Psoriasis: Targets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Risk Factors for Psoriasis Flares: A Narrative Review

Luca Potestio, Giuseppe Lauletta, Nello Tommasino, Antonio Portarapillo, Antonia Salsano, Teresa Battista, Fabrizio Martora, Matteo Megna

Section of Dermatology - Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

Correspondence: Luca Potestio, Section of Dermatology - Department of Clinical Medicine and Surgery, University of Naples Federico II, Via Pansini 5, Naples, 80131, Italy, Tel +39 - 081 – 7462457, Fax +39 - 081 - 7462442, Email potestioluca@gmail.com

Abstract: Psoriasis is a chronic inflammatory cutaneous disease with multifactorial pathogenesis involving both genetic and environmental factors as well as the innate and acquired immune response. Several triggering factors may exacerbate or worsen the disease. In this context, we performed a review manuscript with the aim of investigating current literature on psoriasis risk factors, also showing possible mechanisms by which they act on psoriasis. Globally, risk factors can be divided in classic risk factors (eg, mechanical stress, infections and dysbiosis of the skin, common drugs, environment and pollution, lifestyle, psychological stress, hormonal and metabolic alterations) which have long been known to be responsible for worsening and/or reoccurrence of psoriatic manifestations, and emerging risk factors (eg, biological drugs, immunotherapy for oncologic disease, Covid-19, and vaccines) defined as those newly identified risk factors. Accurate patient information and monitoring of risk factors as well as planned follow-ups may help to prevent and treat the worsening of psoriasis and consequently improve the quality of life of psoriatic patients.

Keywords: psoriasis, flare, risk factors, pathogenesis

Introduction

Psoriasis is a chronic inflammatory cutaneous disease affecting up to 3% of the worldwide population.[1] Clinically, psoriasis vulgaris is the commonest phenotype affecting 85–90% of psoriasis patients and characterised by sharply demarcated erythematous plaques, usually involving the extensor surface of elbows and knees, lower back, scalp and umbilical areas, but any skin surface can be involved.[2] Psoriasis prevalence varies in different countries around the world and is affected by ethnicity, genetic background and environmental factors.[3]

Several diseases can be associated with psoriasis, making this condition a systemic disorder. Indeed, it is estimated that 20–30% of psoriasis patients will develop psoriatic arthritis (PsA),[4] as well as several studies have reported association between psoriasis, PsA and Inflammatory bowel disease (IBD).[5] Similarly, psoriasis patients also have an increased risk of developing metabolic syndrome (MetS),[6] and type 2 diabetes.[7]

Psoriasis has multifactorial pathogenesis involving both genetic and environmental factors as well as the innate and acquired immune response.

Globally, the interleukin (IL)-23/17 signalling pathway stands out as the primary pathogenic mechanism.[3] Environmental triggers or breakdowns in self-tolerance, possibly through autoantibodies, stimulate plasmacytoid dendritic cells (DCs) to secrete tumor necrosis factor-alpha (TNF-α) and interferon-alpha (IFN-α).[3] These inflammatory cytokines then activate myeloid DCs to release IL-23 and IL-12.[3] IL-23 fosters the proliferation of T helper (Th) 17 and Th22 cells, amplifying the production of IL-17 and IL-22, respectively.[3] Meanwhile, IL-12 prompts the differentiation of Th1 cells, which produce IFN-γ and TNF-α, further fueling the inflammatory cascade.[3]

In regard to genetic factors which may affect psoriasis development and severity, several genetic markers and susceptibility loci have been identified.[3] Among these, HLA-Cw6, which is part of the major histocompatibility complex (MHC) on chromosome 6, is the major genetic risk factors reported.[3] Indeed, variants of the human leukocyte antigen-C (HLA-C) gene, particularly the HLA-Cw6 allele, have been strongly associated with psoriasis susceptibility.[3] Moreover, the PSORS1 locus on chromosome 6p21.3 is the major genetic determinant of psoriasis susceptibility outside of the HLA

Received: 2 March 2024
Accepted: 25 May 2024
Published: 30 May 2024

region.[3] Other genetic markers and susceptibility loci include variants of IL-23R, variants of IL12B, variants in the TNFAIP3-interacting protein 1 (TNIP1) gene, variants in the late cornified envelope (LCE) gene cluster, variants in the caspase recruitment domain family member 14 (CARD14) gene, etc.[3]

Psoriasis flare refers to a sudden worsening or exacerbation of psoriasis symptoms.[8] In this scenario, several triggering factors may exacerbate or worsen the disease.[8] The knowledge on this risk factors is important to control psoriasis. Therefore, we performed a review manuscript with the aim of investigating current literature on psoriasis risk factors, also showing possible mechanisms by which they act on psoriasis.

Materials and Methods

The current narrative review was conducted using the PubMed, Google Scholar, Cochrane Skin, MEDBASE and Embase databases until February 2024. The search was performed by combining the terms 'psoriasis' AND 'flares' AND "triggers" AND/OR "exacerbation" and involved all fields, including title, keywords, abstract and full text. Real-life studies, reviews, meta-analyses, case series, case reports and letters to the editor on factors contributing to flare-ups of psoriatic manifestations were chosen to be investigated. Non-English literature was excluded. The review is based on previously published articles and does not include studies with human or animal participants performed by any of the authors.

Results

Risk factors that can trigger or exacerbate psoriasis are classically divided into extrinsic and intrinsic.[3] The former include external mechanical stress, infections, medications, lifestyle, environment and pollution; the intrinsic include psychological stress, hormonal and metabolic alterations, and dysbiosis of the skin and intestinal microbiota.[9] However, another possible classification is between classic and emerging risk factors for psoriasis flare-ups. Classic risk factors have long been known to be responsible for worsening and/or reoccurrence of psoriatic manifestations; emerging risk factors are defined as those newly identified risk factors being represented by newly developed drugs and vaccines or newly identified infectious agents.

Classic Risk Factors for Psoriasis Flares

Classic risk factors for psoriasis flares are summarized in Table 1.

Mechanical Stress

In patients with psoriasis, various types of traumas to sites not involved in psoriatic lesions can cause them to appear. This phenomenon is called reactive isomorphism or Koebner's phenomenon, which is characteristic but not specific or even constant in psoriasis. The underlying mechanism is not fully elucidated, but undoubtedly, as a result of the trauma, there is an increased production of cathelicidin LL-37, an antimicrobial peptide that increases in response to damage and forms complexes with genetic material from the damaged cells themselves, which in turn stimulate plasmacytoid dendritic cells to secrete type 1 interferons (IFN), such as IFN-α and IFN-β.[9] These are crucial for the proliferation of basal keratinocytes and in increasing Nerve Growth Factor (NGF) with consequent angiogenesis and activation of memory T-cells resident in the affected tissue, which is followed by the development of the psoriatic lesion.[10] A characteristic example that can induce this phenomenon is tattooing. It is not uncommon for a patient with psoriasis to ask their dermatologist if they can undergo this practice, in which case the patient should be reminded that they are exposing themselves to a potential risk of inducing new lesions at the site of the tattoo.[11] Not only trauma can induce this phenomenon but also other factors such as radiotherapy,[12] the use of masks,[13] injections,[14] ultraviolet (UV) radiation. For the latter, it should be mentioned that UV radiation is often used as a therapeutic weapon against psoriasis through phototherapy, particularly nb-UVB. There is, however, a minority of psoriatic patients who manifest a pronounced photosensitivity, with the disease rebounding or worsening during the summer months, mainly affecting photo-exposed sites, such as the face, neckline, back of the hands and scalp in bald subjects.[15]

