ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 19, Issue 1, 2026

Online - 2455-3891
Print - 0974-2441

Review Article

PSORIASIS: AN INTEGRATED REVIEW OF A COMPLEX IMMUNE-MEDIATED DISEASE

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Received: 30 October 2025, Revised and Accepted: 20 December 2025

ABSTRACT

Psoriasis manifests as persistent inflammation of the skin, often presenting with distinct scaly plaques. However, the precise cause of this condition is not clear but is known to be a complex consequence of several factors. These factors include environmental, genetic, microbial, and immunity dysregulation. An estimate of the total number of affected persons pertaining to psoriasis is estimated at more than 125 million at present. Recent innovations in therapeutics, chiefly "biologics" therapeutics, have introduced new possibilities for developing highly targeted personalized treatments with more efficacy. This multifactorial disease is characterized by various types, where "Plaque Psoriasis" is the prevalent one. This article explores the multifaceted aspects of psoriasis, an inflammatory long-term disease defined by distinct plaques as well as scales. This review provides an integrated perspective on psoriasis by outlining recent insights into its immunopathogenesis and highlighting how these advances have supported the development of targeted biologic treatments while continuing to shape future research and clinical innovation.

Keywords: Psoriasis, Immune-mediated inflammation, Inflammatory pathways, Phototherapy, Gene therapy, Biologic therapies.

 DOI: http://dx.doi.org/10.22159/ajpcr.2026v19i1.57074. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Worldwide, around 2–3% of individuals suffer from psoriasis, a long-term disorder caused by immune system dysfunction [1,2]. Although it primarily appears as disorder of the skin, presently acknowledged as a systemic inflammatory condition that is frequently connected to several comorbidities, placing a considerable clinical, psychological, and social burden on patients as well as healthcare systems [2-4]. The immune imbalance in psoriasis involves T-helper cell activation and cytokine pathways, particularly interleukin (IL)-23 as well as IL-17, contributing to chronic inflammation with abnormal skin cell growth [3,5,6]. Along with cutaneous symptoms, psoriasis is also linked to psoriatic arthritis (PsA), cardiovascular disorders, depression, and metabolic syndrome, highlighting its chronic as well as systemic nature [1,3]. The plaques involve one or more patches that are red in color and have silvery scales. A definite border is marked between the demarcated patches and the normal skin. Since no established therapy is there for this disease, timely treatment can help in easing out its symptoms [4].

Prevalence

This condition is highly observed in adults than in children. The occurrence of this condition varies geographically and tends to be higher in regions with an older population [4]. As per the World Psoriasis Day consortium, worldwide, more than 125 million individuals deal with psoriasis, accounting for roughly 2–3% global population. Affecting men as well as women, it most likely appears first between the 15 and 25 years of age [5,6]. Due to various research methods, it is difficult to track the trends in prevalence. Many countries have reported a rising trend in psoriasis occurrence. Recent studies report that the prevalence range extends from 0% to 11.8% worldwide. It has a prevalence range of 0.44–2.8% in India [7,8]. Higher prevalence is common among the populations in northern Europe besides lower in the eastern Asia [9-11].

Overall life impact

Psoriasis is long-term, recurring, as well as an inflammatory condition that can be associated with adverse health effects not only physically but also mentally. As some studies indicate, patients having psoriasis experience moderate to higher levels of depression and anxiety, and some studies have linked the condition to increased levels of suicidal tendencies [12,13]. Furthermore, the pain and discomfort caused by it affect day-to-day routines [12]. In psoriasis, the immune system becomes hyperactive. Tissue or organ damage may result from the activation of inflammatory immune cells, which typically protect the body from injury and infection. Psoriasis primarily affects the skin, but some studies show that it can affect other organs also causing dementia, asthma, and cardiovascular diseases. It may also affect the liver, resulting in poor metabolism and digestion [14-16].

Clinical manifestations

Clinical manifestations can vary widely – the frequently occurring clinical form is plaque-type psoriasis, which represents about 90% cases. This disease is classified by demarcated and erythematous scaly plaques covering large areas of skin. There is inverse psoriasis, and its classical clinical manifestations are mild erosive erythematous plaques and patches. There are variants, namely guttate type psoriasis and pustular psoriasis, classified by small erythematous plaques and a number of coalescing sterile pustules, respectively [17,18].

IMMUNOPATHOGENESIS AND GENETIC BASIS

Genetic disposition

Numerous studies indicated the strong genetic basis underlying the onset and pathogenesis of psoriasis [19,20]. At least two major forms of psoriatic disease – psoriasis vulgaris as well as PsA – are found to have a hereditary link. Based on familial and epidemiologic twin studies,

the disease is considered a multifactorial, multigenic condition, but its mode of inheritance remains uncertain [19-21].

