Psoriasis : A Comprehensive Review of Current and Emerging Therapies

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ABSTRACT :

The inflammatory skin condition known as psoriasis is a chronic immune-mediated condition marked by keratinocyte hyperproliferation and a number of systemic comorbidities. With an emphasis on recent developments in our knowledge of the functions of particular immune cells and cytokines in the onset and maintenance of disease, we examine the intricate interactions between genetic, environmental, and immunological factors that contribute to its pathogenesis. There is a thorough discussion of the clinical signs and symptoms of psoriasis, which include guttate, inverted, pustular, and erythrodermic psoriasis, as well as localized plaque psoriasis. Topical treatments (corticosteroids, vitamin D analogs, retinoids), phototherapy (UVB, PUVA), traditional systemic therapies (methotrexate, cyclosporine), and the growing number of biologic agents that target particular immune pathways (TNF-α inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, and IL-23 inhibitors) are also critically evaluated in this review. In addition, we discuss new therapeutic developments and individualized treatment plans based on patient characteristics, phenotype, and disease severity. This emphasizes the value of a multidisciplinary approach for the best possible management of psoriasis and better patient results.

KEY WORDS : Interleukin inhibitor

INTRODUCTION :

About 3% of Americans and an estimated 125 million individuals worldwide suffer from psoriasis, a chronic, immune-mediated skin condition. Over 80% of instances of psoriasis are Plaque Psoriasis, making it the rarest type. Psoriasis is characterized by erythematous, scaly patches or plaques that are usually found on extensor surfaces but can also affect the intertriginous areas, palms, soles, and nails. Psoriasis affects both men and women equally, and it is more common in adults than in children.[1] It is completely reversible with the right treatment, however it is characterized by excessive keratinocyte proliferation and abnormal differentiation. The activation of the cellular immune system, which includes cells, dendritic cells, and immune-related cytokines and chemokines implicated in pathogenesis, is believed to be the cause of the keratinocyte response. It is completely reversible with the right treatment, however it is characterized by excessive keratinocyte proliferation and abnormal differentiation. The activation of the cellular immune system, which includes cells, dendritic cells, and immune-related cytokines and chemokines implicated in pathogenesis, is believed to be the cause of the keratinocyte response. The most recent psoriasis treatments focus on the immune system and could foretell future therapies for other inflammatory human conditions. Psoriasis is similar to other immune-mediated diseases such as juvenile-onset diabetes, multiple sclerosis, rheumatoid arthritis, and Crohn's disease. According to the definition of an autoimmune disease, which is "a clinical syndrome caused by the activation of T cells and B cells, or both, in the absence of an ongoing infection or other discernible cause," they are all included. Compared to other human autoimmune illnesses, psoriasis's cellular and genetic characteristics have been well studied since it affects an organ that is easily accessible.[1] Clinical factors such the patient's age at illness beginning, the shape of skin lesions, and the duration of the disease can be used to differentiate between several types of psoriasis. Psoriasis vulgaris, sometimes known as chronic

"plaque-type" psoriasis, affects the great majority of patient various for papriatic illnesses, there are a number of medical treatments available, such as topical medicines, phototherapy, oral drugs, and biologics. Through clinical trials and long-term registries, the safety and effectiveness of prescription medications and medical phototherapy have been thoroughly assessed. Almost all patients want to know how their food impacts their psoriatic condition, regardless of their prescribed medications or other recognized medical treatments. In particular, nutritional interventions are infrequently emphasized during professional appointments, despite the fact that the majority of patients believe they are relevant to managing their psoriatic condition overall. Furthermore, research indicates that dietary modifications are highly driven by psoriasis sufferers since they are seen as safe, natural, and patient-initiated. However, because there are so few studies summarizing the evidence on psoriasis and food, the majority of patients and doctors are unaware of how effective dietary therapies are. Overall, the data synthesis about the connection between food and psoriatic illnesses is severely lacking. This gap in the literature highlights the necessity of providing patients and clinicians with evidence-based dietary recommendations. Key topics regarding the role of dietary therapies in psoriatic illness are addressed in this article through the synthesis of evidence from a comprehensive review.

We provide the National Psoriasis Foundation (NPF) Medical Board's evidence-based recommendations about the role of dietary therapies in psoriatic illnesses, which are based on this comprehensive study.[2][3]

SIGNS AND SYMPTOMS:

The most common sites for these asymptomatic or irritating lesions are the scalp, sacrum, buttocks (frequently the gluteal cleft), extensor surfaces of the elbows and knees, and genitalia. Affected areas may also include the perianal region, axillae, umbilicus, eyebrows, and nails.

Although plaques may appear pink or red in individuals with light skin and violaceous in those with dark skin, important characteristics like scaling and distribution (e.g., on extensor elbows, trunk, legs, and periumbilical area) are the same for all skin tones.

Confluent areas of skin that span between these locations may be affected by the disease, which can be widespread.[1]

Table 1 Types of psoriasis

SR.NO.	TYPES	CHARACTERISTICS	PERCENTAGE%
1.	Plaque psoriasis	appearing as raised, red patches with silvery-white scales. These patches can appear on the elbows, knees, lower back, and scalp	80-90%
2.	Guttate psoriasis	Small, red, drop-shaped spots that appear on the trunk, arms, or legs. This type is often linked to strep infections and primarily affects children and young adults.	30%
3.	Pustular psoriasis	A rare type of psoriasis that appears as pus-filled bumps called pustules surrounded by red skin. The pustules contain white blood cells and are not contagious	3%
4.	Inverse psoriasis	Smooth, red patches that appear in skin folds, such as beneath the breasts or in the groin or armpits. This type worsens with friction and sweating.	1%
5.	Erythrodermic psoriasis	A severe type of psoriasis that affects a large area of the skin, causing	1-2.25%

		widespread skin discoloration and skin shedding	
6.	Sebopsoriasis	A type of psoriasis that appears on the face and scalp as bumps and plaques with a greasy, yellow scale.	1%
7.	Nail psoriasis	A common manifestation of psoriasis that can cause nail pitting, grooves, discoloration, and more.	80%

ETIOLOGY:

Psoriasis has a variety of causes. In addition to genetic predisposition, risk factors for psoriasis include stress, alcohol, smoking, sunlight, metabolic variables, drugs, trauma, infections, and infections. Among the drugs that can exacerbate psoriasis include antimalarials, beta-blockers, bupropion, calcium channel blockers, captopril, fluoxetine, glyburide, granulocyte colony-stimulating factor, interferon, interleukins, lipid-lowering drugs, lithium, penicillin, and terbinafine.