Table 1 Classic Risk Factors for Psoriasis Development

Classic Risk Factors	Definition	Mechanism of Action
Mechanical stress	Various types of trauma to sites not involved in psoriatic lesions can cause them to appear. This phenomenon is called reactive isomorphism or Koebner's phenomenon	Increased production of cathelicidin LL-37, an antimicrobial peptide that increases in response to damage and forms complexes with genetic material from the damaged cells themselves, which in turn stimulate plasmacytoid dendritic cells to secrete type I interferons (IFN)
Infection and dysbiosis	*S. Pyogenes*, *S. Aureus*, *Candida* spp, *Malassezia* spp, EBV, VZV, CMV, HIV.	Hyperactivation of the immune system
Environment and pollution	C_6H_6, CO, PM10, PM2.5, cadmium	Oxidative stress with formation of ROS which damage cellular structures and hyperactivate the immune system
Lifestyle	Smoking, alcohol, obesity	Increase in inflammatory cytokines and innate immunity
Common drugs	Lithium, beta-blockers, synthetic antimalarial drugs, antibiotics (especially tetracyclines), ACE inhibitors, and interferons	Drug-induced decrease of intracellular cAMP levels, resulting in increased cell proliferation and lack of differentiation
Psychological stress	State of worry or mental tension caused by a difficult situation	Disturbance of the hypothalamic-pituitary-adrenal axis with reduced cortisol response to stress that has been observed in patients with psoriasis, with generally lower cortisol levels compared to higher levels of adrenaline and adrenocorticotropic hormone
Hormonal and metabolic alterations	Reduction in blood levels of estrogen and progesterone, increase in FFAs	Increase in inflammatory cytokines and innate immunity

Infections and Dysbiosis of the Skin

S. pyogenes infection is associated with the onset of guttate psoriasis, especially in adolescents or young adults. Sore throat and serum evidence of *S. pyogenes* infection are present in about two-thirds of patients with guttate psoriasis.[16] The underlying mechanism is believed to be based on bacterial superantigens that stimulate the proliferation of T cells, without prior intracellular processing by an antigen-presenting cell.[16] Another theory concerns the peptidoglycan of the bacterium's cell wall, fragments of which are transported from macrophages or dendritic cells in the tonsils to T cells resident in the skin, resulting in a pro-inflammatory response from them.[16] Dysregulation of the skin microbiota is another factor related to psoriasis, as evidenced by the presence of *S. Aureus* in the psoriatic lesions of 60% of the affected population, compared with 5–30% of the population with healthy skin.[9] The increased presence of this bacterium is associated with a reduction in *S. epidermidis* and *Propionibacterium* acnes, compared to healthy patients.[9] Furthermore, in patients with psoriasis, a higher presence of Firmicutes was observed in the skin lesions than Actinobacteria, which was higher in the skin of healthy subjects.[9] Although the significance of these alterations in the microbiota is unknown, it is believed that leads to an increase in skin T-cells conducted by IL-17 and IL-22, a hypothesis similar to that of the role of the intestinal microbiota in Crohn's disease.[17] Regarding mycoses, the literature indicates a higher OR of colonisation by Candida in patients with psoriasis compared to controls;[18] in addition, a meta-analysis observed that in patients with psoriasis, Candida colonization of the oral mucosa is greater than in controls.[19] Finally, a possible association between psoriasis and colonisation by Malassezia spp. has been proposed, especially on the scalp, as this yeast is able to upregulate the expression of keratinocytes. In fact, it has been shown that there is a positive correlation between the amount of Malassezia in the lesions and the severity of psoriasis.[16] Another well-known association is that between psoriasis and HIV infection, which may result in the onset of the disease de novo or its exacerbation. It should be remembered that this is a paradoxical phenomenon since psoriasis is a T-cell-mediated disease, whereas HIV infection is characterized by the decrease of TCD4+ cells, so the mechanisms involved in this association are unclear. Probably, the neuropeptide substance P that is released by immune cells infected with this virus is responsible for the stimulation of keratinocytes and the inflammatory response underlying psoriatic lesions.[9] Among

viruses, a 2020 study of 66,274 human papillomavirus (HPV) patients showed an increased prevalence of psoriasis among infected patients compared to healthy ones.[20] Other viruses are involved with the exacerbation of psoriasis, such as Epstein-Barr virus, Varicella zoster virus and Cytomegalovirus.[9] Regarding SARS-CoV-2, given its recent time of emergence, please refer to the section on emerging risk factors.

Common Drugs

Drugs may induce the appearance of psoriasis in genetically predisposed individuals or those without a family history of psoriasis, in other cases they may lead to the appearance of psoriatic lesions on previously healthy skin in psoriatic patients, or they may cause a re-exacerbation of existing psoriatic lesions. Drug-induced psoriasis flare-ups can be caused by numerous classes of drugs, both drugs taken occasionally for acute conditions and drugs taken for chronic co-morbidities of the patient. Drugs with a closer causal relationship to psoriasis flare-ups include lithium, beta-blockers, synthetic antimalarial drugs, antibiotics (especially tetracyclines), ACE inhibitors, and interferons.[21] Lithium salts are indicated for the treatment of bipolar disorder and other psychiatric disorders. Psoriasis is the most frequent skin side effect caused by lithium therapy.[22] The mechanism by which lithium is able to induce psoriasis flare-ups is not fully known but would appear to be attributable to reducing intracellular cAMP levels and blocking cell differentiation.[23] Beta-blockers are usually administered for hypertension, ischemic heart disease, arrhythmias and heart failure and are among the drugs most often responsible for psoriasis flare-ups. Beta-adrenergic receptors are present in the skin and their blockade leads to decreased intracellular cAMP levels, resulting in increased cell proliferation and lack of differentiation, as observed in psoriasis.[24] Synthetic antimalarial drugs (chloroquine, hydroxychloroquine) are frequently reported as causative agents of psoriasis flare-ups. The mechanism by which synthetic antimalarials induce a flare-up of psoriasis would appear to be related to altering the activity of enzymes involved in epidermal cell proliferation, such as transglutaminase.[25] The role of antibiotics in the course of psoriasis is controversial. Although in the literature some authors report a beneficial effect on psoriasis by antibiotics such as rifampicin, penicillin and erythromycin,[26,27] psoriasis flare-ups have often been reported in patients treated with tetracyclines.[26] Tetracyclines probably cause psoriasis flare-ups by reducing intracellular cAMP levels.[28] A significant correlation between ACE inhibitor therapy and psoriasis flare-ups has been demonstrated. The mechanism is not entirely clear and appears to be a correlation between ACE gene polymorphism and the risk of psoriasis.[29] Finally, there are case reports in the literature of psoriasis flare-ups following therapy with recombinant IFN-a2b and IFN-gamma for hepatitis C.[30,31]

Environment and Pollution

Air pollution is due to the modification of its natural conditions by biological, chemical or physical agents. The main pollutants are benzene (C_6H_6), carbon monoxide (CO), fine particulate matter with diameter <2.5 μm (PM2.5) and coarse PM with diameter 2.5–10.0 μm (PM10).[32] Several studies establish the negative influence of environmental pollution on the skin. This is due to oxidative stress caused by the molecules mentioned above, which leads to the formation of ROS and free radicals that damage cellular structures and stimulate the release of inflammation mediators. Acne and atopic dermatitis are two examples of skin conditions worsened by air pollution.[9] Regarding psoriasis, studies are also available in the literature asserting the negative influence of environmental pollutants on this disease. In a cohort of 369 patients with psoriasis flares, it was observed that the concentration of pollutants in the 60 days prior to the flare was significantly higher than in controls, with an odds ratio (OR) of 1.55 and 1.25 for mean PM10 exposure over 20 μg/m3 and mean PM2.5 over 15 μg/m3, respectively.[32] Liaw et al studied the effects of exposure to cadmium, another environmental pollutant that can influence immune system activity and increase markers of inflammation. The study included 5297 participants, 2.5% of whom had psoriasis, and their blood levels of cadmium were assessed. Patients with psoriasis not only had higher cadmium levels than controls (0.67 vs 0.52 μg/L), but these also correlated positively with disease severity and predisposed to its worsening.[33]

