INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Research Article

Management Of Psoriasis: A Global Clinical Challenge And Future Treatment

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ARTICLE INFO

Received: 17 Jan 2024
Accepted: 21 Jan 2024
Published: 24 Jan 2024

Keywords:
Types, Severity, Biologics, Treatment

DOI:
10.5281/zenodo.10563571

ABSTRACT

Inflammatory disease that relapses and affects the skin, joints, or both. It is linked to multiple comorbidities, including metabolic, cardiovascular, mental, and renal diseases. Psoriasis has a complex etiopathogenesis that is primarily caused by an abnormal immune response as a result of genetic susceptibility and a variety of environmental variables, including trauma, infections, and medications. Treatment options for psoriasis vary depending on the disease's severity. Treatment as well but problems still exist, including side effects, resistance to therapy, exorbitant expenses, and individual differences in response. Promising new developments in psoriasis treatment are being observed for the future. Improved efficacy is provided by new biologic medicines that target novel pathways, such as interleukin 23 inhibitors like mirikizumab. RORγt inhibitors, among other small molecule inhibitors, offer supplementary therapeutic alternatives. Combination treatments, such as methotrexate and biologics, may enhance patient response to treatment. Personalised therapy techniques utilising biomarkers and multi-omics technology could help with diagnosis, treatment response prediction, and therapeutic decision-making.

INTRODUCTION

About 2-3% of people suffer from psoriatic disease, a chronic, recurrent inflammatory illness [1]. Psoriatic arthritis, which affects joints, and psoriasis vulgaris, which affects skin, makes up psoriatic illness. Psoriasis patients have severe psychosocial stress and a substantial reduction in quality of life [2]. Psoriasis has a complex immunopathogenesis that is largely caused by an abnormal immune response that is further altered by the interaction of environmental variables and genetic predisposition. The inflammatory

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

processes result in systemic inflammation, which raises the risk of morbidity and causes diseases of the heart, metabolism, and kidneys [3]. Recent developments in the comprehension of molecular and cellular pathways have revealed the involvement of tumour necrosis factor-α (TNF-α), interleukin-17 (IL-17), IL-23, and IL-22 as primary players in the pathogenesis of psoriasis. As a result, highly effective targeted therapeutic agents have been developed, such as receptor blockers or inhibitors of TNF-α, IL-17, IL-23, IL-1 α/β, or IL-36, as well as small molecule medications such as phosphodiesterase-4 inhibitors (apremilast), Janus kinase (JAK) inhibitors, and retinoic acid receptor-related orphan receptor γT (RORγT) inhibitors [4].

EPIDEMIOLOGY

Both men and women can have psoriasis, but women and those with a familial history are more likely to develop it earlier. Its age of beginning exhibits a bimodal distribution, peaking 10 years earlier in women and 30–39 and 60–69 years older in men. Psoriasis is thought to affect 60 million individuals globally; prevalence varies by nation, ranging from 0.05% in Taiwan to 1.88% in Australia. Older populations and affluent locations seem to have higher incidence of it. It affects 1.52% of the general population in the UK [5].

AETIOLOGY

Psoriasis has a complex pathophysiology, but genetics plays a major role, particularly in cases with early-onset (before 40 years of age) plaque psoriasis. Large-scale population-level studies, twin studies, and family-based research all supported this, with heritability estimates ranging from 60 to 90%. Genome-wide association studies have now revealed more than 60 susceptibility loci. Antigen presentation (HLA-C and ERAP1), NF-kappa B signalling (TNIP1), type 1 interferon pathway (RNF113 and IFIH1), interleukin (IL)-23/Th17 axis (IL23R, IL12B, and TYK2), and skin barrier function (LCE3) are among the many probable causative genes. This implies that the pathophysiology of psoriasis is most likely caused by a complicated interaction between T cells, dendritic cells, and keratinocytes, with the IL-23/Th17 axis acting as the primary regulator of immune activation, chronic inflammation, and keratinocyte growth. Six Psoriasis has been shown to worsen in response to environmental stimuli, including smoking, beta blockers, obesity, stress, and lithium. Pustular psoriasis appears to be genetically unique, despite the relative lack of evidence, with different susceptibility genes identified (IL36RN, AP1S3 in those of European heritage and CARD14) [6-8].