Plaque psoriasis does have a genetic component; if one person already has the condition, their chance of getting it is significantly increased. The condition is more likely to occur in patients who have vulnerable loci (PSOR1) on chromosome 6.

Plaque psoriasis is recognized to be linked to nearly every kind of trauma. Excessive scratching can also cause or worsen localized psoriasis. The Koebner reaction is the formation of psoriatic plaques at any trauma site. Although it is well known that sunlight helps people with plaque psoriasis, light can actually make the condition worse for certain people.

Psoriasis has been linked to pharyngeal streptococcal infections as well as HIV. HAART-treated HIV patients, however, typically have less severe illness. [1]

Although the exact origin of psoriasis is unknown, T cells appear to be a key player in the immunological activation of epidermal keratinocytes. Psoriasis is linked to specific genes and human leukocyte antigens (Cw6, B13, and B17), and family history is prevalent. Many psoriasis susceptibility loci have been found by genomewide linkage analysis; the PSORS1 locus on chromosome 6p21 is the most important in predicting a patient's likelihood of getting psoriasis. It is believed that an environmental trigger causes an inflammatory response, which leads to keratinocyte hyperproliferation. [4]

Triggers include :

Injury (Koebner phenomenon)
Sunburn
HIV infection
Beta-hemolytic streptococcal infection (leading to guttate psoriasis)
Medications (especially beta-blockers, chloroquine, lithium, angiotensin-converting enzyme inhibitors, indomethacin, terbinafine, interferon-alfa, immune checkpoint inhibitors, and tumor necrosis factor inhibitors)
Emotional stress
Alcohol consumption
Tobacco smoking
Obesity

EPIDEMIOLOGY:

About 80 new instances of psoriasis are reported for every 100,000 person-years in the United States, where it affects 3.2% of adults and 0.13 percent of children. Psoriasis affects over 125 million people globally, and its frequency varies greatly by area, ranging from 0.5% in some parts of Asia to 8% in Norway. Men and women are equally impacted in the majority of areas.[3]

Despite the fact that psoriasis can manifest at any age, there is a bimodal age distribution for its onset: 28–39 years old and 50–69 years old. Both hereditary and environmental variables may have an impact on the age at which psoriasis initially manifests. For example, the human leukocyte antigen (HLA)-C*06 allele is associated with an earlier onset age of psoriasis.[5]

The disease's burden in a tropical or subtropical nation like India cannot be understated, despite the fact that it is known to be more common in the world's polar areas. Due to a variety of hereditary and environmental factors, the frequency of psoriasis may differ from one region to another in a multicultural nation like India. Only six studies from North India that estimated the illness prevalence among adult dermatology patients were available, and they were primarily conducted in hospitals. [6,7,8,9,10,11] There have been reports of a higher prevalence in males, with the third and fourth decades of life being the peak onset ages [10,11]. The estimated point prevalence of pediatric psoriasis in one of the bigger Northern Indian investigations was 0.0002% [12]. Boys' peak age at onset is between 6 and 10 years old, while females' peak age is between 11 and 15 years old [13].

Two clinical manifestations of psoriasis, type I and type II, were identified by Henseler and Christophers after analyzing a group of 2147 patients. They were differentiated by a bimodal age of onset. Type 1 starts about age 40, whereas Type II starts beyond that. Over 75% of cases are caused by type I illness.7 Compared to patients with type II psoriasis, which develops later, patients with early onset, or type I psoriasis, tended to have more relatives affected and more severe illness. The path and advancement are uncertain. According to one study, 39% of patients experienced total illness remission for a period of one to fifty-four years [14].

CLINICAL FEATURES :

A papulosquamous condition, psoriasis varies in appearance, distribution, severity, and progression. Scaling papules (raised lesions less than 1 cm in diameter) and plaques (raised lesions more than 1 cm in diameter) are characteristics of papulosquamous illnesses. Lichen planus, pityriasis rosea, and tinea infections are additional papulosquamous diseases that should be taken into account in the differential diagnosis. Psoriasis lesions are different from these other conditions and are typically round, red, and well-defined, with a dry, silvery-white or grey scale Furthermore, the lesions are usually symmetrically distributed in the body folds, lumbosacral region, knees, elbows, and scalp. Koebner's phenomenon is the development of psoriasis at the site of trauma or damage. Generalized exfoliative erythroderma may develop from unmanaged or progressing psoriasis. There may be involvement of the nails, especially if there is psoriatic arthritis (PsA). Psoriasis can occasionally affect the tongue or oral mucosa. There may be finely defined gyrate red areas with a white-yellow border on the dorsal surface when the tongue is implicated. The phrase "geographic tongue" refers to the patches' potential to change everyday, evolve, and spread. They may also take on unique annular patterns and resemble maps. Psoriasis can vary widely in appearance, severity, and spread. The appearance can range from pustules (pustular psoriasis) to little tear-shaped papules (guttate psoriasis) to widespread erythema and scale (erythrodermic psoriasis). notwithstanding the basic presentation mentioned above. Furthermore, these various types of psoriasis might be extensive and incapacitating or localized and disabling. Additionally, psoriasis can occur abruptly, with quick growth and widespread involvement, or it can present as chronic, stable plaques. Patients with psoriasis may experience severe burning or itch as symptoms. [14]

Plaque psoriasis, guttate psoriasis, erythrodermic psoriasis, and pustular psoriasis are among the variations of psoriasis, and their clinical characteristics vary. A human may have multiple variants at any given time, even though one version usually predominates in an individual. Erythema, thickness, and scale are the three main clinical characteristics shared by the majority of psoriasis types. This review focuses on the clinical presentation of plaque psoriasis because it is the most prevalent type.