Lifestyle

Cigarette smoking is an independent risk factor for psoriasis. An analysis of 2410 patients with psoriasis compared those who had never smoked, former smokers and current smokers. A relative risk of 1.39 was established for former smokers

compared to never smokers and 1.94 when compared to current smokers.[34] In addition, a direct proportionality was determined between the risk of psoriasis and the number of cigarette packs consumed per year and/or the duration of exposure to smoking.[34] Concerning alcohol consumption, we know that psoriasis, especially in its severe forms, is related to psychophysical stress and psychiatric pathologies, which in turn are often associated with alcoholism. In addition to this, it has been shown how alcohol worsens this disease, increasing inflammation through direct action on keratinocytes through the formation of reactive oxygen species (ROS) and on the cells of the immune system, with increased production of pro-inflammatory cytokines such as TNF.[35] It should not be forgotten that alcohol reduces patient compliance and adherence to therapies and doctor's recommendations, as well as interacting with psoriasis drugs, reducing their efficacy and increasing their toxicity.[35] Diet also influences the risk of developing psoriasis, as obesity, metabolic syndrome, diabetes mellitus and dyslipidemia are comorbidities that can induce the onset of the disease and/or its exacerbation. In particular, several studies have shown that weight gain is an important risk factor for psoriasis and that the affected patient population has a higher average Body Mass Index (BMI) than the general population.[36] In addition, higher BMI is associated with greater severity of skin manifestations and less response to systemic therapies.[37] Supporting this close association is probably the over-expression of cytokines in both conditions. Adipose tissue, increased in overweight conditions, is in fact a tissue secreting pro-inflammatory cytokines, also shared by psoriasis, such as TNFα and IL-6.[36] Adipokines such as resistin and leptin are also increased in both overweight and psoriasis patients.[38]

Psychological Stress

Although it is described that 26–88% of patients believe that their psoriasis is a consequence of stress and that 54% remember stressful events associated with the onset of skin manifestations, there is insufficient evidence to establish that psychological stress is associated with the onset and exacerbation of the disease in an unequivocal manner.[3,39] A systematic review evaluated six studies with 4744 patients with psoriasis and 10,817 controls and of these only in one study no differences were observed between the rates of stress disorders preceding the onset of psoriasis, while in the other five, a pooled OR of 3.4 was established.[40] Thus, these events may contribute to the worsening and onset of the disease, with a probable association both in terms of time and severity of manifestations. For example, Evers et al observed that in people with high levels of stress, exacerbations of psoriasis were more frequent. In addition, an RR of 4.92 was calculated for psoriasis flares compared to controls among those who were exposed to stressful events.[39] Although the exact mechanism is not known, it is believed that a disturbance of the hypothalamic–pituitary–adrenal axis underlies it. A reduced cortisol response to stress has been observed in patients with psoriasis, with generally lower cortisol levels compared to higher levels of adrenaline and adrenocorticotropic hormone. These alterations result in an increase in pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 and interferon α (IFN-α), which we know are at the root of psoriatic manifestations.[41] Further evidence in favour of the association between psychological stress and psoriasis is the observation of the favourable effect on disease progression of regular physical activity. Balato et al observed that in a group of 416 athletes, psoriasis was less frequent than among the 489 controls with 1.7% vs 5.4%, respectively, despite the presence of familial psoriasis in 9.6% of both groups. A group of 400 psoriasis patients was also analysed, and it was observed that among these only 11% practised sport regularly, compared to 21% of the controls. Furthermore, 35 of the 44 psoriasis patients who practised sport reported that this activity had a positive influence on their disease.[42]

Hormonal and Metabolic Alterations

Some dermatological pathologies are influenced by the hormonal alterations underlying the menstrual cycle and are called catamenial dermatoses. For example, acne is worsened by the peak of androgens that is observed during menstruation and that stimulate their receptors in the skin by going to stimulate sebum production.[43] Although there are fewer studies to support this, psoriasis is also influenced by female sex hormones. In fact, it has been shown that psoriasis tends to worsen during the menstrual cycle, while its manifestations may even disappear during pregnancy.[43] Murase et al in a case–control study of 47 pregnant and 27 non-pregnant patients with psoriasis observed that a higher oestrogen/progesterone ratio correlated negatively with the BSA of the skin condition, suggesting a beneficial effect of oestrogen on psoriasis.[44] A 2022 paper by Adachi and Honda clarified the immune regulatory role of oestrogens, showing that they inhibit the production of IL-23 by dendritic cells and, although there is less evidence for this, their

levels correlate negatively with those of IL-1 and TNF. In addition, it appears that oestrogens also have an inhibitory effect on keratinocyte activity.[45] Of interest, a recent-review on pregnancy-related psoriasis showed that in more than 40% of cases psoriasis improved during pregnancy, whereas a worsening of the disease has been reported in almost 20% of cases, as well as 21% to 56% of patients remaining stable.[46] Finally, more than half of cases worsened in the postpartum period.[46]

Numerous studies have established the close relationship between psoriasis and comorbidities such as metabolic syndrome or obesity. These diseases are characterised by major metabolic alterations, with changes in lipid and glucose homeostasis. To what extent can these alterations be associated with psoriasis flares? Herbert et al fed a group of mice with saturated fatty acids (SFAs) for 20–25 weeks to an obese phenotype and compared them to a control group of mice fed a low-fat diet. In both groups, psoriasiform lesions were induced with a topical administration of imiquimod and it was observed that in the group of mice on the high SFAs diet, the skin pathology was more severe and at the molecular level there were significantly more inflammation mediators and myeloid cell infiltrate. Furthermore, this protocol was repeated but for only five weeks to induce only the serum increase in free fatty acids without inducing obesity. The results were essentially confirmed, suggesting that increased blood FFAs can induce psoriasis flares by promoting the inflammatory changes characteristic of psoriasis, regardless of the presence of obesity.[47]

Emerging Risk Factors for Psoriasis Flares

Emerging risk factors are defined as those newly identified risk factors being represented by newly developed drugs and vaccines or newly identified infectious agents. Emerging risk factors for psoriasis flares are summarized in Table 2.