Psoriasis in genome-wide study era

Through genome-wide studies, researchers have discovered multiple genetic variations, particularly single-nucleotide polymorphisms, connected to psoriasis, thereby advancing our knowledge of the genetic factors of this complex skin condition. The candidate genes with genome-wide significance belong to functional pathways involved in maintaining skin barrier integrity, innate immunity-related genes with specific involvement of nuclear factor-kappa B (NF-κB) and interferon (IFN) signaling, and adaptive immunity-related genes involving $CD8^+$ T and $CD4^+$ T lymphocytes (T helper [Th]), especially Th17 signaling [22,23]. Moreover, many studies have identified multiple genes within the major histocompatibility complex (MHC) region on chromosome 6. In addition, various additional genetic loci outside the MHC region encode cytokines, cytokine receptors, and proteins that activate T cells. These genetic loci are strongly associated with psoriasis susceptibility loci, contributing to disease predisposition [24,25]. There is, however, a limitation in genome-wide studies, which is that they only uncover statistical relationships between genetic markers and disease traits**.** While Genome-Wide Association Studies (GWAS) have been instrumental in revealing numerous susceptibility loci, they often face challenges in translating statistical associations into confirmed biological causality and functional understanding of disease mechanisms. Integrative analyses combining genomic, transcriptomic, and functional data are therefore essential to establish the biological relevance of these findings [26]. After redefining GWAS signals, meta-analysis of Immunochip and exome chip data has highlighted additional psoriasis susceptibility loci. A refined imputation strategy revealed a novel psoriasis susceptibility locus at DLEU1, which is linked to apoptosis, in previously analyzed GWAS data [27].

Immune dysregulation

In the individuals suffering from this condition, mistakenly the immune system starts targeting the healthier skin cells, causing inflammatory response and rapid skin cell turnover. Immune dysregulation plays a key role in its progress, involving various immune cells and cytokines. Environmental triggers such as stress, infection, or skin injury initiate an abnormal immune response in genetically predisposed individuals. This activation stimulates dendritic cells, which subsequently release IL-23, a pivotal cytokine accountable for promoting differentiation and activation of Th17 cells. The activated Th17 cells then produce effector cytokines such as IL-17, IL-22, and tumor necrosis factor-alpha (TNF-α), which act on keratinocytes and induce their hyperproliferation [28,29]. These keratinocytes further release additional cytokines, chemokines, and antimicrobial peptides, establishing a self-perpetuating inflammatory cycle that amplifies psoriatic lesions [28]. The presence of the hypothalamic–pituitary–adrenal (HPA) axis in patients can lead to immune dysregulation. The immune and nervous systems communicate through cytokines, proteases, neuropeptides, and chemokines, influencing both immune activation and nerve activity [30,31]. Furthermore, cross-talk between immune cells and sensory nerves enhances IL-23 release, reinforcing the pathogenic loop and chronic inflammatory state characteristic of psoriasis [29,32].

Environmental triggers

Environmental components can trigger psoriasis through different ways, which include stress, infections, weather, medications, smoking, alcohol, and skin injuries [33].

Stress can trigger psoriasis symptoms by causing the activation of the HPA axis, releasing the stress hormones such as cortisol and adrenaline. These hormones can dysregulate the immune system that eventually increases the inflammation levels in the body [34].

Infections, especially streptococcal infections, can exacerbate Psoriasis. When the immune system responds to infections, they start a cross-reactivity with skin components which then stimulates inflammation and triggers the psoriasis symptoms [35,36].

Medications, such as beta-blockers, antimalarial drugs, non-steroidal anti-inflammatory drugs, and lithium, can modulate the immune system and proliferation of skin cells, exacerbating the psoriasis symptoms [37].

Smoking enhances the psoriasis risk due to chemicals found in cigarettes. Smoke can modulate the immune system and produce oxidative stress which may damage the cells and tissues. Furthermore, smoking affects the flow of blood and vascular function which can trigger psoriasis flares. Alcohol, if consumed heavily and on daily basis, can trigger the psoriasis symptoms. Alcohol, if consumed heavily on a daily basis, can trigger psoriasis symptoms, as it adversely affects the immune system and leads to inflammation.

Skin injuries, such as burns, scratches, cuts, insects' wounds, or sunburns, can also trigger the Koebner phenomenon, which can trigger psoriatic lesions at the site of injury. It dysregulates the immune system and can disrupt the skin barrier function which triggers an inflammatory response [38].

Major inflammatory mechanisms, such as inflammatory pathways, can trigger psoriasis symptoms, including:

TNF-α pathway: TNF-α is a major proinflammatory cytokine involved in regulations of inflammation and immune system and is overproduced in psoriasis affected people. Such elevated levels of TNF-α result in inflammation which then leads to redness and proliferation of skin cells [39,40].