Plaque Psoriasis

Between 80% and 90% of all psoriasis symptoms are plaque psoriasis. Sharply defined, erythematous, scaly patches or plaques are the hallmark of plaque psoriasis. Plaque psoriasis can occur anywhere on the body, although it most frequently affects the scalp, trunk, gluteal fold, and extensor surfaces like the knees and elbows. Large, thick plaques and tiny, erythematous, scaly papules are both possible lesions in plaque psoriasis. The impacted regions are often symmetrical and well defined. New psoriasis lesions may appear at the site of trauma, such as from scratches, wounds, or peessures, in the Koebner phenomenon. An Auspitz sign may be produced by localized bleeding that happens when the scale is removed from the plaque. With moderate to severe psoriasis or during an exacerbation, patients may have significant itching.

When plaque psoriasis affects specific areas, such the face, palms and soles, nails, or intertriginous areas (also known as inverse psoriasis; refers to psoriasis involving the skin folds), it has a disproportionately negative impact on quality of life. Interginious psoriasis lacks the characteristic scale associated with psoriasis in interginous areas because of the moist skin environment in which it develops. As a result, it is sometimes misdiagnosed as a fungal infection. About one-third of psoriasis patients have genital psoriasis, which is linked to a significantly lower quality of life. [5]

Other Variants of Psoriasis

There are 3 other less frequently observed variants of psoriasis:

A: Guttate Psoriasis

B: Erythrodermic psoriasis

C: Pustular Psoriasis

Two percent of psoriasis cases are guttate, which is characterized by many 3- to 5-mm pink scaly patches that resemble confetti. An upper respiratory tract infection, such as a treptococcal infection, precedes about 66% of new-onset guttate psoriasis cases. Most of these instances go away on their own in a matter of weeks to months, however some may be more persistent. Patients with erythrodermic psoriasis, a rare severe form, experience exfoliation, scales, or coalescent erythema on at least 75% of their body. Even though erythrodermic psoriasis only affects 2% to 3% of people with psoriasis, it is handled as a dermatological emergency since it can be linked to potentially fatal electrolyte imbalances and sepsis. Another rare variation is pustular psoriasis, which is typified by erythema and sterile pustules. It is linked to a change in the interleukin 36 receptor antagonist (IL36RN) sequence and can be brought on by pregnancy, infection, rapid steroid tapering, or hypocalcemia. Pustular psoriasis can also be generalized, as in generalized pustular psoriasis. As in the case of palm and sole pustulosis, pustular psoriasis can also be localized.[5][15]

Flexural (inverse) psoriasis

The morphology of psoriasis affecting the flexures, especially the axillaxry, perineum, and inframammary, differs from that of conventional plaques found on the trunk and limbs. Lacking scale, flexural lesions manifest as red, glossy, clearly defined plaques that are sometimes mistaken for dermatophyte, candidal, and intertrigo infections.[14]

Palmoplantar pustulosis

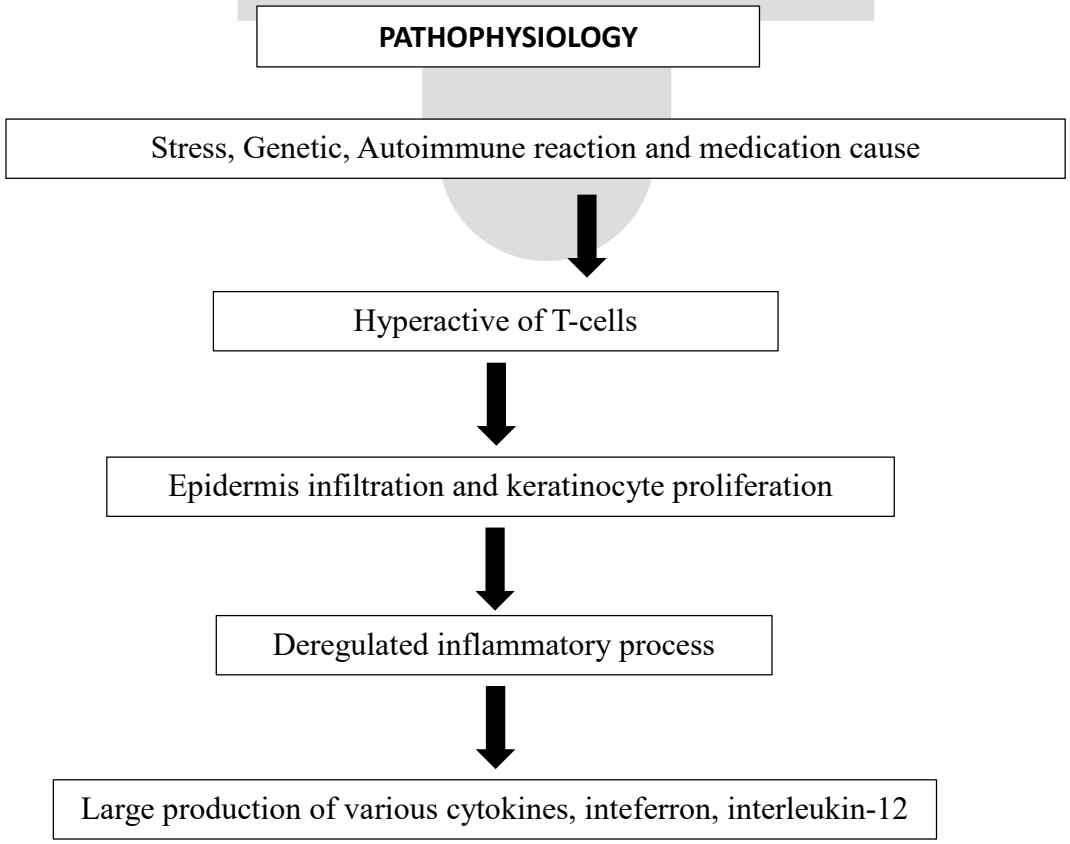
When palmoplantar pustulosis affects the palms and/or soles, it manifests as sterile, yellow pustules on an erythema and scaling background. The painful pustules eventually fade to a dark brown hue with a crust or scale that sticks to them. Psoriatic nail involvement is often linked to palmoplantar pustulosis. It is now thought that palmoplantar pustulosis may not be a kind of psoriasis, but it is linked to typical psoriasis vulgaris in about 25% of cases. [16] This result is based on genetic research that found no correlation with chromosome 6p markers, such as HLA-Cw6, which are associated with guttate psoriasis and persistent plaque. The demographics of palmoplantar pustulosis differ significantly from those of chronic plaque psoriasis. It is more common in women (9:1), typically manifests between the ages of 40 and 60, and is significantly linked to smoking, either past or present, in up to 95% of cases. [3]