Biological Drugs: Paradoxical Psoriasis

Since the 2000s, a better understanding of the pathogenetic mechanisms responsible for psoriasis has enabled the development and marketing of several biological therapies based on monoclonal antibodies directed against key cytokines in the formation and maintenance of psoriatic plaque. It has been shown that 2–5% of patients with moderate-to-severe psoriasis treated with biological drugs experience exacerbation of pre-existing psoriatic lesions during the treatment.[48] Therefore, this immune-mediated side effect induced by biological therapy is called paradoxical psoriasis (PP). Given the central role played by TNF- α in the pathogenesis of psoriasis, TNF- α inhibitors were the first class of biological drugs approved for the treatment of plaque psoriasis. The first case of PP induced by anti-TNF-α treatment was described in a patient affected by inflammatory bowel diseases (IBD) in 2004,[49] and since then, with the ever-increasing use of anti-TNF-α for the treatment of numerous diseases, numerous other cases have been reported.[50–53] It is reported in the literature that 2–5% of patients treated with TNF-alpha inhibitors develop PP, with a slight predilection for women

Table 2 Emerging Risk Factors for Psoriasis Development

Emerging Risk Factors	Definition	Mechanism of Action
Biological drugs: Paradoxical Psoriasis	Paradoxical psoriasis is a drug side effect that results in the development of psoriasis during biological therapy for different diseases	The selective inhibition of specific cytokines may inadvertently disrupt the immune balance, leading to the onset or worsening of psoriasis.
Immunotherapy for oncologic disease	Anti CTLA4 (Ipilimumab) Anti PD-1 (Nivolumab, Pembrolizumab, Cemiplimab) Anti PD-L1 (Atezolizumab, Durvalumab, Avelumab) Sorafenib, Imatinib	Overactivation of Th1, Th17, and Th22 lymphocytes secondary to inactivation of the PD1 pathway (ICIs) Alteration of the balance between the regulatory and the effector function normally carried out by T cells (Sorafenib, Imatinib)
Covid-19	SARS-CoV-2 infection	Binding of SARS-CoV-2 to ACE2 receptors present in cutaneous blood vessels, epithelial cells of eccrine glands and the basal layer of hair follicles
Vaccines	Influenza vaccine, Pneumococcal vaccine, Td vaccine, yellow fever vaccine, COVID-19 vaccine	Induction of immune response leading to an inflammatory state and activation of the immune system

and individuals in their fourth to fifth decades.[54,55] The onset time of PP from the start of treatment with anti-TNF-α can vary from one month[56] to three years,[57] with an average time of about 11 months.[58] Although TNF-alpha inhibitors are the biological drugs most frequently responsible for PP, cases have also been reported for IL-17/17R (Secukinumab, Ixekizumab, Brodalumab), IL-12/23 (Ustekinumab), and IL-23 inhibitors (Risankizumab, Guselkumab).[59] The etiology of paradoxical psoriasis is not fully understood. Unlike classic idiopathic psoriasis, paradoxical psoriasis appears to be mediated by the overexpression of plasmacytoid dendritic cells (pDCs)-derived IFN-α without T-cell induction.[60] Several studies have shown that patients suffering from autoimmune diseases and treated with anti-TNF-alpha presented an increase in IFN-α levels after treatment.[61,62] According to this, in PP the inhibition of TNF-α results in the dysmaturity of DCs and sustained production of IFN-α leading to a persistent type 1 IFN-mediated inflammation without the developing of a T-cell-mediated autoimmune process like in classic idiopathic psoriasis.[60] The pathogenetic mechanisms responsible for PP in patients treated with biological drugs of a different class than TNF-alpha inhibitors are less well understood. It is hypothesized that the selective inhibition of specific cytokines may inadvertently disrupt the immune balance, leading to the onset or worsening of psoriasis. Furthermore, recent insights from pharmacogenetic studies suggest a crucial role of single-nucleotide polymorphisms (SNPs) that can predispose to adverse events. For instance, genetic variants of the IL-23R have been associated with paradoxical psoriasiform reactions in patients treated with anti-TNF agents.[63] In conclusion, PP seems to be a multifactorial condition and several studies suggest that additional risk factors are active smoking, psychological stressors, and a family history of psoriasis. The clinical presentation of PP can be variable, although clinical manifestations tend to be similar to classic idiopathic psoriasis. The most frequent clinical types are plaque, pustular, guttate, palmoplantar and inverse psoriasis.[18] Scalp involvement is also frequent, while nail involvement is described less frequently than in idiopathic psoriasis and may present with pitting, onycholysis and discoloration.[64] PP management is still challenging. A personalized approach is always desirable, taking into account the severity of paradoxical psoriasis, the patient's general health status and the effectiveness of the biologic drug in treating the primary disease. Skin-directed therapy is a reasonable initial strategy except in severe cases.[54]

Immunotherapy for Oncologic Disease

The increasing availability of antineoplastic drugs allows nowadays a targeted therapy in the neoplastic patient. However, modern antineoplastic drugs often exhibit skin toxicity. Among them, immune checkpoint inhibitors (ICIs) are often responsible for immune-related cutaneous adverse events that can also manifest themselves with the appearance of de novo psoriasis or with the reactivation of a pre-existing psoriasis.[65] ICIs commonly include Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) inhibitors (Ipilimumab), programmed cell death 1 (PD-1) inhibitors (Nivolumab, Pembrolizumab, and Cemiplimab), and programmed cell death ligand 1 (PD-L1) inhibitors (Atezolizumab, Durvalumab and Avelumab). ICIs have been utilized successfully in patients with metastatic melanoma, renal cell carcinoma, head and neck cancers and non-small lung cancer.[66] Several cases of psoriasis flare-ups in neoplastic patients treated with ICIs are reported in the literature.[67–77] The mechanism by which ICIs would be responsible for this adverse event appears to be attributable to an overactivation of Th1, Th17, and Th22 lymphocytes secondary to the inactivation of the PD1 pathway.[78] It should be underlined that psoriasis flares were manageable with standard psoriasis treatments and few required ICI discontinuation.[79]

Small molecules, like imatinib and sorafenib, are also reported among the drugs that can cause psoriasis flare-ups.[80,81] Although there are fewer reports in the literature for imatinib and sorafenib than for ICIs, these drugs can block signaling pathways in regulatory T cells, thus altering the balance between the regulatory and the effector function normally carried out by T cells, favoring the onset and/or reactivation of psoriasis.[82]

Covid-19

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has had a profound impact on global health and daily clinical practice.[83,84] COVID-19 is a highly contagious respiratory tract infection caused by SARS-CoV-2. SARS-CoV-2 infection, in addition to being able to cause severe bilateral pneumonia with a poor prognosis in the weaker sections of the population, can also be associated with manifestations of dermatological interest.[85] The incidence of cutaneous manifestations secondary to the SARS-CoV-2 infection is between 4% and 20.4%.[86] The dermatological manifestations associated with COVID-19 most frequently described in the literature include maculopapular eruptions,

urticarial eruptions, vesicular eruptions, chilblain-like lesions and livedo or necrosis.[87] COVID-19 can also lead to flare-ups of chronic inflammatory skin diseases such as atopic dermatitis and psoriasis.[88,89] Indeed, COVID-19 infection can trigger a systemic inflammatory state that can alter the delicate cytokine balance and lead to a flare-up of pre-existing psoriasis. Wang et al showed that psoriasis and SARS-CoV-2 infection negatively influence each other. In the analysed population (3581 patients), the rate of COVID-19 infection was significantly higher in psoriatic patients than in those without psoriasis (89.59% vs 77.93%, $p < 0.0001$), and the rate of relapse and/or worsening of psoriasis was also higher in psoriatic patients with SARS-CoV-2 infection than in those without (75.29% vs 47.75%, $p < 0.0001$).[90] Aram et al found that flares of psoriasis were common after COVID infection, but many cases were attributed to the use of anti-malarial drugs or discontinuation of psoriasis therapy after SARS-CoV-2 infection.[91] COVID-19-induced psoriasis flare-ups would appear to be related to the binding of SARS-CoV-2 to angiotensin-converting enzyme-2 (ACE2) receptors present in cutaneous blood vessels, epithelial cells of eccrine glands and the basal layer of hair follicles.[92] Furthermore, psoriasis was also associated with higher levels of ACE2 than the general population, and this could explain the association between psoriasis and COVID-19 infection.[93]