IL-23 pathway: Overexpression of IL-23 in psoriasis activates and stabilizes Th17 cells, which subsequently release key effector cytokines IL-17A, IL-17F, and IL-22. These cytokines drive keratinocyte proliferation, sustain chronic inflammation, contributing to the development of psoriatic plaques. This IL-23/Th17 axis represents a central immune pathway linking innate and adaptive immune responses in psoriasis [39,40].

IL-1 pathway: IL-1 stimulates the production of keratinocytes, neutrophils, and angiogenesis; thickens the skin; and promotes the activation of immune cells in the skin, resulting in the inflammatory response in psoriasis [39,40].

IL-6 Pathway: IL-6, a cytokine elevated in psoriasis, results in the immune system dysregulation. It stimulates the proliferation of skin cells that contribute to skin thickening, characteristic of psoriatic lesions [39,40].

NF-κB Pathway: NF-κB is a transcription factor that regulates the expression of genes linked to inflammation and immune responses in the body. Its activation is increased in psoriasis and promotes the production of inflammatory cytokines and chemokines [39,40].

Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway: Many cytokines, such as IL-6, IL-22, and IFNs, transmit their signal through the JAK–STAT pathway. This pathway helps pass messages from cytokine receptors to the cell nucleus, leading to inflammation and keratinocyte activation. Because of this role, JAK inhibitors have become an important target for psoriasis treatment [39,40].

CLINICAL SUBTYPES AND VARIANTS

There are various types of psoriasis affecting various areas of the body. Even though most of them result from the same triggers, they can have different symptoms and treatments.

Plaque psoriasis

The most frequent psoriasis type contributes to 80–90% of total cases. Commonly termed as "psoriasis vulgaris," typically defined by red-colored flamed patches covered with white scales. These patches may appear purplish with gray scales on darker skin. They may occur in any part of the body but are generally seen on the elbows, knees, scalp, torso, and lower back [41,42]. Histopathologically, plaque psoriasis shows hyperkeratosis, parakeratosis, elongation of the rete ridges, and collections of neutrophils known as Munro microabscesses that serve as a diagnostic hallmark of the disease [43]. Some of the common triggers include:

- Certain medications
- Infection
- Smoking
- Skin injury
- Stress
- Alcohol or Tobacco

It is caused when there is accelerated skin cell growth. Skin cells are normally matured and shed every 28–30 days from the surface, but in plaque psoriasis, this cycle is overactively accelerated and takes as little as 3–4 days only, which leads to cells building up on the skin's surface. Plaque psoriasis symptoms can differ in terms of severity and may involve itching, pain, and discomfort [44].

The treatment for plaque psoriasis aims at reducing the speed of skin cell growth and dealing with the inflammatory components. Treatment approaches for plaque psoriasis involve topical treatments, phototherapy treatments, oral treatments, and biologics. The diagnosis and severity of the symptoms and medical history will guide the decision of a health care provider to determine the best treatment plan for the patient [45].

Guttate psoriasis

This type is often found in young adults or in children, though it may arise at any age. It contributes to 7–8% of total psoriasis cases [46]. Guttate psoriasis is normally defined by tiny, pink-red lesions on the skin. On darker skin, the spots may be purplish or dark brown. These spots are smaller as compared to the spots seen in plaque psoriasis. They are generally present on the trunk, upper arms, limbs, thighs, and scalp but may also occur on the face and ears [47]. This type is often linked to human leukocyte antigen (HLA)-Cw6 genetic predisposition and streptococcal throat infection, both of which are strongly associated with its onset [43]. There are three stages of this type as follows:

Mild, which covers <3% of skin.

Moderate, which covers between 3% and 10% of skin.

Severe, which covers over 10% or more of the skin, sometimes the entire body.

It has not been concluded what leads to this type of psoriasis exactly, but some studies show that it could be a combination of environmental triggers and genetic predisposition. This psoriasis can go within a few weeks, sometimes even without going through any treatment. But in some cases, it stays and will require treatment [48]. The management of Guttate type of Psoriasis may include the use of topical corticosteroids or creams that can treat itching and inflammation, taking in antibiotics, light therapy, and systemic medications in serious cases [49].