Psoriatic nail disease

Compared to toenails, fingernails are more frequently impacted. Small pits in the nail plate, which arise from poor nail development in the proximal section of the nail matrix, are the most frequent finding. Onycholysis is the process by which the nail separates from the bed at its lateral or distal attachments. "Oil spots" are orange-yellow patches that can appear beneath the nail plate. Furthermore, the nail plate may become discolored, thicker, and dystrophic. Sublingual hyperkeratosis is a condition where yellow, keratinous material may accumulate beneath the nail plate.[14]

PATHOPHYSIOLOGY :

Excessive feed forward activation of the adaptive immune system is a pathophysiological feature of psoriasis. Excess IL-12 and IL-23 are secreted by activated myeloid dendritic cells. Naive T cells differentiate into T helper cells type 1 (TH1) in response to IL 12. For TH17 and TH22 cells to survive and proliferate, IL 23 is essential. Tumor necrosis factor a (TNF-α) is secreted by TH1 cells, IL22 is secreted by TH22 cells, and IL17 is secreted by TH17 cells (as well as numerous other inflammatory cells). In keratinocytes, these released cytokines trigger intracellular transduction, which results in the transcription of cytokine and chemokine genes. This causes a chain reaction of inflammation that culminates in the symptoms of psoriatic illness. IFN stands for interferon; NK for natural killer; and DC for dendritic cell.[5]



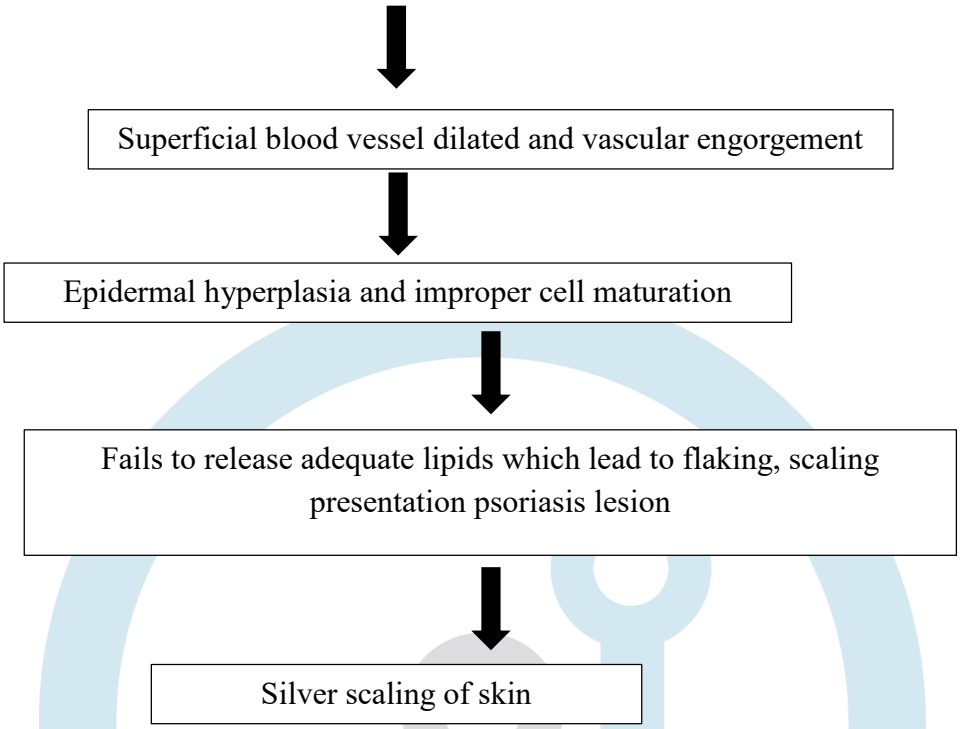


Figure.1 Pathophysiology of Psoriasis

PATHOGENESIS OF PAORIASIS:

The cathelicidin antimicrobial peptide LL37 has been demonstrated to attach to self-Dna fragments generated by "stressed" or dying keratinocytes during the development of psoriasis. This induces the production of iL-23, tnF, and interferon (iFn)-α by plasmacytoid DCs (pDCs) [15] Vascular endothelial growth factor (veGF), which encourages vasodilatation and enhanced vascular permeability, and iL-1β, iFn-γ, and tnF, which aid in DC activation, are produced by stressed keratinocytes.[17] After activation, DCs move into lymph nodes that drain the skin to provide naive CD4+ and CD8+ t cells an unidentified antigen, which encourages their differentiation into iL-12-induced tH1 cells and iL-23-induced tH17 cells, respectively.[18] Inflammatory cells enter the skin through blood and lymphatic channels, drawn by substances generated from keratinocytes.