Vaccines

Vaccination is an uncommon trigger for psoriasis flares. Before the COVID-19 pandemic, cases of psoriasis flare-ups were reported following vaccination for influenza, pneumococcal pneumonia, tetanus and diphtheria, and yellow fever.[94–96]

Due to the high transmissibility of SARS-CoV-2 preventive measures like wearing masks, physical distancing was necessary, and in this context, COVID-19 vaccination was the main measure to overcome the pandemic.[97] The European Medicines Agency (EMA) approved four vaccines based on two different mechanism of action: mRNA vaccines (Pfizer/BioNTech; BNT162b2 and Moderna; mRNA-1273) and viral vector-based vaccines (AstraZeneca; AZD1222 and Johnson & Johnson; Ad26.COV2.S).[98] Several cutaneous adverse reactions have been described in patients receiving COVID-19 vaccination, and in particular cases of psoriasis occurring de novo or psoriasis flare-ups have been reported.[99,100] Relapses of psoriasis have been described for all available vaccines, although most cases occurred after vaccination with the mRNABNT162b2 vaccine, followed by AZD1222 and mRNA-1273.[101] In addition, worsening of psoriasis was described after any dose of vaccine,[101] and no difference was shown between patients receiving homologous vaccination and those receiving heterologous vaccination.[102] In most cases, patients developed a flare of plaque psoriasis, followed by guttate and pustular psoriasis, but cases of flares presenting with erythrodermic psoriasis or even with palmoplantar and nail involvement were also described.[101] The mechanism responsible for the exacerbation of psoriasis in patients receiving COVID-19 vaccination is not fully understood. It is well known that vaccines induce an immune response that results in an inflammatory state and activation of the immune system.[103] Stimulation of the immune system by the vaccination can involve plasmacytoid and dermal myeloid dendritic cells which may be a trigger for the psoriasis cascade. Furthermore, vaccinations can also activate the production of IL6, which may be a trigger for Th17 cells to produce IL22, which itself stimulates keratinocyte proliferation.[103] Finally, all of the cases have been successfully treated with topical or systemic medications, including biologics,[101] and considering the overall benefit–risk profile of COVID-19 vaccination, there is no reason to discourage psoriatic patients to attend vaccination.

Discussion

Psoriasis is nowadays recognized as a systemic inflammatory disease with a complex pathogenesis.[104] Psoriasis occurs as the interaction of intrinsic genetic factors and environmental endogenous and exogenous risk factors which act as triggers for the clinical manifestations of psoriasis.[3]

The aim of our manuscript was to review current literature on psoriasis risk factors, also investigating possible mechanisms by which they act on psoriasis. Globally, risk factors may be divided into classic risk factors, which have long been known to be responsible for worsening and/or reoccurrence of psoriatic manifestations, and emerging risk factors, defined as those newly identified risk factors.

Classical risk factors include mechanical stress, infections and dysbiosis of the skin, common drugs (lithium, beta-blockers, synthetic antimalarial drugs, antibiotics, ACE inhibitors, and interferons), environment and pollution, lifestyle, psychological stress, hormonal and metabolic alterations.

On the contrary, emerging risk factors comprise biological drugs (paradoxical psoriasis), immunotherapy for oncologic disease, Covid-19, and vaccines.

Prevention of psoriasis onset or its worsening is one of the most difficult challenges for dermatologists. As reported before, there are several risk factors that can act as triggers for psoriatic flare-ups. The elimination of the triggering factors is important for controlling the disease. A correct lifestyle, deletion of bad habits such as smoking, alcohol and high-calorie diets as well as some practices such as tattooing and piercing are often required to avoid flare-ups. In addition, psoriasis is also linked to air pollution. Stricter regulations of pollution could reduce its role in the pathogenesis of psoriatic disease. Moreover, the exacerbation of psoriasis induced by drugs can be avoided by clinicians' knowledge. However, several factors interact with each other and may directly and/or indirectly affect psoriasis course. Certainly, further studies will allow to establish possible preventive options in order to provide patients personalized treatment strategies and personalized care plans.

To sum up, accurate patient information and monitoring of risk factors as well as planned follow-ups may help to prevent and treat the worsening of psoriasis and consequently improve the quality of life of psoriatic patients.

Data Sharing Statement

Data are reported in the current study.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Kanda N. Psoriasis: pathogenesis, comorbidities, and therapy updated. *Int J Mol Sci*. 2021;22(6):2979. doi:10.3390/ijms22062979
2. Yan BX, Chen XY, Ye LR, Chen JQ, Zheng M, Man XY. Cutaneous and systemic psoriasis: classifications and classification for the distinction. *Front Med*. 2021;8:649408. doi:10.3389/fmed.2021.649408
3. Kamiya K, Kishimoto M, Sugai J, Komine M, Ohtsuki M. Risk factors for the development of psoriasis. *Int J Mol Sci*. 2019;20(18):4347. doi:10.3390/ijms20184347
4. Ocampo DV, Gladman D. Psoriatic arthritis. *F1000Research*. 2019;8:1665. doi:10.12688/f1000research.19144.1
5. Zohar A, Cohen AD, Bitterman H, et al. Gastrointestinal comorbidities in patients with psoriatic arthritis. *Clin Rheumatol*. 2016;35 (11):2679–2684. doi:10.1007/s10067-016-3374-y
6. Yamazaki F. Psoriasis: comorbidities. *J Dermatol*. 2021;48(6):732–740. doi:10.1111/1346-8138.15840
7. Hao Y, Zhu YJ, Zou S, et al. Metabolic syndrome and psoriasis: mechanisms and future directions. *Front Immunol*. 2021;12:711060. doi:10.3389/fimmu.2021.711060
8. Roberts W. Air pollution and skin disorders. *Int J Women's Dermatology*. 2021;7(1):91–97. doi:10.1016/j.ijwd.2020.11.001
9. Liu S, He M, Jiang J, et al. Triggers for the onset and recurrence of psoriasis: a review and update. *Cell Commun Signal*. 2024;22(1):108. doi:10.1186/s12964-023-01381-0
10. Ahad T, Agius E. The Koebner phenomenon. *Br J Hosp Med (Lond)*. 2015;76(11):C170–2. doi:10.12968/hmed.2015.76.11.C170
11. Orzan OA, Popa LG, Vexler ES, Olaru I, Voiculescu VM, Bumbăcea RS. Tattoo-induced psoriasis. *J Med Life*. 2014;7(2):65–68.
12. Charalambous H, Bloomfield D. Psoriasis and radiotherapy: exacerbation of psoriasis following radiotherapy for carcinoma of the breast (the Koebner phenomenon). *Clin Oncol*. 2000;12(3):192–193. doi:10.1053/clon.2000.9149
13. Gulsunay IE, Erdem Y, Altunay IK. Mask-induced Koebner Phenomenon in pemphigus patients during COVID-19 pandemic. *Sisli Etfal Hastan tip Bul*. 2023;57(4):567–568. doi:10.14744/SEMB.2023.38107
14. Thijs S, Balti E, Degraeve C, Coremans P. Isomorphic (Koebner) phenomenon induced by insulin analogue injections in psoriasis. *JCEM Case Reports*. 2023;1(1):luac016. doi:10.1210/jcemcr/luac016
15. Rutter KJ, Watson REB, Cotterell LF, Brenn T, Griffiths CEM, Rhodes LE. Severely photosensitive psoriasis: a phenotypically defined patient subset. *J Invest Dermatol*. 2009;129(12):2861–2867. doi:10.1038/jid.2009.156
16. Zhou S, Yao Z. Roles of Infection in Psoriasis. *Int J Mol Sci*. 2022;23(13). doi:10.3390/ijms23136955
17. Roszkiewicz M, Dopytalska K, Szymańska E, Jakimiuk A, Walecka I. Environmental risk factors and epigenetic alternations in psoriasis. *Ann Agric Environ Med*. 2020;27(3):335–342. doi:10.26444/aaem/112107
18. Patini R, Gioco G, Rupe C, et al. Oral Candida and psoriasis: is there association? A systematic review and trial sequential analysis. *Oral Dis*. 2023;29(8):3121–3135. doi:10.1111/odi.14422
19. Pietrzak A, Grywalska E, Socha M, et al. Prevalence and possible role of candida species in patients with psoriasis: a systematic review and meta-analysis. *Mediators Inflamm*. 2018;2018:9602362. doi:10.1155/2018/9602362
20. Chen ML, Kao WM, Huang JY, Hung YM, Wei JCC. Human papillomavirus infection associated with increased risk of new-onset psoriasis: a nationwide population-based cohort study. *Int J Epidemiol*. 2020;49(3):786–797. doi:10.1093/ije/dyaa027
21. Basavaraj KH, Ashok NM, Rashmi R, Praveen TK. The role of drugs in the induction and/or exacerbation of psoriasis. *Int J Dermatol*. 2010;49 (12):1351–1361. doi:10.1111/j.1365-4632.2010.04570.x
22. Heng MC. Cutaneous manifestations of lithium toxicity. *Br J Dermatol*. 1982;106(1):107–109. doi:10.1111/j.1365-2133.1982.tb00911.x
23. Paduart O, Heenen M. Pharmacological action of lithium in the pathogenesis of psoriasis. *Eur J Dermatol*. 1995;5:425–443. 413–415.