Inverse psoriasis

This type is defined by smooth red, shiny, and inflamed patches appearing on the skin. On darker skin, the spots may appear in purplish, brown color. Unlike other types of psoriasis, its lesions seem flat and are often seen in the skin folds, namely armpits, buttocks, groin area, under the breasts, and genitals. These areas of inflamed skin are sometimes moist to the touch and could get worse during sweating or rubbing. Certain discomfort, itching, or both may be felt in the areas showing features of inverse psoriasis. Suffering individuals are potentially at risk of having a fungal or yeast infection in skin folds as a result of the moist environment. The red lesions normally cover very large areas within skin folds [50-52]. Histologically, it exhibits reduced hyperkeratosis and parakeratosis compared to plaque psoriasis, but with marked epidermal infiltration of lymphocytes [43]. Some of the common triggers included are sweating, friction, and fungal infections. A certain abnormality in the immune system also leads to the development of inverse psoriasis. In some cases, medications, injuries, alcohol, or smoking may also result in developing inverse psoriasis just like other autoimmune diseases [53,54]. Management of inverse psoriasis typically includes topical treatments, namely corticosteroid medications, Vitamin D analogs, etc. Depending on the severity, phototherapy and systemic medications may also be prescribed to treat inverse psoriasis. It is always considered favorable for people with inverse psoriasis to maintain good hygiene to avoid any flare-ups [55].

Pustular psoriasis

This kind of psoriasis represents a rare and severe form of the disease. It mostly appears in adults. It leads to white blisters filled with pus and surrounded by red or purplish, inflamed skin. Even though they look infectious, these patches are non-infectious [56-58]. This type may appear on various body parts, such as hands and feet. Sometimes, it is widespread and covers most of the body. There are three subtypes of this type of psoriasis, such as:

- Generalized pustular psoriasis, involving widespread pustules which cover large areas of the body.
- Palmoplantar pustulosis involving pustules appearing on the palm or sole of the feet.
- Acrodermatitis continua of Hallopeau, involving rare pustules which appear on the fingertips and toes. Some of the common triggers include infections, topical medications, pregnancy, stress, and injury [59,60]. The root cause of pustular psoriasis remains unclear but dysregulation of immune system, genetic as well as environmental components may contribute to it. This form is closely related to mutations in the *IL-36RN* gene, which contribute to dysregulated inflammatory responses and pustule formation [43]. Topical treatments, phototherapy, oral medications, and systemic medications are all possible treatment options for pustular psoriasis. The treatment aims to decrease inflammation, reduce symptoms, and prevent complications. The most suitable treatment for the suffering individual depends on the intensity of the symptoms as well as the medical history [61].

Erythrodermic psoriasis

This rare form of psoriasis presents with widespread redness and inflammation on some or all parts of the body. It can develop at once or evolve from other psoriasis types, mainly plaque-type psoriasis. It dysregulates the body's normal temperature as well as fluid balance [62-64].

Symptoms associated with this type of psoriasis may include:

- Intense redness/discoloration
- Shedding of skin in sheets or scales and inflammation covering large areas of the body
- Fever and shivering
- Increase heart rate
- Severe itch, pain, and burning
- Body temperature rising up and down, due to fluid imbalances [62-64].

Clinically, this subtype can be accompanied by systemic complications such as high-output cardiac failure, dehydration, and hypoalbuminemia, reflecting the intense inflammatory and metabolic burden on the body [43]. Erythrodermic psoriasis, like other types of psoriasis, may be induced by various factors such as medication, sunburns, infections, severe illness, stress, and an existing flare-up of another type of psoriasis. Due to its intensity, this type of psoriasis requires immediate medical treatment and may require hospitalization. Topical treatments, systemic medications, and biologic therapies are usual treatments for erythrodermic psoriasis [65-68].

PsA

This type is considered a combination of both psoriasis along with arthritis (joint inflammation). This form of inflammatory arthritis arises only in some individuals dealing with psoriasis. As per some studies, in more than 80% of cases involving PsA, people had psoriasis for an average of 12 years prior [69-71]. Its signs and symptoms comprise:

- Joints that become painful and stiff, especially in the morning and after rest, similar to the other forms of arthritis like rheumatoid arthritis.
- Swelling and tenderness of fingers and toes.
- Decreased rate of motion in affected joints and fatigue.
- Thickened, tendered and painful nails and nail separating from the bed [72].

A combination of environmental factors as well as genetic predisposition can trigger this psoriasis type. PsA management aims toward reducing the inflammation, reducing joint pain, and elevating the quality of life which include treatments such as NSAIDs, conventional and targeted disease-modifying antirheumatic drugs (DMARDs), biologic therapies, and physical therapies [73-76].

DIAGNOSTIC APPROACHES

Diagnosing a psoriatic condition may involve a combination of methods. In general, symptoms of psoriasis can be noticed during a physical examination, but that alone it is not always enough to confirm psoriasis [77]. There are different diagnostic approaches to identify the psoriatic condition as follows:

Physical examination

Many health conditions lead to itchy skin highlighted with scales along with rashes. In general, healthcare providers – especially dermatologists – can determine if the symptoms are of psoriasis or not, by examining visually. A dermatologist normally typically looks for various characteristic symptoms and signs which includes red patches with scales, plaques, inflammation, nail thickening or pitting, scalp, and itching. Doctors use a handy tool that is named "dermatoscope" which has a magnifying glass to properly check the skin. It allows them to thoroughly assess the skin to check the intensity of the condition and then advise the most suitable management plan [78].