DISEASE SEVERITY

Based on the amount of BSA involved, the US Food and Drug Administration (FDA) classify psoriasis into three categories: mild, moderate, and severe. The FDA arbitrarily defines "severe" illness as including 20% or more of the patient's BSA. The FDA has urged the use of changes to the Psoriasis Area and Severity Index (PASI) to determine therapy benefit for the recently approved "biologicals." The PASI is a composite scoring system that considers the BSA impacted in four distinct body regions (the head and neck, trunk, upper and lower extremities), lesional erythema, and induration and scale. Recent research, however, indicates that there is poor correlation between BSA and PASI and the quality of life impact of the condition on patients. The National Psoriasis Foundation's Medical Advisory Board updated its mild, moderate, and severe disease classification standards based on these findings, taking patient impact into account. It is believed that while choosing the therapy plan for a particular patient, the established criteria—which are mostly focused on quality of life—should take precedence [9].

PSORIASIS TYPES

Psoriasis and genetics

Psoriasis affects people of all ages. Thus, heredity is a significant factor. Recent findings into the molecular causes of the common skin ailment psoriasis underscore the potential for genetic research to result in novel and potent biological therapies as well as modest pharmacological inhibitors. Among complex illnesses, psoriasis has an especially high hereditary component—over 60% is said to be inherited. Compared to dizygotic twins, monozygotic twins experience it more frequently. First- and second-degree relatives who have psoriasis have a higher frequency than the overall population. Psoriasis susceptibility 1 locus (PSORS1-9) is a set of at least nine genomic regions (loci) that have been found to connect with psoriasis in polymorphic pedigrees through linkage study. Using highly-improved microarrays, millions of genetic loci across the human genome may be consistently and efficiently genotyped in genome-wide association studies (GWAS). Because GWAS can detect even smallest differences in the frequency of alleles between disease patients and unaffected participants, it is far more successful than linkage analysis. The principal method utilised to confirm zygosity was extensive serological testing. The analysis's findings show that the presence of the specific genotype is nearly required for the disease to start. The PSORS2 gene is located near the telomeric end of chromosome 17q. The exact location of the risk allele has varied somewhat in many examinations. With respect to psoriasis, the central histocompatibility complex region at 6p21 has a substantially higher genetic danger. Across the major histocompatibility complex (MHC), the type I human leukocyte antigens (HLA) gene HLA-C demonstrates a significant dependence of sensitivity to psoriasis. The effectiveness of GWAS analysis has generated a lot of interest in the transformative application of GWAS data. Through GWASs, more than 10,000 loci have been discovered thus far. But the genetic variation (i.e., heritability) shown in twin studies differs from that seen in such large GWAS data. In the case of PV GWAS data, the most recent P-value represents around 30% of the total inheritance. Thus, greater progress in the sequencing process is needed before large-scale GWASs may be carried out on a regular basis [10].

Pustular psoriasis

The most common disease subgroups in this set of varied therapeutically unique subgroups are palmoplantar psoriasis and generalised pustular psoriasis. Although phenotypically and genetically distinct from psoriasis vulgaris, these variants may be associated with symptoms of plaque psoriasis, supporting their inclusion in the dermatitis spectrum. The most typical manifestation of it is aseptic pustules. Any one of the three genes—primarily interleukin 36 receptor antagonist (IL36RN), caspases recruitment domain (CARD14), and adaptor-related protein complex 1 subunit sigma 3 (AP1S3)—can get mutated to create them. Recent advancements in therapeutic research have led to the creation of biological medications that directly target the primary sources of inflammation in pustular psoriasis, with interleukin-36 agonists being the most advanced example. Acrodermatitis pustular psoriasis, localised pustular psoriasis, and generalised pustular psoriasis are the basis for defining clinical signs and symptoms [11].