24. O'Brien M, Koo J. The mechanism of lithium and beta-blocking agents in inducing and exacerbating psoriasis. *J Drugs Dermatol*. 2006;5(5):426–432.
25. Namazi MR. Aggravation of psoriasis by antimalarials: a comment on the pathogenic mechanism. *Indian J Dermatol Venereol Leprol*. 2008;74(6):675–676. doi:10.4103/0378-6323.45131
26. Rosenberg EW, Noah PW, Zanolli MD, Skinner RBJ, Bond MJ, Crutcher N. Use of rifampin with penicillin and erythromycin in the treatment of psoriasis. Preliminary report. *J Am Acad Dermatol*. 1986;14(5):761–764. doi:10.1016/s0190-9622(86)70090-x
27. Tsankov N, Krasteva M. Rifampin therapy in severe forms of psoriasis. *J Dermatol Treat*. 1992;3:69–71. doi:10.3109/09546639209089062
28. Counis R, Koumanov K, Raulin J, Infante R. [Antilipolytic role of tetracycline. Inhibition of adenylate cyclase in vitro]. *Eur J Biochem*. 1973;37(2):244–247. French. doi:10.1111/j.1432-1033.1973.tb02981.x
29. Tanhapour M, Falahi B, Vaisi-Raygani A, et al. Angiotensin-converting enzyme insertion/deletion (rs106180) and angiotensin type 1 receptor A (1166) C (rs106165) genotypes and psoriasis: correlation with cellular immunity, lipid profile, and oxidative stress markers. *J Cell Biochem*. 2019;120(2):2627–2633. doi:10.1002/jcb.27569
30. Kartal ED, Colak H, Ozgunes I, Usluer G. Exacerbation of psoriasis due to peginterferon alpha-2b plus ribavirin treatment of chronic active hepatitis C. *Chemotherapy*. 2005;51(2–3):167–169. doi:10.1159/000085626
31. Garcia-Lora E, Tercedor J, Massare E, López-Nevot MA, Skiljo M, Garcia-Mellado V. Interferon-induced psoriasis in a patient with chronic hepatitis C. *Dermatology*. 1993;187(4):280. doi:10.1159/000247266
32. Bellinato F, Adami G, Vaienti S, et al. Association between short-term exposure to environmental air pollution and psoriasis flare. *JAMA dermatol*. 2022;158(4):375–381. doi:10.1001/jamadermatol.2021.6019
33. Liaw FY, Chen WL, Kao TW, Chang YW, Huang CF. Exploring the link between cadmium and psoriasis in a nationally representative sample. *Sci Rep*. 2017;7(1):1723. doi:10.1038/s41598-017-01827-9
34. Li W, Han J, Choi HK, Qureshi AA. Smoking and risk of incident psoriasis among women and men in the United States: a combined analysis. *Am J Epidemiol*. 2012;175(5):402–413. doi:10.1093/aje/kwr325
35. Szentkereszty-Kovács Z, Gáspár K, Szegedi A, Kemény L, Kovács D, Törőcsik D. Alcohol in psoriasis-from bench to bedside. *Int J Mol Sci*. 2021;22(9):4987. doi:10.3390/ijms22094987
36. Musumeci ML, Nasca MR, Boscaglia S, Micali G. The role of lifestyle and nutrition in psoriasis: current status of knowledge and interventions. *Dermatol Ther*. 2022;35(9):e15685. doi:10.1111/dth.15685
37. Toussirot E, Aubin F, Dumoulin G. Relationships between Adipose Tissue and Psoriasis, with or without Arthritis. *Front Immunol*. 2014;5:368. doi:10.3389/fimmu.2014.00368
38. Kunz M, Simon JC, Saalbach A. Psoriasis: obesity and Fatty Acids. *Front Immunol*. 2019;10:1807. doi:10.3389/fimmu.2019.01807
39. Rousset L, Halioua B. Stress and psoriasis. *Int J Dermatol*. 2018;57(10):1165–1172. doi:10.1111/ijd.14032
40. Snast I, Reiter O, Atzmony L, et al. Psychological stress and psoriasis: a systematic review and meta-analysis. *Br J Dermatol*. 2018;178(5):1044–1055. doi:10.1111/bjd.16116
41. Torales J, Echeverría C, Barrios I, et al. Psychodermatological mechanisms of psoriasis. *Dermatol Ther*. 2020;33(6):e13827. doi:10.1111/dth.13827
42. Balato N, Megna M, Palmisano F, et al. Psoriasis and sport: a new ally? *J Eur Acad Dermatol Venereol*. 2015;29(3):515–520. doi:10.1111/jdv.12607
43. Zachary C, Fackler N, Juhasz M, Pham C, Mesinkovska NA. Catamenial dermatoses associated with autoimmune, inflammatory, and systemic diseases: a systematic review(,). *Int J Women's Dermatology*. 2019;5(5):361–367. doi:10.1016/j.ijwd.2019.09.008
44. Murase JE, Chan KK, Garite TJ, Cooper DM, Weinstein GD. Hormonal effect on psoriasis in pregnancy and post partum. *Arch Dermatol*. 2005;141(5):601–606. doi:10.1001/archderm.141.5.601
45. Adachi A, Honda T. Regulatory roles of estrogens in psoriasis. *J Clin Med*. 2022;11(16):4890. doi:10.3390/jcm11164890
46. Simionescu AA, Danciu BM, Stanescu AMA. State-of-The-art review of pregnancy-related psoriasis. *Medicina*. 2021;57(8). doi:10.3390/medicina57080804
47. Herbert D, Franz S, Popkova Y, et al. High-fat diet exacerbates early psoriatic skin inflammation independent of obesity: saturated fatty acids as key players. *J Invest Dermatol*. 2018;138(9):1999–2009. doi:10.1016/j.jid.2018.03.1522
48. Lu J, Lu Y. Paradoxical psoriasis: the flip side of idiopathic psoriasis or an autocephalous reversible drug reaction? *J Transl Autoimmun*. 2023;7:100211. doi:10.1016/j.jtauto.2023.100211
49. Dereure O, Guillot B, Jorgensen C, Cohen JD, Combes B, Guilhou JJ. Psoriatic lesions induced by antitumour necrosis factor-alpha treatment: two cases. *Br J Dermatol*. 2004;151(2):506–507. doi:10.1111/j.1365-2133.2004.06107.x
50. Pugliese D, Guidi L, Ferraro PM, et al. Paradoxical psoriasis in a large cohort of patients with inflammatory bowel disease receiving treatment with anti-TNF alpha: 5-year follow-up study. *Aliment Pharmacol Ther*. 2015;42(7):880–888. doi:10.1111/apt.13352
51. George LA, Gadani A, Cross RK, Jambaulikar G, Ghazi LJ. Psoriasiform skin lesions are caused by anti-TNF agents used for the treatment of inflammatory bowel disease. *Dig Dis Sci*. 2015;60(11):3424–3430. doi:10.1007/s10620-015-3763-0
52. Denadai R, Teixeira FV, Steinwurz F, Romiti R, Saad-Hossne R. Induction or exacerbation of psoriatic lesions during anti-TNF-α therapy for inflammatory bowel disease: a systematic literature review based on 222 cases. *J Crohns Colitis*. 2013;7(7):517–524. doi:10.1016/j.crohns.2012.08.007
53. Cullen G, Kroshinsky D, Cheifetz AS, Korzenik JR. Psoriasis associated with anti-tumour necrosis factor therapy in inflammatory bowel disease: a new series and a review of 120 cases from the literature. *Aliment Pharmacol Ther*. 2011;34(11–12):1318–1327. doi:10.1111/j.1365-2036.2011.04866.x
54. Brown G, Wang E, Leon A, et al. Tumor necrosis factor-α inhibitor-induced psoriasis: systematic review of clinical features, histopathological findings, and management experience. *J Am Acad Dermatol*. 2017;76(2):334–341. doi:10.1016/j.jaad.2016.08.012
55. Baeten D, Kruithof E, Van den Bosch F, et al. Systematic safety follow up in a cohort of 107 patients with spondyloarthropathy treated with infliximab: a new perspective on the role of host defence in the pathogenesis of the disease? *Ann Rheum Dis*. 2003;62(9):829–834. doi:10.1136/ard.62.9.829
56. Lian N, Zhang L, Chen M. Tumor necrosis factors-α inhibition-induced paradoxical psoriasis: a case series and literature review. *Dermatol Ther*. 2020;33(6):e14225. doi:10.1111/dth.14225