Review of medical history

A dermatologist may spend some time to question the patient on medical history. This is done to help them assess the situation and suggest a management plan accordingly.

Since different forms of psoriasis are there, some cause symptoms that not just affect the skin, but the body too. Hence, the clinician typically records if anything else is troubling the patient and if the patient has conditions such as blepharitis, uveitis, and joint pain.

In general, a dermatologist asks about the medical history or any kind of treatments the patient has gone through in the past and their effectiveness. In addition, the patient will be inquired about the symptom patterns, on how they first appeared, and how they have progressed so far. Moreover, doctors may question on any of the following factors:

- Any family history of autoimmune conditions.
- Any comorbidities like PsA, cardiovascular disease, or metabolic syndrome.
- Any previous treatments or vaccines.
- Any condition that leads to weakening of immune system.
- Any additional autoimmune condition like celiac disease, Crohn's disease, or thyroid disorder.

The doctors gather this relevant information by following a structured approach and then tailor a customized treatment plan to address the condition [79].

Labs and tests

Healthcare providers may conduct various types of tests to properly assess the condition and its severity and monitor its treatment. As it is known, rashes can arise on the skin for several reasons. To confirm psoriasis, a dermatologist might suggest a skin biopsy. A small skin sample is taken first after injecting a local anesthetic into the skin to numb it. Depending on the size and location of the patch area, the doctor will use a device that is tube-shaped, snaps down when pressed, and removes a small skin piece. A blue dye called hematoxylin-eosin is used to stain this tissue sample, which makes the skin cells easier to examine under the microscope. In psoriasis, these skin cells appear dense and compact. Even though skin biopsy is the most effective method to identify the psoriasis condition, there are other tests that can be conducted additionally for the same or to identify any other associated conditions, which include-

- Complete blood count, in which levels of white and red blood cells are evaluated to indicate inflammation.
- C-reactive protein (CRP), in which CRP levels in the blood are evaluated to indicate any inflammation.
- Liver/kidney function tests, to ensure the normal functionality of the liver and kidney, since psoriasis can adversely affect the liver and kidney.
- X-rays of the joints or other affected areas, to identify any joint damage or inflammation in case of PsA [80].

Genetic testing and imaging techniques (dermoscopy)

At the moment, genetic testing cannot reliably diagnose the psoriatic condition. It is not a regular method of diagnosing psoriasis. However, some studies identify that certain genes and their variations may predispose someone to develop psoriasis as they regulate the immune system and inflammation. Genetic testing currently has only a marginal ability in predicting the future progression of PsA among individuals suffering from psoriasis, as most susceptibility loci overlap between the two conditions and lack sufficient predictive power for clinical use [71]. The primary genetic risk factor for psoriasis is HLA-Cw6 allele, which certainly can enhance the risk of developing psoriasis [81]. Genetic studies continue to advance our knowledge of this condition and provide us with an indication of a person's risk of developing psoriasis. These ongoing studies, while scientifically valuable, are not yet part of routine diagnostic practice and remain largely research tools aimed at understanding disease mechanisms rather than guiding clinical decisions [71,81]. Genetic predisposition deoxyribonucleic acid testing has made researchers believe that there is a possible connection between psoriasis and genetic actions, which could lead to refined treatment of the disease or possibly even a cure [81]. Imaging techniques like dermoscopy are useful to assess and examine lesions associated with psoriasis appearing in sites such as nails, soles, scalp, palms, and genital regions, with enhanced visualization. It is a non-invasive technique offering a horizontal view of the skin, allowing visualization of superficial structures and vascular patterns. The predominant vascular pattern of psoriatic skin lesions observed on dermoscopy is the dotted and globular vessels which are commonly seen in psoriasis lesions and represent dilated blood vessels in the skin [82]. Other characteristic signs that can be detected by dermoscopy include the appearance of pinpoint bleeding that becomes apparent following the removal of scales and white scales overlying the red patches, which is a typical phenomenon in psoriatic conditions [83].

CURRENT TREATMENT APPROACHES

Psoriasis treatment involves different types of treatments – topical treatment, phototherapy, oral medications, and biologic therapy. Sometimes, a more targeted treatment involves a combination of all these treatments.