Erythroderma

Erythroderma is the term for the entire or subtotal involvement of the skin in active psoriasis. It can manifest in one of two ways. First of all, as plaques enlarge and confluence, chronic plaque psoriasis may develop gradually. Second, erythroderma could be an indication of unstable psoriasis brought on by tar, medications, medicines, or stopping corticosteroids. Erythroderma may affect the skin's ability to regulate its temperature, which can result in hypothermia, high output heart failure, and metabolic abnormalities such

hypoalbuminaemia and anaemia from iron, vitamin B12, and folate loss [12].

Plaque psoriasis

Plaque psoriasis is the most prevalent type of psoriasis, characterised by nummular (coin-sized) plaques, round-oval, or sharply defined plaques. The lesions can start off as flat, one-centimeter-sized erythematous macules or papules, spread outward, and then combine to create plaques that range in diameter from one to several centimetres. Woronoff's ring, a white blanching ring, can be seen in the skin around psoriatic plaques. As plaques gradually extend outward, they can take on a variety of shapes, such as:

Psoriasis gyrata

In which curved linear patterns predominate

Annular psoriasis

In which ring-like lesions develop secondary to central clearing

Psoriasis follicularis

In which minute scaly papules are present at the openings of pilosebaceous follicles.

Rupioid and ostraceous refer to different morphological subtypes of psoriasis on plaque. Rupioid plaques are hyperkeratotic, tiny (2–5 cm in diameter), and resemble limpet shells. Ostraceous psoriasis is characterised by hyperkeratotic plaques that resemble oyster shells and have cores that are somewhat concave. Psoriasis is usually accompanied by scale, which has a silvery white appearance and varies in thickness. When scale is removed, little bleeding spots (Auspitz sign) may become visible. Patients differ in how much they scale, and within a single patient, scaling can occur at different locations. When it comes to acute inflammatory or exanthematic psoriasis, erythema may be the main clinical symptom and scaling may be absent [12].

Psoriatic nail disease

Compared to toenails, fingernails are more frequently impacted. The most typical observation is the presence of tiny pits in the nail plate, which are caused by improper nail development in the nail matrix's proximal region. Onycholysis, a condition where the nail separates from the bed at its lateral or distal attachments, is another possibility. "Oil spots" are orange-yellow patches that can exist under the nail plate. Furthermore, the nail plate may develop dystrophic, discoloured, and thicken. Subungual hyperkeratosis is the term used to describe the accumulation of yellow, keratinous material beneath the nail plate [12] Figure 1.

