imperative to address the increased mental health burden and PsoProtect*Me* findings highlighted the urgent need to provide this during the COVID-19 pandemic.

5.2 Risk mitigating behaviour

As part of the international recommendations from the World Health Organization (WHO), public health risk-mitigating measures such as social distancing were rapidly undertaken as a global measure to reduce the community spread of COVID-19[23]. High risk groups were advised to undertake strict social distancing measures defined as 'shielding'. Those with IMIDs who were receiving immune-modifying therapies were initially thought to be at higher risk of severe COVID-19 due to pre-COVID 19 observational studies of drug related risk of serious infection [6,7]. However as detailed above, initial research from the PsoProtect registry and others indicated that use of biologic therapy was associated with a lower risk of COVID-19–related hospitalization than non-biologic systemic therapy. A possible explanation of this finding is a difference in behaviour such as risk mitigating behaviour across treatment groups. To explore this, an analysis of 2869 participants from the PsoProtect*Me* registry and 851 from the parallel CORE–UK registry was undertaken. Stringent risk mitigating behaviour (shielding) during the pandemic was associated with use of biologic therapies compared with non-biologic systemic therapies [OR 1.39, 95% CI 1.23–1.5] or no treatment [OR 1.63, 95% CI 1.35–1.97]. This difference in behaviour between treatment groups may have contributed to the reported lower risk of adverse COVID-19 outcomes associated with use of biologic therapies compared with standard (non-biologic) systemic therapies. Shielding was also associated with established risk factors for severe COVID-19 (male sex, obesity, and comorbidity burden) and a positive anxiety or depression screen[16].

5.3 Vaccine hesitancy

Vaccination against COVID-19 is crucial in reducing severe COVID-19 outcomes and hospitalisations, however vaccine hesitancy (delayed acceptance or refusal of vaccination despite service availability) threatened vaccination rates and public health COVID-19 risk mitigation strategies [24]. A UK cross-sectional study of 5,114 adults in the general population assessed vaccine hesitancy in the months prior to the COVID-19 vaccine rollout, reporting that 29% of respondents were vaccine hesitant. Vaccine hesitancy was higher in women, younger people and ethnic minority groups [25]. Individuals with psoriasis, particularly those treated with immune-modifying therapies, were prioritised for vaccination. However, there were limited data on vaccine hesitancy amongst people with psoriasis [26]. Therefore, PsoProtect*Me* was updated 1 year following its launch to include questions on COVID-19 vaccine hesitancy. Analysis of self-report data from 802 PsoProtect*Me* participants (data extracted 9 August 2021) indicated that 8.3% (n=63) participants were vaccine hesitant [27], consistent with other published data [26]. These individuals were younger, more likely to be of non-white ethnicity and live outside the UK, compared to those who were not hesitant. They were also less likely to be taking immune-modifying therapy. The most common reasons for vaccine hesitancy were concerns regarding vaccine side-effects, the vaccine being new and psoriasis worsening post vaccination.

6. Medication on-adherence

Prior to the pandemic, an association between mental health conditions and medication non-adherence was found in people with psoriasis [28]. The negative impact of the pandemic on the mental health of people with psoriasis [20] lead to concerns regarding medication adherence in this group. The PsoProtect*Me* data resource was leveraged to explore this, including the extent of and reasons underlying non-adherence. 1611 (40.5%) of 3980 PsoProtect*Me* participants were prescribed a systemic immune-modifying therapy. Of this group, 25.3% reported non-adherence during the pandemic, most commonly due to concerns about their immunity. In an unadjusted logistic regression model, a positive anxiety screen was associated with non-adherence to systemic immune-modifying therapy, however this association was not present following adjustment for potential confounders, although the direction of effect remained [29]. In an earlier assessment, non-adherence was also shown to be associated with worsening psoriasis [22]. This information highlights the need for clinicians to identify which groups are non-adherent to their treatment and therefore at risk of worsening psoriasis and a greater disease burden. Current guidelines (informed by reassuring data on immune-modifying therapy-related risks of severe COVID-19) recommend continuing immunosuppression in people without COVID-19 to maintain disease control [30]. Given the level of reported non-adherence in PsoProtect*Me* participants and the association with worsening psoriasis, close communication with patients to encourage medication adherence is important.