Topical treatment

It is usually the first line of defense for people having mild to moderate psoriasis, according to the American Academy of Dermatology

Association. The treatment involves applying lotions, sprays, ointments, and solutions. Because they are applied directly on skin or scalp, they are called topical treatments. In some cases of psoriasis, treatment will involve combinations of two or more treatments. It is important to follow the doctor's advice for application frequency and duration of these treatments. These treatments include:

- Corticosteroids: These are the creams that are used to reduce redness, inflammation, and itching. The help trapping the moisture in the skin which reduces inflammation. Weaker formulas should work on sensitive areas of the body and can be bought without a prescription. Stronger formulas need a doctor's prescription.
- Retinoids: Retinoids, which are usually derived from Vitamin A, help decrease the inflammatory response as well as skin cell growth. Topical retinoids comparatively have potential side effects than corticosteroids, like birth irregularities.
- Vitamin D analogs: They are synthetic derivatives of Vitamin D which help control the flare-ups of symptoms. They help in normalizing the growth of skin cells, reducing inflammation, and removing scales. Prescriptions may include calcipotriene (dovonex) or calcitriol (rocaltrol) for the treatment.
- Coal tar: Being one of the primarily used topical treatments, it helps decreasing the excess growth of skin cells. It is available in different forms such as shampoos, moisturizers, creams, and bath gels. While coal tar is very effective, it may have a strong odor that does not smell good and can stain the clothing. Although earlier unrefined preparations raised concerns regarding odor, staining, and potential irritation, modern pharmaceutical-grade coal tar products are considered safe and effective when used under medical supervision. Hence, it is always important to follow the dermatologist's recommendation for its usage.
- Salicylic acid: This treatment promotes shedding of dead skin cells, which reduces scaling and itching. It is available in forms such as lotions, soaps, shampoos, foams, cloth pads, and gels. Although they are effective, topical treatment can have some side effects as well. Extended or long-term corticosteroid usage may lead to skin burning and stinging and it can also result in thinning of the skin. It may as well get absorbed through the skin and affect the internal organs. Some of the topical treatments, like creams and ointments, may also result in hypopigmentation and increase skin sensitivity to sunlight. It is recommended to follow the instructions of the dermatologist to counter any potential side effects when using topical treatments [84-87].

Phototherapy (light therapy)

As the name suggests, phototherapy includes exposing skin to the UV lights to get treated. There are different types of phototherapies, including Psoralen plus Ultraviolet A therapy, Ultraviolet B (UVB) phototherapy, and Excimer Laser Therapy.

- UVB phototherapy: This therapy includes exposing skin to Ultraviolet B light. It helps decreasing the growth of skin cells affected by psoriasis. It is to be noted that the skin is exposed to UV light ranging between 311 and 313 nanometers. The idea is that limiting the light spectrum in this way minimizes any risk of side effects. UVB light therapy can be conducted at home also under medical guidance. Small UVB-emitting light boxes can be used for this treatment or some also use full body units to target more areas of the body.
- Photochemotherapy or psoralen plus ultraviolet A: This therapy includes ingesting an oral medication called psoralen that causes increased sensitivity of the skin to light. This can be followed with UVA light therapy to help treat psoriasis. This combination limits the overformation of skin cells. While it is normally considered secure and effective for treating psoriasis, it may lead to some complications. A dermatologist needs to be consulted about phototherapy before exposing skin to high doses of UV light. Long-term phototherapy has been associated with skin cancer, such as squamous cell carcinoma and melanoma. Additional side effects comprise blistering, redness, and burning of the skin owing to overexposure of the skin to UV light. Moreover, long-time exposure to UV lights may also lead to premature aging of skin and fine lines [4,88-91].

Biologic treatment

Biologic treatments differ from conventional systemic therapies that act on the whole immune system. Biologics work by targeting particular parts of the immune system which contribute to the development of psoriasis, mainly by blocking pro-inflammatory cytokines such as TNF-α, IL-17, and IL-23 that drive keratinocyte hyperproliferation and inflammatory responses [92,93]. Dermatologists prefer biologic treatments in cases of moderate and severe levels of psoriasis that have been unresponsive to traditional psoriasis therapies. The biologics contribute significantly to reducing the development of psoriasis and PsA by blocking the action of specific immune cells which exacerbate the inflammation process. These drugs are either injected into the patients or given through intravenous infusion.

Common Biologics include:

TNF-α inhibitors, namely etanercept, adalimumab, infliximab, and certolizumab, block the action of TNF-α protein. This protein elevates inflammation. TNF-α inhibitors can make the patients more prone to serious infections, particularly reactivation of latent tuberculosis.

IL inhibitors targeting IL-12/23 (ustekinumab), IL-17 (secukinumab, ixekizumab, and brodalumab), and IL-23 (guselkumab, risankizumab, and tildrakizumab) block the actions of IL proteins involved in immune regulation. IL-17 inhibitors may raise the chances of candidiasis and can exacerbate inflammatory bowel disease. IL-23 inhibitors show good tolerability, with fewer systemic adverse reactions reported.