The triggering phase is followed by the onset of the disease. Following a contact with tH1 cells, DCs activate nKt cells by producing tnF and iFn-γ and operate on keratinocytes by releasing iL-23 and tnF [19] tH17 cells release iL-17a, iL-17F, iL-21, iL-22, tnF, and iFn-γ once they are in the dermis. These cytokines' release triggers the synthesis of iL-6, iL-8, and other cytokines and chemokines generated from keratinocytes, which in turn promote keratinocyte proliferation and hinder keratinocyte differentiation. [19,20] Furthermore, these cytokines cause keratinocytes to release β-defensins, the neutrophil-chemoattractant and antimicrobial S 100 proteins, and the neutrophil-recruiting CXC chemokine ligand (CXCL)-1, CXCL-3, CXCL-5, and iL-8. These mediators then cause neutrophil infiltration into the epidermis, which is a crucial aspect of psoriasis.

Factors including transforming growth factor (tGF)-β, iL-1β, iL-6, iL-20, iL-21, and iL-8 are produced by the interaction of keratinocytes with inflammatory cells. Fibroblasts are induced by these cytokines to release tGF-β, keratinocyte growth factor, and epidermal growth factor. These mechanisms are thought to have a role in the rearrangement and deposition of extracellular matrix, poor differentiation, and hyper proliferation of the epidermis. Memory CD8+t cells that express α1β1 integrin at the dermis–epidermis interface bind to collagen IV, infiltrate the epidermis, and aid in the pathophysiology of illness. They may be drawn to the dermis by keratinocyte-derived factors such iL-8 and iL-23.[21] Additionally, chemokines like fractalkine attract nKt cells or t cells, which then get activated after interacting with glycolipid-CD1d complexes and causing pathogenic inflammation.[22]In this case, cytokines released from keratinocytes, including fibroblast growth factor, platelet-derived growth factor, and veGF, affect the development of vasculature and supporting stromal cells, which make it easier for inflammatory cells to reach the inflammatory region. [23] Finally, keratinocytes are impacted by the resulting cytokine, chemokine, and growth factor milieu, which increases their proliferation and hinders their terminal differentiation. This is in addition to the maintenance and amplification of the chronic inflammatory disease process. Psoriatic plaques are created and maintained by

the growth of keratinocytes in conjunction with the infiltration of neutrophils and T lymphocytes. [24] In general, pro-inflammatory cytokines, chemokines, and growth factors that coordinate the interactions between immune cells, epidermal keratinocytes, dermal fibroblasts, and blood and/or lymphatic arteries cause psoriasis. [25]

TREATMENT OF PSORIASIS:

TREATMENTS FOR MILD PSORIASIS

Mild psoriasis is defined differently, but it often affects less than 3% to 5% of the body's surface area. The existence of active psoriatic arthritis may alter treatment options depending on the severity of psoriasis, favoring those that are advantageous for both conditions. Because of this, the first step in treating psoriasis is to check for psoriatic arthritis.[26] For those with moderate psoriasis, therapeutic options include topical corticosteroids, vitamin D analogs, calcineurin inhibitors, keratolytics, and targeted phototherapy. Mild psoriasis is defined differently, but it often affects less than 3% to 5% of the body's surface area. The existence of active psoriatic arthritis may alter treatment options depending on the severity of psoriasis, favoring those that are advantageous for both conditions. Because of this, the first step in treating psoriasis is to check for psoriatic arthritis.[26] For those with moderate psoriasis, therapeutic options include topical corticosteroids, vitamin D analogs, calcineurin inhibitors, keratolytics, and targeted phototherapy.[27]

Topical corticosteroids

For the majority of patients with mild or localized psoriasis, topical corticosteroids are the primary treatment. Through the down-regulation of genes encoding proinflammatory cytokines, topical corticosteroids provide anti-inflammatory, antiproliferative, and locally vasoconstrictive effects. Topical corticosteroids often work well for mild or localized psoriasis as long as the right dosage is used and the patient takes them as directed. Vasoconstrictive tests are used to define the class of topical corticosteroids, with class I having the maximum potency (superpotent) and class VII having the weakest (least potent to reduce side effects and increase adherence, topical corticosteroid strength and delivery should be chosen according to body region. Topical corticosteroids with high to midpotency can be applied to the trunk and limbs. Superpotent topical corticosteroids are advised if the lesions are thick. Generally speaking, low-potency topical corticosteroids are recommended for the groin, axillary, inframammary, and face regions.

There are several techniques to treat mild or localized psoriasis using topical corticosteroids. During the acute phase of active psoriasis, patients can apply the topical corticosteroid twice daily until the lesions are clear or almost clear. Once the lesions are quiescent, patients can switch to taking a topical drug, such as a calcineurin inhibitor, vitamin D analog, or topical corticosteroid, twice a week. This regimen, which is referred to as proactive care during the maintenance phase, applies topical medications when lesions are quiescent, reducing the likelihood of recurrence.[28]

Topical corticosteroids can be used as a single drug in a combination formulation or as two different drugs applied at different times in combination with topical vitamin D analogs or keratolytic agents. Topical corticosteroids with a keratolytic agent, like the combination of halobetasol propionate and tazarotene, or topical corticosteroids with a topical vitamin D analogue, like betamethasone dipropionate and calcipotriene, are examples of combined formulations. Compared to any medication taken alone, combined formulations usually exhibit greater efficacy, fewer side effects, and longer remission.[29][5]

The first-line treatment for individuals with limited disease is a topical corticosteroid, either alone or in combination with a steroid-sparing medication. The degree of the ailment, the location, the vehicle of choice, the patient's age, and their preferences should all be taken into consideration when determining the potency needed for treatment. The effectiveness of several topical corticosteroids in treating psoriasis has been evaluated in a number of double-blind studies.[30] Clobetasol propionate 0.05% (Temovate), betamethasone dipropionate 0.05% (Diprolene), fluocinonide 0.05% (Lidex), and desoximetasone 0.25% (Topicort) are examples of class I and class II steroids. In an attempt to prevent some of the local toxicities, such as striae, telangiectasia, and skin atrophy, the use of class I steroids should be restricted to an initial treatment period of twice-daily administration for two to four weeks. After the first two to four weeks of treatment, it is recommended to gradually introduce a steroid-sparing medication while reducing the usage of class I topical steroids to one or two times per week.[31]