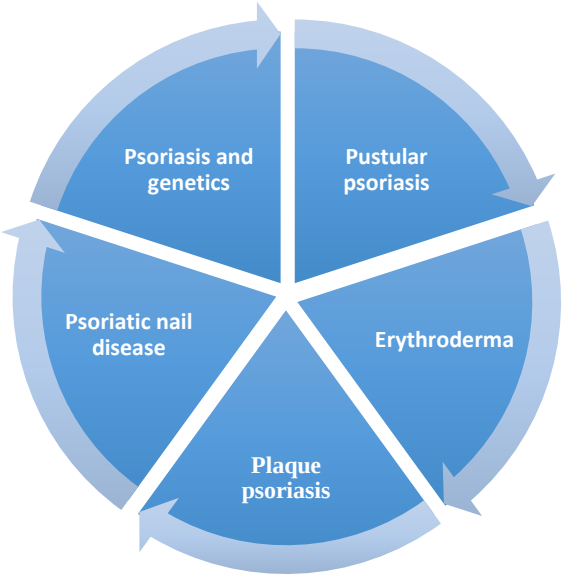

Figure 1: Different types of psoriasis

PRESENT TREATMENT GUIDELINES

Mild Psoriasis

The criteria for mild and moderate-to-severe psoriasis are not universally agreed upon [13, 14]. Generally speaking, less than 3% to 5% of the body's surface is affected with mild psoriasis. For mild psoriasis, a number of treatment alternatives are available, such as calcineurin inhibitors, keratolytics, topical corticosteroids, vitamin D analogues, and targeted phototherapy [15-17]. The location and severity of the lesions, the existence of comorbidities, and the preferences of the individual patient all play a role in the treatment plan selection. For patients with mild or localised psoriasis, topical corticosteroids are frequently the first line of treatment. By downregulating inflammatory pathways, they function by lowering inflammation, preventing cell division, and narrowing blood arteries. To reduce side effects, the location of the lesions should be taken into consideration while choosing the strength and formulation of corticosteroids. In comparison to using them separately, combination formulations of corticosteroids with vitamin D analogues or keratolytic drugs, like halobetasol propionate and tazarotene, are frequently more effective and have fewer side effects [18, 19]. They can also be used twice a week as preventative measures when lesions exhibit improvement [20]. Topical vitamin D analogues work by encouraging keratinocyte differentiation and preventing keratinocyte proliferation. Unless the patient suffers from renal impairment, they can be used extensively. Irritation and a burning feeling are possible side effects; however they normally go away with time. Tacrolimus and pimecrolimus are examples of topical calcineurin inhibitors that are mostly used to treat psoriatic lesions in the face and intertrigonous areas. They work by preventing T cell activation and preventing the manufacture of IL-2 and IFN-γ. Similar to topical vitamin D analogues, the primary adverse effects of topical calcineurin inhibitors include skin irritation and burning. Using topical corticosteroids initially will help lessen the chance of these adverse effects, which can be more noticeable in areas with severe inflammation. Last but not least, targeted phototherapy, such as excimer light therapy, uses specific wavelengths of light to treat localised plaque psoriasis. It has a low potential for carcinogenicity and can lead to significant improvement after approximately two months of treatment. Adverse effects may include a burning sensation and blistering, which are preventable with an appropriate treatment schedule. Topical keratolytics, such as tazarotene and salicylic acid, aid in the breakdown of thick scales on psoriasis plaques. Tazarotene, a retinoid, inhibits keratinocyte proliferation, while salicylic acid reduces scaling [21] Figure 2.

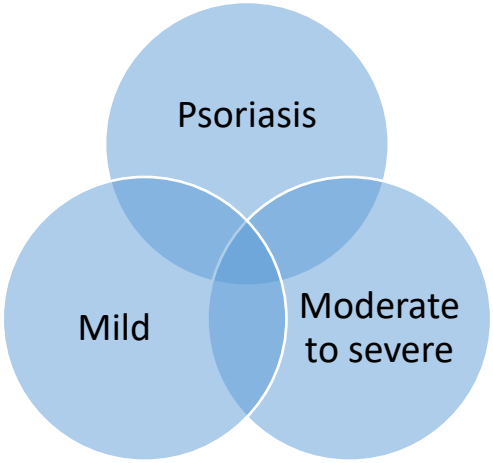

Figure 2: Treatment guidelines

Moderate-to-Severe Psoriasis

A typical definition of moderate psoriasis is affecting 3~5% to 10% of the body's surface area. An average of 10% or higher body surface area covering is indicative of severe psoriasis. The mainstay of treatment for moderate-to-severe psoriasis is systemic therapy; topical medicines may not be useful in treating localised disease. For these individuals, a combination of oral medications, phototherapy, and biologics is advised by both American and European guidelines. Comparing biologics to oral drugs or phototherapy, biologics have demonstrated greater efficacy. For moderate-to-severe psoriasis, topical therapies can be utilised as adjunctive therapies but not as a stand-alone treatment [21].