A dermatologist needs to be consulted to ensure whether Biologic treatment will work or not. Because as much as they are effective in reducing Psoriatic symptoms, they also lead to increased risk of infections and immune-related complications in the body. If the patient starts seeing any symptoms or signs of an infection, such as a fever, cough, or flu-like symptoms, they need to call the doctor [92,94].

Systemic medications

Systemic medications are normally prescribed for moderate to severe cases of psoriasis which remained unresponsive to topical treatments or UV therapy, or for those who cannot have more cycles of UV therapy. Some systemic medications can also be prescribed for PsA. Traditional systemic drugs are taken orally, such as pills or tablets, while newer targeted options can also be administered by injection. These medications help suppress the immune responses and reduce the inflammatory processes. Moreover, they also moderate the growth of skin cells.

The conventional DMARDs class includes the drugs such as methotrexate, cyclosporine, and acitretin, which act broadly to control immune-mediated inflammation and skin cell turnover [95,96].

Targeted synthetic DMARDs such as apremilast, a phosphodiesterase-4 (PDE-4) inhibitor, work more selectively by modulating intracellular signaling to reduce inflammatory cytokine production [97].

Side-effects

Just like other types of psoriatic treatments, systemic medication treatment may have some side effects too. Immunosuppressants (methotrexate and cyclosporine) increase the risk of infections, liver toxicity, kidney problems, and high blood pressure. Moreover, retinoids like acitretin lead to skin-dryness, cholesterol, and increased sensitivity to sunlight. This is why it is always important for patients to weigh the potential risks of taking in systemic medications and managing them [95,96].

THERAPEUTIC INNOVATIONS

Despite notable progress made in managing psoriasis, the current therapeutic approaches still pose certain drawbacks; though ongoing advancements in research and technologies have raised hope for better management of psoriasis.

Biologic therapies and small molecule inhibitors development

Continuing progress in biologic medications is going on which include the design of biologic agents that specifically target the pathways implicated in the development of Psoriasis. These therapies offer targeted inhibition of certain immune pathways. Lately, the progress in the development of small molecule inhibitors targeting specific pathways may offer alternative choices for those individuals who are not responding well to the biologic treatments. Some biologic and small molecule inhibitors being investigated include:

TNF-α, IL-17, and IL-23 inhibitors, which include drugs that block actions of pro-inflammatory cytokines such as TNF-alpha, IL-17, and the p40 subunit shared by IL-12 and IL-23. Among these, a dual IL-17A and IL-17F inhibitor – bimekizumab – revealed significant effectiveness in clinical studies for psoriasis and ankylosing spondylitis.

IL-36 receptor antagonists such as spesolimab have recently emerged as promising candidates to treat generalized pustular psoriasis, providing new hope for individuals dealing with severe form of the disease.

JAK inhibitors block the activity of Janus Kinase enzymes that are involved in the signaling pathways regulating inflammation.

Rho kinase (ROCK) inhibitors have demonstrated encouraging results in preclinical studies of psoriasis treatment. The therapeutic effect of these agents arises from their ability to inhibit Rho kinase and ROCK2, leading to modulation of inflammatory responses and suppression of pro-inflammatory cytokines.

PDE-4 inhibitors block the function of PDE-4, a key enzyme that participates in the breakdown of cyclic adenosine monophosphate levels, which result in reduced levels of inflammation and modulate immune responses [98-101].

Innovations in topical treatment

Over the time, several studies on psoriasis have focused on utilizing biomaterials to enhance the effectiveness of topical treatments. Biomaterials such as microneedles, hydrogels, nanocarriers, and nanofibers have been widely investigated. Ongoing research aims to develop more effective and customized topical treatments which include formulations, delivery systems, and combination of therapies. Recent findings have also highlighted novel topical agents such as the aryl hydrocarbon receptor (AhR) agonist tapinarof and advancements in nanoformulations and transdermal delivery systems showing improved clinical promise [102-104].

Gene therapies

Even though these treatments are still in the early stages of development, they can offer effective long-time solutions for managing the underlying causes of psoriasis. Research is going on gene editing techniques like clustered regularly interspaced short palindromic repeats-associated protein 9, to directly modify genetic behaviors which are involved in triggering psoriasis.

To conclude, the future of treating psoriasis appears bright, with newer novel biologic and topical options and therapies which are expected to offer enhanced effectiveness and better disease management. By leveraging these trends, we can hope for more personalized and holistic approaches to managing this chronic disease [105].