Long-term daily administration of high-potency corticosteroids over broad body surface areas in children should be avoided because of the possibility of systemic consequences, including suppression of the hypothalamus pituitary and adrenal gland axis.[16]

Topical Vitamin D Analogues

In order to inhibit keratinocyte proliferation and promote keratinocyte differentiation, topical vitamin D analogues bind to both the vitamin D receptors on T cells and keratinocytes. In the US, three kinds of topical vitamin D analogs are utilized: When combined with either calcipotriol or calcipotriene, calcitriol When applied alone, topical vitamin D medications have a moderate level of effectiveness alone. [32] As long as the patient does not have renal impairment, topical vitamin D analogues can be utilized extensively. Children with psoriasis should use no more than 50 g of topical vitamin D per week, and adults with psoriasis should use no more than 100 g per week. Burning and irritation are the main side effects, which can happen to up to 35% of patients and usually go away with time.[33]

Topical Calcineurin Inhibitors

Topical calcineurin inhibitors decrease T cell activation by stopping the generation of IL-2 and IFN-γ. Examples of topical calcineurin inhibitors that are frequently used to treat psoriasis in the face and intertriginous areas include tacrolimus and pimecrolimus. These medications do not cause the undesirable side effect of skin atrophy that comes with long-term use. Up to 71% of people may have clear or almost clear psoriasis after eight weeks.[34] Using topical corticosteroids initially, followed by topical calcineurin inhibitors, can help reduce skin irritation, a typical adverse effect, especially in highly inflamed lesions.[5]

Topical Keratolytics

Topical salicylic acid and tazarotene are examples of topical keratolytic agents. Topical tazarotene is a retinoid that helps dissolve the thick scales on the plaque by preventing keratinocyte growth. After 12 weeks, up to 63% of individuals may see at least a 50% improvement in their psoriasis.[35] Burning and irritation are common side effects that can be minimized by using a cream formulation, a lower dose, alternate-day dosing, or topical corticosteroid usage. Another keratolytic that may lessen scaling is topical salicylic acid, which should be avoided in youngsters as it may cause irritation.[35]

Targeted Phototherapy

Exposure to particular light wavelengths is the basis of phototherapy, often known as light therapy. For many years, people with plaque psoriasis have been treated with phototherapy. In contrast to sunshine, phototherapy reduces the emission of wavelengths that cause cancer while delivering particular wavelengths that are beneficial for psoriasisc Targeted phototherapy is used to treat localized plaque psoriasis, and full-body surround phototherapy is used to treat more widespread psoriasis. Excimer light treatment is a type of targeted phototherapy that uses high-intensity UV-B (308 nm) radiation Patients usually receive phototherapy twice a week, and after about two months, they start to notice noticeable improvements. The carcinogenic hazard of excimer light therapy is quite low. Blisters and a burning feeling are the main side effects.[5]

TREATMENTS FOR MODERATE TO SEVERE PSORIASIS:

The definition of moderate to severe psoriasis is still up for debate. Psoriasis is classified as moderate by some clinicians when it affects 3% to 10% of the body's surface area, while moderate psoriasis affects 5% to 105% of the body's surface area. 10% or more of the body's surface area is usually regarded as severe psoriasis. For individuals with moderate to severe psoriasis, systemic therapies are the cornerstone of care. Additionally, systemic drugs can be used to treat persistent local psoriasis that is not responding to topical treatments or localized diseases that affect specific areas including the scalp, palms and soles, and genitalia. Dermatology's American Academy. According to National Psoriasis Foundation standards, people with moderate to severe psoriasis should be prescribed biologics, oral medications, and phototherapy. In general, biologics are more effective than oral drugs or phototherapy. When treating moderate to severe psoriasis, topical therapies can be utilized as an adjuvant but not as a monotherapy.[1]

Phototherapy

Since the introduction of biologics, phototherapy has been less common for moderate to severe psoriasis. The three primary forms of phototherapy used to treat psoriasis are psoralen with UV-A (PUVA), narrowband UV-B, and broadband UV-B. Since narrow band UV-B is generally more effective than broadband, it is recommended for treatment. Additionally, narrowband UV-B is recommended over PUVA due to its better safety profile. For localized psoriasis, targeted phototherapy such as excimer light is utilized. The fact that patients must travel in order to receive office-based phototherapy presents a barrier. Although home phototherapy is a practical option, space and insurance restrictions restrict its use.[5]

UV-B

The kind of skin determines the dosage. In circumstances where medication is not working, adding acitretin (soriatane) while closely monitoring the patient's lipid panel and the levels of aspartate and alanine aminotransferases may be an option. UV-B use reduces DNA synthesis, which causes keratinocytes to die and T cells to produce fewer proinflammatory cytokines. Plaque psoriasis can be treated with UV-B phototherapy using both narrowband (311 nm) and broadband (290-320 nm) wavelengths. The first course of treatment is usually given in the

clinic or at home three times a week. To maintain efficacy, treatment frequency can typically be lowered to twice weekly after two to three months. Depending on the patient's reaction, this frequency can then be further decreased. Erythema, pruritus, blistering, photoaging, and photocarcinogenesis are among the side effects. Narrowband UV-B is more widely utilized than broadband UV-B because it is more effective, has a longer length of remission, has a reduced propensity to cause photocarcinogenesis, and causes less erythema at the same physical dose. When combined with systemic retinoids, narrow band UV-B radiation may be more effective and less carcinogenic. [5]

For moderate to severe psoriasis, narrow-band ultraviolet B light, or light with wavelengths between 311 and 313 nm, is the first line of treatment. It can be used alone or in conjunction with other therapies. Patients who are taking medication or who have comorbidities that would make treatment with other systemic agents impossible find it to be an extremely alluring choice.