57. Boggs JME, Ramsay B, Lynch M. Paradoxical psoriasis caused by tumour necrosis factor inhibitor therapy. *Clin Exp Dermatol*. 2021;46(3):580–582. doi:10.1111/ced.14500
58. Mazloom SE, Yan D, Hu JZ, et al. TNF-α inhibitor-induced psoriasis: a decade of experience at the Cleveland Clinic. *J Am Acad Dermatol*. 2020;83(6):1590–1598. doi:10.1016/j.jaad.2018.12.018
59. Murphy MJ, Cohen JM, Vesely MD, Damsky W. Paradoxical eruptions to targeted therapies in dermatology: a systematic review and analysis. *J Am Acad Dermatol*. 2022;86(5):1080–1091. doi:10.1016/j.jaad.2020.12.010
60. Conrad C, Di Domizio J, Mylonas A, et al. TNF blockade induces a dysregulated type I interferon response without autoimmunity in paradoxical psoriasis. *Nat Commun*. 2018;9(1):25. doi:10.1038/s41467-017-02466-4
61. Palucka AK, Blanck JP, Bennett L, Pascual V, Banchereau J. Cross-regulation of TNF and IFN-alpha in autoimmune diseases. *Proc Natl Acad Sci U S A*. 2005;102(9):3372–3377. doi:10.1073/pnas.0408506102
62. Niewold TB. Interferon alpha as a primary pathogenic factor in human lupus. *J Interf Cytokine Res off J Int Soc Interf Cytokine Res*. 2011;31(12):887–892. doi:10.1089/jir.2011.0071
63. Cabaleiro T, Prieto-Pérez R, Navarro R, et al. Paradoxical psoriasiform reactions to anti-TNFα drugs are associated with genetic polymorphisms in patients with psoriasis. *Pharmacogenomics J*. 2016;16(4):336–340. doi:10.1038/tpj.2015.53
64. Collamer AN, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: clinical features and possible immunopathogenesis. *Semin Arthritis Rheum*. 2010;40(3):233–240. doi:10.1016/j.semarthrit.2010.04.003
65. Merli M, Accorinti M, Romagnuolo M, et al. Autoimmune bullous dermatoses in cancer patients treated by immunotherapy: a literature review and Italian multicentric experience. *Front Med*. 2023;10:1208418. doi:10.3389/fmed.2023.1208418
66. Tan S, Day D, Nicholls SJ, Segelov E. Immune checkpoint inhibitor therapy in oncology: current uses and future directions: JACC: cardioOncology State-of-The-Art Review. *JACC CardioOncology*. 2022;4(5):579–597. doi:10.1016/j.jaccao.2022.09.004
67. Fattore D, Annunziata MC, Panariello L, Marasca C, Fabbrocini G. Successful treatment of psoriasis induced by immune checkpoint inhibitors with apremilast. *Eur J Cancer*. 2019;110:107–109. doi:10.1016/j.ejca.2019.01.010
68. De Bock M, Hulstaert E, Kruse V, Brochez L. Psoriasis vulgaris exacerbation during treatment with a PD-1 checkpoint inhibitor: case report and literature review. *Case Rep Dermatol*. 2018;10(2):190–197. doi:10.1159/000491572
69. Nikolaou V, Sibaud V, Fattore D, et al. Immune checkpoint-mediated psoriasis: a multicenter European study of 115 patients from the European network for cutaneous adverse event to oncologic drugs (ENCADO) group. *J Am Acad Dermatol*. 2021;84(5):1310–1320. doi:10.1016/j.jaad.2020.08.137
70. Bonigen J, Raynaud-Donzel C, Hureaux J, et al. Anti-PD1-induced psoriasis: a study of 21 patients. *J Eur Acad Dermatol Venereol*. 2017;31(5):e254–e257. doi:10.1111/jdv.14011
71. Voudouri D, Nikolaou V, Laschos K, et al. Anti-PD1/PDL1 induced psoriasis. *Curr Probl Cancer*. 2017;41(6):407–412. doi:10.1016/j.currproblcancer.2017.10.003
72. Maiezza S, Greliak A, Rached HA, Mortier L. Exacerbation of skin psoriasis when associating an MEK inhibitor with anti-PD1 immunotherapy for metastatic melanoma. *Melanoma Res*. 2019;29(4):447–448. doi:10.1097/CMR.0000000000000601
73. Wan Z, Huang J, Ou X, Lou S, Wan J, Shen Z. Psoriasis de novo or exacerbation by PD-1 checkpoint inhibitors. *An Bras Dermatol*. 2024;99:425–432. doi:10.1016/j.abd.2023.09.003
74. Politi A, Angelos D, Mauri D, Zarkavelis G, Pentheroudakis G. A case report of psoriasis flare following immunotherapy: report of an important entity and literature review. *SAGE Open Med Case Reports*. 2020;8:2050313X19897707. doi:10.1177/2050313X19897707
75. Monsour EP, Pothen J, Balaraman R. A novel approach to the treatment of pembrolizumab-induced psoriasis exacerbation: a case report. *Cureus*. 2019;11(10):e5824. doi:10.7759/cureus.5824
76. Mullangi S, Ponnam S, Lekkala MR, Koya S. A case of de novo psoriasis secondary to nivolumab in a patient with metastatic renal cell carcinoma. *Cureus*. 2021;13(6):e15703. doi:10.7759/cureus.15703
77. Seervai RNH, Heberton M, Cho WC, et al. Severe de novo pustular psoriasiform immune-related adverse event associated with nivolumab treatment for metastatic esophageal adenocarcinoma. *J Cutan Pathol*. 2022;49(5):472–481. doi:10.1111/cup.14185
78. Matsumura N, Ohtsuka M, Kikuchi N, Yamamoto T. Exacerbation of psoriasis during nivolumab therapy for metastatic melanoma. *Acta Derm Venereol*. 2016;96(2):259–260. doi:10.2340/00015555-2212
79. Halle BR, Betof Warner A, Zaman FY, et al. Immune checkpoint inhibitors in patients with pre-existing psoriasis: safety and efficacy. *J Immunother Cancer*. 2021;9(10):e003066. doi:10.1136/jitc-2021-003066
80. Shim JH, Oh SH, Jun JY, et al. Exacerbation of Psoriasis after Imatinib Mesylate Treatment. *Ann Dermatol*. 2016;28(3):409–411. doi:10.5021/ad.2016.28.3.409
81. Adachi T, Hiraoka A, Okazaki H, et al. Exacerbation of psoriasis vulgaris by sorafenib treatment for hepatocellular carcinoma. *Clin J Gastroenterol*. 2020;13(5):891–895. doi:10.1007/s12328-020-01134-3
82. Thachil J. T-regulatory cell response in psoriasis and changes with imatinib therapy. *Clin Exp Dermatol*. 2009;34(8):e1022. doi:10.1111/j.1365-2230.2009.03696.x
83. Martora F, Battista T, Marasca C, Genco L, Fabbrocini G, Potestio L. Cutaneous reactions following COVID-19 vaccination: a review of the current literature. *Clin Cosmet Invest Dermatol*. 2022;15:2369–2382. doi:10.2147/CCID.S388245
84. Kaul V, Gallo de Moraes A, Khateeb D, et al. Medical education during the COVID-19 pandemic. *Chest*. 2021;159(5):1949–1960. doi:10.1016/j.chest.2020.12.026
85. Martora F, Villani A, Fabbrocini G, Battista T. COVID-19 and cutaneous manifestations: a review of the published literature. *J Cosmet Dermatol*. 2023;22(1):4–10. doi:10.1111/jocd.15477
86. Carrascosa JM, Morillas V, Bielsa I, Munera-Campos M. Cutaneous Manifestations in the Context of SARS-CoV-2 Infection (COVID-19). *Actas Dermosifiliogr*. 2020;111(9):734–742. doi:10.1016/j.ad.2020.08.002
87. Galván Casas C, Català A, Carretero Hernández G, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *Br J Dermatol*. 2020;183(1):71–77. doi:10.1111/bjd.19163
88. Shah H, Busquets AC. Psoriasis flares in patients with COVID-19 infection or vaccination: a case series. *Cureus*. 2022;14(6):e25987. doi:10.7759/cureus.25987