Combination of therapies

To come up with a more personalized approach and meet individual's specific needs, psoriatic treatment often includes combining the therapies. Recent studies display an evidence-backed review stating how combination of therapies ends up in enhancing the efficacy of treatments and lessen drug toxicities. For instance, using vitamin D derivatives together with topical corticosteroids has been shown to provide faster relief and better symptom control than using either treatment alone. Similarly, combining biologic therapy with methotrexate is also beneficial, as methotrexate may reduce the emergence of anti-drug antibodies and enhance treatment response. In addition, pairing acitretin with narrow-band UVB phototherapy has demonstrated improved disease clearance and helps lower the total UV exposure required to achieve results. The combination of novel biologic and systemic medications offers long-term management of this chronic disease. The main purpose of combining these therapies is to lower the risk of side effects that emerge while taking in a high constant dose of one single treatment and make the condition less resistant to the treatments over time [106,107].

CHALLENGES AND FUTURE PERSPECTIVES

Challenges associated with present psoriasis treatment

Within the present landscape of treating psoriasis, there are several challenges that persist which are discussed as follows:

- One of the major challenges is primary and secondary treatment failures. What works well for one patient might not be as effective for another patient, resulting in failure of primary treatment. To sort this out, we need better predictors of treatment responses to establish who will or will not benefit from a specific treatment. Secondary treatment failure occurs when even after responding well to the primary treatment, the level of effectiveness starts decreasing, possibly due to the development of neutralizing antibodies.
- Second major challenge that persists is the side effects of these prolonged treatments. These potential side effects can include severe infections, internal organ failure, skin cancer, hypersensitive skin, heart diseases, and many more. These side effects may range from moderate to severe.
- Cost and accessibility are another major concerns. These medications are not cheap and can become a burden. Moreover, they are not accessible to everyone, considering factors such as geographic location and insurance coverage.
- Treatment adherence and compliance remain another challenging factor for patients. It cannot be considered convenient going through such consistent treatments as they require long-term commitment. It may become quite difficult for patients to fully adhere to these treatments, which can impact the treatment outcomes.
- Living with psoriasis can greatly affect someone's mental health, contributing to shame, decreased self-esteem, anxiety, and depression in the patients. It may markedly downgrade the patient's quality of life because of its noticeable appearance as well as the stigma it may carry.

Addressing these challenges often requires multidisciplinary research to tailor more effective and safer treatments, as well as combining the efforts of dermatologists, rheumatologists, and psychologists to improve access to available therapies and provide continuous support for patients to better manage their physical and mental aspects of living with psoriasis [108].

Potential areas of future investigation

As discussed above, there are some gaps in the current understanding and treatment of Psoriasis. There are some areas of investigation to gain more insight into its pathogenesis and to recognize novel therapeutic targets and come up with a more holistic approach to treatments.

Genetics and epigenetics: Exploring the activities of genetic factors which are responsible for Psoriasis susceptibility and severity, analyzing epigenetic modifications and their control on gene expression patterns could lead to more personalized and tailored approaches to the psoriatic treatments.

Pathogenesis advances: Performing a deep analysis of the complex immune pathways and cellular interactions, the functionality of skin microbiome could really help us in refining the current treatment approaches. This could lay out the foundation for microbiome-based interventions as well.

Optimizing the treatments: To further improve the efficacy of psoriatic treatments, there is a need for more research on combination therapies, sequencing of treatments, and drug delivery systems. Moreover, incorporating patient preferences and patient-reported outcomes into clinical research could lead to more personalized and beneficial treatments that align with patients' requirements and preferences.

Environmental and psychological aspects: For treatments to accommodate both physical and psychological needs of the patients, it is a need to keep exploring the environmental triggers such as stress, medications, infections, diet, and psychological aspects such as anxiety, stigma, and social awkwardness [109,110].

CONCLUSION

To summarize, psoriasis is a persistent, non-infectious skin disorder marked by inflammation that impacts not just the physical well-being of the patient but also social and emotional too. Psoriasis treatment is chosen based on how severe the condition is including topical creams, phototherapy, systemic medications, or biologic therapies. In recent years, ongoing research exploring the root cause of psoriasis has contributed to important improvements in treatment to address all their current limitations. Continuous research and innovation in psoriasis treatment are crucial for many reasons: Better outcomes, improved safety profiles, personalized and targeted medicine, meeting the specific needs, and economic impact on the patients.

ACKNOWLEDGMENTS

None

FUNDING

None

CONFLICT OF INTEREST STATEMENT

None

AUTHOR CONTRIBUTIONS

Shruti Sharma contributed to conceptualization, manuscript drafting, review, and editing. Dileep Singh Baghel contributed to conceptualization and supervision. Ravinder Kumar contributed to literature collection and manuscript review and editing. Gurvinder Singh and Saurabh Singh provided supervision and assisted with review and editing. All authors reviewed and approved the final manuscript.

ETHICS APPROVAL

Not applicable

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