It may work by immunosuppressing Langerhans cells, changing cytokines and adhesion molecules, which causes Th2 cells to proliferate, and causing T lymphocytes to undergo apoptosis. UV light also has an impact on keratinocyte development and proliferation.[36] Treatment typically consists of two or three weekly visits for a total of 15 to 20 treatments, with extra therapy for maintenance. Dosage is determined by skin type.. Adding acitretin (soriatane) with close monitoring of aspartate aminotransferase and alanine aminotransferase levels and the patient’s lipid panel, can be considered in treatment resistant cases.[37][31]

PUVA

An alternative is to use psoralen in conjunction with UVA. If narrow-band UVB treatment is unsuccessful, it may be taken into consideration. Because UVA penetrates deeper than UVB, it is especially beneficial for patients with thicker plaques and darker skin. UVA treatment comes when psoralen is applied topically or taken orally. Compared to narrow-band UVB, the duration of remission is significantly prolonged with psoralen plus UVA. However, this treatment has a high risk of melanoma and cutaneous squamous cell carcinoma, particularly in light-skinned individuals and those who get high doses of cyclosporine or UVA (200 or more treatments).[38,39,40] Telangiectasia’s, lentigines, and photoaging are long-term consequences. This treatment is less commonly utilized as a result of these well-established negative effects. [31]

PUVA treatment entails applying a psoralen, like methoxalen, topically or orally before being exposed to UV-A (320–400 nm) light. To inhibit DNA synthesis, psoralens are intercalated into DNA. Patients usually receive oral PUVA two to three times a week during the first phase of treatment, until their psoriasis is clear or almost clear; after that, the frequency of treatment gradually drops. Even though oral PUVA treatment is more effective than UV-B, it is no longer recommended because prolonged usage can cause skin cancer.[41] Additional negative consequences include photoaging, pruritus, burning, hypertrichosis, and upset stomach. Due to the possibility of serious burns, PUVA should not be used in conjunction with tanning beds. Patients

with palmoplantar psoriasis are usually treated with topical PUVA therapy, which entails bathing hands and feet in psoralen-containing water and then exposing them to UV-A radiation.[42]

BIOLOGICS FOR THE TREATMENT OF MODERATE TO SEVERE

Plaque psoriasis

The use of biologics to treat moderate to severe plaque psoriasis is one of the most significant therapeutic advancements in dermatology. Biologics that block TNF-a, p40IL-12/23, and IL-17 have been approved by the US Food and Drug Administration to treat psoriatic arthritis. All biologics used to treat psoriasis are administered subcutaneously, with the exception of infliximab. Biologic treatment for psoriasis generally does not increase the risk of serious infections or internal malignancies. All biologics can cause injection site responses, nasopharyngitis, and upper respiratory tract infections, which happen a little more frequently than placebo.[5]

TNF-a Inhibitors

The oldest class of biologics currently licensed for the treatment of psoriasis and psoriatic arthritis are TNF-a inhibitors. These biologics reduce the downstream inflammatory cascade that is essential to the pathophysiology of psoriasis by blocking TNF-a. Different TNF-a inhibitors have varying degrees of effectiveness in treating plaque psoriasis. When head-to-head studies are not available, network meta-analyses reveal that infliximab is the most

effective TNF-a inhibitor for psoriasis, followed by certolizumab and adalimumab, which have comparable efficacies, and etanercept. [40] When compared to the majority of IL-17 and IL-23 inhibitors, the dose of subcutaneously administered TNF-a inhibitors is more common as a class. The standard strategy for treatment escalation is to increase the frequency of TNF-a inhibitor administration if the permitted dose proves ineffective and the patient decides to continue using the medication.

Overall, there are no documented elevated incidence of severe infections linked to TNF-a inhibitors used to treat psoriasis, according to postmarketing registry studies. However, although direct head-to-head comparisons are not possible, the risks of serious infections were numerically greater for TNF-a inhibitors than for ustekinumab in a registry analysis that included patients receiving treatment with several biologics. TNF-a inhibitor-treated psoriasis patients did not have higher rates of internal malignancies than the general population.[43] Other population-based studies indicate higher rates of nonmelanoma skin cancers, which may be related to a history of PUVA treatment among many psoriasis patients in the TNF-a inhibitor trials, even though phase IV observational studies have not revealed possible increased rates of skin cancer.[44] Injection site responses, upper respiratory tract infections, and nasopharyngitis are the most frequent side effects. People with advanced congestive heart failure, hepatitis B infection, active TB, and demyelinating illnesses like multiple sclerosis should not take TNF-a inhibitors. As long as they are simultaneously receiving treatment for latent TB, patients with latent TB can get concurrent TNF-a inhibitor treatment. Since patients using TNF-a inhibitors may be more likely to convert to active TB than those receiving other classes of biologics for psoriasis, it is crucial that patients with latent TB who are receiving treatment with a TNF-a inhibitor continue their TB treatment. These include ustekinumab (Stelara) and TNF-alpha inhibitors.[5]

Adalimumab (Humira), etanercept (Enbrel), and infliximab (Remicade) are examples of TNF-alpha inhibitors. They work quite effectively and are usually well tolerated. However, individuals with class III or IV congestive heart failure, a personal history of demyelinating disease, or a family history of demyelinating disease should not take TNF-alpha inhibitors or other biologic medicines. Since reactivation has been documented after starting TNF-alpha inhibitors, patients should be checked for active infections, such as hepatitis B and tuberculosis.[15]

Adalimumab

Adalimumab is an anti-TNF-alpha human monoclonal antibody. It prevents TNF-alpha from attaching to p55 and p75 cell-surface TNF receptors by binding to soluble and membrane-bound TNF-alpha.