89. Chen Y, Qiu Y, Chen M, et al. Transition from secukinumab to Adalimumab in COVID-19-induced psoriasis flare-up treatment: a case report. *Clin Case Rep*. 2023;11(10):e8047. doi:10.1002/ccr3.8047
90. Wang X, Yuan L, Qiu X, Yang B, Man MQ. Psoriasis and COVID-19 Infection Negatively Impact Each Other: an Analysis of 3581 Cases. *Clin Cosmet Invest Dermatol*. 2023;16:1933–1936. doi:10.2147/CCID.S421394
91. Aram K, Patil A, Goldust M, Rajabi F. COVID-19 and exacerbation of dermatological diseases: a review of the available literature. *Dermatol Ther*. 2021;34(6):e15113. doi:10.1111/dth.15113
92. Abuelgasim E, Dona ACM, Sondh RS, Harky A. Management of urticaria in COVID-19 patients: a systematic review. *Dermatol Ther*. 2021;34(1):e14328. doi:10.1111/dth.14328
93. Shahidi-Dadras M, Tabary M, Robati RM, Araghi F, Dadkhahfar S. Psoriasis and risk of the COVID-19: is there a role for angiotensin converting enzyme (ACE)? *J DermatolTreat*. 2022;33(2):1175–1176. doi:10.1080/09546634.2020.1782819
94. Shi CR, Nambudiri VE. Widespread psoriasis flare following influenza vaccination. *Vaccine*. 2017;35(36):4785–4786. doi:10.1016/j.vaccine.2017.06.067
95. Munguía-Calzada P, Drake-Monfort M, Armesto S, Reguero-Del Cura L, López-Sundh AE, González-López MA. Psoriasis flare after influenza vaccination in Covid-19 era: a report of four cases from a single center. *Dermatol Ther*. 2021;34(1):e14684. doi:10.1111/dth.14684
96. Macias VC, Cunha D. Psoriasis triggered by tetanus-diphtheria vaccination. *Cutan Ocul Toxicol*. 2013;32(2):164–165. doi:10.3109/15569527.2012.727936
97. Ilgen O, Saatli B, Timur T, et al. Measures against COVID-19 pandemic - a single tertiary center experience. *J Obstet Gynaecol J Inst Obstet Gynaecol*. 2022;42(5):1532–1538. doi:10.1080/01443615.2021.2021506
98. Fiolet T, Kherabi Y, MacDonald CJ, Ghosn J, Peiffer-Smadja N. Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review. *Clin Microbiol Infect off Publ Eur Soc Clin Microbiol Infect Dis*. 2022;28(2):202–221. doi:10.1016/j.cmi.2021.10.005
99. Ruggiero A, Martora F, Picone V, et al. The impact of COVID-19 infection on patients with psoriasis treated with biologics: an Italian experience. *Clin Exp Dermatol*. 2022. doi:10.1111/ced.15336
100. Megna M, Potestio L, Battista T, et al. Immune response to Covid-19 mRNA vaccination in psoriasis patients undergoing treatment with biologics. *Clin Exp Dermatol*. 2022;47:2310–2312. doi:10.1111/ced.15395
101. Potestio L, Battista T, Cacciapuoti S, et al. New onset and exacerbation of psoriasis following COVID-19 vaccination: a review of the current knowledge. *Biomedicines*. 2023;11(8):2191. doi:10.3390/biomedicines11082191
102. Mercuri SR, Pacifico A, Malagoli P, et al. Heterologous versus homologous primary and booster COVID-19 vaccination do not increase flare rate in patients with psoriasis and/or psoriatic arthritis: insights from a real-life, multicenter, case-control study. *J Eur Acad Dermatol Venereol*. 2023;37(6):e693–e694. doi:10.1111/jdv.18943
103. Ewer KJ, Barrett JR, Belij-Rammerstorfer S, et al. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a Phase 1/2 clinical trial. *Nat Med*. 2021;27(2):270–278. doi:10.1038/s41591-020-01194-5
104. Korman NJ. Management of psoriasis as a systemic disease: what is the evidence? *Br J Dermatol*. 2020;182(4):840–848. doi:10.1111/bjd.18245