Phototherapy

To treat moderate-to-severe psoriasis, phototherapy techniques such as narrowband UV-B, broadband UV-B, and PUVA have been employed. The narrowband UV-B variant has a superior safety profile and is more effective than the broad band type. UV-B phototherapy inhibits DNA synthesis, which causes keratinocytes to undergo apoptosis and produces less pro-inflammatory cytokines. Erythema, pruritus, blistering, photoaging, and photocarcinogenesis are examples of adverse consequences. Since narrowband UV-B is more effective than broadband UV-B and has a longer period of remission, a lower risk of skin cancer, and less erythema, it is used more frequently. The combination of systemic retinoids and narrowband UV-B may improve efficacy and lower the risk of skin cancer. In PUVA therapy, UV-A radiation is used after psoralens, such as methoxalen, are used to decrease DNA synthesis. Despite being more effective than UV-B, oral PUVA is no longer recommended since prolonged usage increases the risk of skin cancer. Gastrointestinal distress, burning, itching, hypertrichosis, and photoaging are possible side effects. For palmoplantar psoriasis, topical PUVA therapy—which involves immersing hands and feet in psoralen-infused water and then exposure to UV-A radiation—is frequently employed. The primary obstacle associated with phototherapy is the requirement for patients to travel for in-office sessions. Although it's a practical choice, space and insurance restrictions may apply to home phototherapy [22].

Oral Systemic Treatments

Oral medications were frequently utilised to treat moderate to severe plaque psoriasis prior to the development of biologics. Methotrexate, apremilast, acitretin, and cyclosporine are among the oral therapeutic choices for plaque psoriasis [23]. With the exception of cyclosporine, oral therapies often have lower efficacies than biologics. For individuals who prefer non-injectable therapy or have restricted access to biologics, oral medicines may still be taken into consideration. The adverse effect profiles of the oral alternatives vary greatly, and because each oral medication has a different set of precautions and contraindications, choosing one requires considerable thought.

BIOLOGICS TREATMENT (Moderate-to-Severe Plaque Psoriasis)

TNF-α inhibitors

A class of drugs known as TNF-α inhibitors targets the cytokine tumour necrosis factor-alpha (TNF-α), which is involved in inflammation. The three TNF-α inhibitors that are often utilised are adalimumab, infliximab, and etanercept. With the exception of infliximab, which shows a response after 8 to 10 weeks, the response to TNF-α inhibitors is usually shown after 12 to 16 weeks of continuous treatment. In moderate-to-severe psoriasis, their efficacies and long-term safety profiles have been shown. Nonetheless, a number of serious side effects were noted, including severe infections, TB, reactivation of hepatitis B and C, drug-induced lupus, and demyelinating central

nervous system disorders. Certain TNF-α inhibitors are licenced for the treatment of inflammatory bowel disease, and they may be helpful for people with a history of the condition [21].

IL-23 inhibitors

For the treatment of psoriasis, stekinumab, guselkumab, risankizumab, and tildrakizumab are useful IL23 inhibitors. Use of mirikizumab is recommended for late-stage development. The only biologic that inhibits the common p40 component of IL-12 and IL-23 is uzekinumab. Ustekinumab dosages of 45 mg and 90 mg demonstrated, at week 12, PASI 75 response rates of 67.5% and 73.8%, respectively, in clinical trials. Notable safety profiles, easy dosing regimens, and strong efficacy are also seen by other IL 23 inhibitors. Risankizumab at 150 mg exhibited rates of 90.8%/74.8%/50.7%, while guselkumab at 100 mg showed PASI 75/90/100 response rates of 91.2%/73.3%/37.4%, respectively, at week 16. At week 28, tildrakizumab at 100 mg showed corresponding PASI 75/90/100 response rates of 77%/54%/23% [21]. Comparably acceptable safety profiles exist, with no elevated risk of life-threatening infections or cancers. Fatigue, headaches, upper respiratory tract infections, and nasopharyngitis were among the frequent adverse effects.