7. Limitation of findings

There are several limitations to these findings which are important to consider when interpreting the data. PsoProtect*Me* respondents were dominated by females of white ethnicity residing in the UK, therefore limiting the generalisability of the results. Data collection via online surveys may limit engagement from individuals who are less technology-literate or not connected to the media. Furthermore, self-report assessments may underestimate the true extent of medication non-adherence, and there may be ascertainment bias since those more concerned about COVID-19 risk may be more likely to participate. Data collection was also limited to people with psoriasis, so direct comparisons with the general population cannot be performed.

8. Communication of PsoProtect*Me* findings to the psoriasis community

The dissemination of the findings from the PsoProtect*Me* project was global and consistent. Multiple avenues of information transmission were utilised, including via partner organisations, social media and publications. Information was delivered in a variation of formats including infographics, lay summaries, newsletters and presentations. The content and presentation of the findings were optimised by PsoProtect's partner organisations. Results were presented at the IFPA World Conference 2021, Psoriasis Association Conferences 2021 & 2022, International Psoriasis Council events, Skin Inflammation and Psoriasis International Network (SPIN) congress 2022 and at Patient and Public Involvement (PPI) webinars (delivered by St John's DermAcademy in 2020 and 2021). The PsoProtect*Me* (and PsoProtect) website provided open access to 'current data' detailing the total number of participants and summary data in simple infographics. The websites also linked to lay summaries of the associated publications.

9. A summary of the findings

PsoProtect*Me* allowed for an international cross-sectional assessment of the impact of the COVID-19 pandemic in people with psoriasis. It found that worsening psoriasis was common in the pandemic and associated with a positive mental health screen, shielding behaviour, obesity and female sex. The results highlighted that stringent risk-mitigating behaviour, or shielding, during the pandemic was associated with the use of targeted biologic therapies compared with standard non-biologic systemic therapies or no treatment. Shielding was also associated with established risk factors for severe COVID-19 (male sex, obesity, and comorbidity burden) and a positive anxiety or depression screen. A quarter of patients on systemic immune-modifying therapy reported medication non-adherence, citing concerns about their immunity as the main reason for stopping treatment. Finally, PsoProtect*Me* data indicated low vaccine hesitancy amongst people with psoriasis.

10. What's next

The use of patient-facing registries such as PsoProtect*Me* allow for a novel and exciting means to further understanding of inflammatory skin diseases. PsoProtect*Me* has catalysed the creation of a novel patient self-report platform that aims to understand inflammatory skin disease onset, progression and treatment outcomes over time and to facilitate tools to improve disease outcomes. Co-designed using multi-stakeholder input, it will collect information about current treatments, physical health, mental wellbeing and everyday behaviours such as diet and physical activity. It also aligns with the Biomarkers and Stratification To Optimise outcomes in Psoriasis (BSTOP) UK observational study and population studies including Our Future Health [31]. Following participant eConsent, self-report data will be linked to healthcare records and existing research, thus enriching the data.

11. Conclusion

PsoProtect*Me* (and PsoProtect) provided valuable insight into the health impacts, behaviour changes and experiences of people with psoriasis during the COVID-19 pandemic, a unique period of unknowns and uncertainty. The findings informed clinical guidelines in psoriasis, including the National Psoriasis Foundation COVID-19 guidance and International Psoriasis Council COVID-19 statement [30,32]. It underscored the huge potential offered by online data collection from an engaged and motivated global patient community, enabling an accelerated translation of research to patient benefit. The regular, wide dissemination of results supported by partner organizations sustained patient community engagement and recruitment. This adaptive, time/resource efficient means of data collection, analysis and dissemination may enable future research efforts to rapidly address unmet health needs.

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