IL-17 inhibitors

The IL-17 ligand or their receptors are the two targets of IL-17 inhibitors. Bimekizumab suppresses both IL-17A and IL-17F, whereas secukinumab and ixekizumab only inhibit IL-17A. IL-17 receptor alpha is the target of brodalumab. For plaque psoriasis, IL-17 inhibitors exhibit a significant response, quick beginning of action, and long-lasting effectiveness. Week 16 PASI 75/90/100 response rates of 77.1%/54%/24% were shown for secukinumab at 300 mg, 90%/70%/40% for ixekizumab at 80 mg following an initial 160 mg dose, and 83%/70%/42% for brodalumab at 210 mg [24–26]. For psoriatic arthritis, they are also authorised. Furthermore, it has been shown that ixekizumab and secukinumab are especially useful in treating nail psoriasis. With no elevated risk of cancer or major infections, the safety profile of IL-17 inhibitors is acceptable. Nonetheless, reports of worsening of inflammatory bowel disease and mucocutaneous candidiasis have been made [27, 28]. Effects at the injection site and upper respiratory tract infections are common adverse effects. The relationship between the two has not yet been elucidated, but a case of suicidal thoughts has been recorded in a patient receiving brodalumab [29].

FUTURE TREATMENT OF PSORIASIS

As was covered in earlier parts, there are still a number of drawbacks to the psoriasis treatments available today, despite tremendous advancements in the field. Still, current investigations and clinical trials have identified novel therapy strategies and encouraging medicines that could completely change the way psoriasis is treated. The purpose of this discussion is to examine the future directions in psoriasis therapy, including the development of innovative drugs, improvements in topical therapies, customised methods, the creation of biomarkers, and the use of multi-omics technology.

Biologic Agents and Small Molecule Inhibitors under Clinical trials

The creation of biologic medicines and small molecule inhibitors that target particular pathways involved in the pathogenesis of psoriasis has attracted a lot of attention in recent years.

pDCs, then mDCs, are essential in the early stages of the onset of psoriasis. Pro-inflammatory factors (IL-12, IL-23, and TNF-α) are released by stimulated DCs. In turn, these cytokines promote the development of Th17, Th22, and/or Th1 cells. Moreover, keratinocyte TYK2/STAT3 signals are promoted by activated Th17 cells. These stimulate innate immunity, tissue reorganisation,

inflammatory infiltration, and epidermal hyperplasia. Plamacoid dendritic cell (pDC), myeloid dendritic cell (mDC), interferon (IFN), tumour necrosis factor-α (TNF-α), interleukin (IL), Langerhans cell (LC), T helper cell (Th), retinoic acid receptor-related orphan receptor gamma-t (ROORηt), Rho-associated protein kinase 2 (ROCK2), tyrosine kinase 2 (TYK2), Janus kinase (JAK), and signal transducer and activator of transcription (STAT) [21].

IL-23 Inhibitors

The interleukin (IL)-23 inhibitor mirikizumab has demonstrated encouraging outcomes in clinical trials. Mikikizumab significantly reduces inflammation and improves psoriatic skin lesions by focusing on the IL-23/Th17 pathway [30]. The IL-23/IL-17 axis is important in the pathophysiology of psoriasis, and biologics that are now on the market are made to target this molecule.

JAK Inhibitors

The Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways are critical for the function of type 1 and type 2 cytokine receptors. JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) are intracellular protein tyrosine kinases. On the other hand, the STAT family includes STAT1, STAT2, STAT3, STAT4, STAT5 (STAT5A and STAT5B), and STAT6. The important IL-23 receptor is linked to JAK2, TYK2, and STAT3 in psoriasis [31]. Although JAK 1-3 inhibitors have shown promise in treating moderate-to-severe psoriasis, safety concerns have not been allayed, and as of now, no JAK inhibitor has been approved by the FDA for the treatment of psoriasis [32]. Conversely, deucravacitinib is a specific TYK2 inhibitor that targets important inflammatory pathways implicated in the pathophysiology of psoriasis. Its efficacy in lessening psoriasis symptoms and enhancing patients' quality of life has been shown in clinical trials [33].

IL-36 Inhibitors

A member of the IL-1 family, IL-36 attaches itself to its receptor and uses the MyD88/IRAK complex to trigger the NF-κB and MAPK pathways. Both plaque psoriasis and a severe type of generalised pustular psoriasis (GPP) have been linked to loss-of-function mutations in the IL-36Ra gene. It has been demonstrated recently that A-552, a small molecule inhibitor of IL-36, may efficiently block the production of IL-36γ and other cytokines in both human and animal cells. Additionally, a Phase I research on the effectiveness of spesolimab, a monoclonal antibody that targets the IL-36 receptor, has been completed, and Phase II and III studies assessing its application in GPP are presently in progress. Thus, more study is required to assess the safety and efficacy of anti-IL-36 drugs in the treatment of psoriasis, as they offer great promise in this regard. Furthermore, new research has indicated that the MAST cell cytokines IL-37 and IL-38 may have a therapeutic use in the management of psoriasis [21].

RORγT ANTAGONISTS

Th17 cell differentiation depends on RORγT, a transcription factor that controls the production of Th17 cytokines, including IL-17A, IL-17F, IL-22, and IL-23 receptor [34]. Thus, RORγT inhibition appears to be a useful treatment approach for psoriasis. A phase III trial is being conducted on VTP-43742, an oral RORγT inhibitor, to treat plaque psoriasis. In a phase IIa research, patients receiving 700 mg and 350 mg of VTP 43742, respectively, showed reductions in PASI of 29 and 23% at 4 weeks, accompanied by a 75% decrease in IL-17A and IL-17F levels in both groups [35]. Headache, flushing, increased liver enzymes, and nausea were among the side effects. Other medications for treating moderate to severe psoriasis are presently in phases 2 and 1, respectively, of development. These medications include oral RORγT inhibitors JTE-451 and ABBV-157. Potential options for treating psoriasis

could include novel topical and systemic RORγT inhibitors [36].

A3 ADENOSINE RECEPTOR AGONIST

G-protein coupled A3 adenosine receptors are involved in a number of intracellular processes. In psoriasis patients, these receptors have been shown to be significantly expressed on peripheral mononuclear cells [37]. It has been discovered that the oral A3 adenosine receptor agonist piclidenoson inhibits T-lymphocyte proliferation and downregulates the NF-κB signalling pathway and pro-inflammatory cytokines such TNF-α, IL-6, and IL-12. In a phase II trial, the medication was well accepted and at 12 weeks, there was a substantial decrease in PASI when compared to a placebo [38]. Phase III trials for the medication are now underway.

CONCLUSION

Psoriasis is a complicated skin condition that affects affected people physically and psychologically. Notwithstanding the advancements in comprehending the fundamental systems involved and the creation of diverse therapy alternatives, obstacles persist in attaining the best possible results. With the advent of innovative biologic drugs that target specific pathways, such RORγt inhibitors and IL-23 inhibitors like mirikizumab, the therapy of psoriasis appears to have a bright future. There is a chance that these agents will improve disease control and efficacy. By reducing side effects and enhancing patient adherence, these cutting-edge techniques might offer more effective and focused treatments. Using multi-omics technology to identify and validate biomarkers is a critical first step towards personalised treatment methods. Biomarkers have the potential to monitor disease activity, predict treatment response, and inform therapeutic decisions—all of which can result in more customised and efficient treatment plans. Even if these developments have a lot of promise, it will take cooperation between scientists, medical professionals, and industry partners to put these findings into clinical practise. Furthermore, optimising the management of psoriasis requires tackling the issues of drug resistance, side effects, and excessive costs. We can keep making great progress in the management of psoriasis by embracing new trends, encouraging teamwork, and customising medicines to meet the needs of each patient. In the end, those who have this chronic skin problem will benefit from better results and a higher quality of life.

AUTHOR'S CONTRIBUTIONS

Mohd Rafi Reshi, Mariya Muzaffar and Muzamil Muzaffar took involved in the collecting, composition, and layout of the manuscript. . Nausheen Yusuf also assists in data collection and manuscript preparation. The idea for the study was brought to by Nusrat Nabi, who also finished the report. All authors approved of the work's final draught.

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HOW TO CITE: Mohd Rafi Reshi, Mariya Muzaffar, Muzamil Muzaffar, Nusrat Nabi, Nausheen Yusuf, Management Of Psoriasis: A Global Clinical Challenge And Future Treatment, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 1, 612-623. https://doi.org/10.5281/zenodo.10563571