Adalimumab's recommended dosage is 80 mg subcutaneously during the first week, 40 mg the following week, and then 40 mg every two weeks after that.[31]

Etanercept

Etanercept is a recombinant human TNF-alpha receptor (p75) protein that binds to soluble TNF-alpha by fusing it with the Fc region of IgG1. For the first 12 weeks, 50 mg subcutaneously twice a week is the recommended dosage for etanercept; beyond that, 50 mg weekly.[31]

Infliximab

A mouse variable region and a human IgG1 constant region are joined to create the chimeric antibody infliximab, which binds to both soluble and membrane-bound TNF-alpha. 58 In weeks 0, 2, and 6, as well as every 8 weeks after that, infliximab is administered as an infusion at a dose of 5 mg/kg over 2 to 3 hours.[31]

Alefacept

The human Fc IgG1 receptor alefacept (Amevive) is fused to the alpha subunit of LFA3. It binds to CD2, inhibits costimulatory signaling, and causes activated memory T cells to undergo apoptosis.

Alefacept was one of the few biologic drugs that produced long-term remission and the first biologic agent approved by the FDA for the treatment of psoriasis. However, because its onset of action was far later than that of other drugs and few people experienced considerable clearance of their psoriasis, its use has decreased.[45]

FOR PSORIATIC ARTHRITIS:

systemic medications

It is strongly advised that people with known or suspected psoriatic arthritis be evaluated by a rheumatologist.

For mild psoriatic arthritis, nonsteroidal anti-inflammatory medications (NSAIDs) are typically the first line of treatment. Because methotrexate is inexpensive, it is a viable option for treatment if no improvement is seen after two to three months of NSAID medication. Methotrexate alone, however, has not been demonstrated to stop the disease's radiologic development.[46,47]

When compared to one another, the TNF-alpha inhibitors have demonstrated comparable effectiveness in treating psoriatic arthritis.[47,48] Ustekinumab has not been demonstrated to be as effective as TNF-alpha inhibitors in treating psoriatic arthritis based on radiologic evidence. TNF inhibitors ought to be the primary line of treatment for psoriatic arthritis as a result. [49,48] The effectiveness of various therapy and the order in which they should be taken to treat psoriatic arthritis have not been well studied. If, after 12 to 16 weeks of oral methotrexate treatment, no discernible improvement is obtained, the American Academy of Dermatology's Psoriasis Guidelines of Care advise adding or switching to a TNF-alpha inhibitor.[50]

Agents for psoriatic arthritis:

Biological DMARDs (TNFi, IL-12/23 inhibitors, and IL-17 inhibitors), non-steroidal anti-inflammatory drugs (NSAIDs), targeted synthetic DMARDs (apremilast, a phosphodiesterase 4-inhibitor), and conventional disease modifying anti-rheumatic drugs (DMARDs) (methotrexate, leflunomide, sulfasalazine, ciclosporin) are all used to treat PsA.[51,52]

IL-12/23 Inhibitor

Ustekinumab, which has been licensed by the US Food and Drug Administration to treat psoriasis and psoriatic arthritis, is the only biologic that inhibits both IL-12 and IL-23 by blocking their shared p40 component. Ustekinumab mainly works by inhibiting IL-23 to produce its therapeutic effect. Ustekinumab is given once every three months and has a weight-based dosage; it works quite well. Reducing the interval between injections is advised if ustekinumab therapy escalation is required. Ustekinumab's safety profile is deemed satisfactory. When compared to a placebo, there are no higher rates of serious infections or cancers. Headaches and upper respiratory tract infections were the most frequent side events in the clinical studies, occurring at rates marginally higher than the placebo.[5]

IL-17 Inhibitors

IL-17 inhibitors are biologics that specifically target the ligand or receptor for IL-17. Secukinumab and ixekizumab inhibit the IL-17A ligand, whereas memekizumab suppresses both the IL-17A and IL-17F ligands. Brodalumab inhibition of the IL-17 receptor results. IL-17 inhibitors as a class show a rapid onset of action, a robust response, and good sustainability when treating plaque psoriasis in responders. IL-17 inhibitors are also approved for the treatment of psoriatic arthritis in the US and other nations. IL-17 inhibitors have a sufficient safety profile because they do not increase the risk of serious infections or cancer. There have been reports of mucocutaneous candidiasis and an exacerbation of inflammatory bowel disease in people on IL-17 inhibitors. Injection site responses and upper respiratory tract infections are the most common and manageable adverse effects.[5]

IL-23 Inhibitors

A class of biologics known as IL-23 inhibitors reduces the activity of the TH 17 pathway by selectively inhibiting the p19 component of IL-23. The US Food and Drug Administration has approved gusel kumab, tildrakizumab, and risankizumab as IL-23 inhibitors to treat adult plaque psoriasis. The development of mirkikizumab is nearing completion. IL-23 inhibitors as a class offer a simple infrequent dose schedule, good safety profiles, and strong effectiveness. International approval has also been granted for the treatment of psoriatic arthritis with risankizumab. These IL-23 inhibitors have different short- and long-term effects. With no elevated rates of severe infections or cancers to date, the safety profiles of these IL-23 inhibitors seem likewise acceptable. The most common but controllable adverse effects include injection site responses and upper respiratory tract infections.[5]

Oral Systemic Treatments:

Prior to the development of biologics, oral medications were used for many years to treat moderate to severe plaque psoriasis. Methotrexate, apremilast, acitretin, and cyclosporine are among the oral medications used to treat plaque psoriasis. In general, oral therapies for psoriasis are less effective than biologics, with the exception of cyclosporine. Oral therapies, however, might be an option for individuals who might not have easy access to biologics or who would rather not take injectable drugs. It has numerous negative effects, thus choosing an oral drug requires cautious thought because some of them have numerous contraindications and precautions.[5]

Methotrexate

Methotrexate was authorized by the US Food and Drug Administration (FDA) in 1972 to treat severe psoriasis.36% to 68% of patients with severe plaque psoriasis who received weekly dosages of 15 to 20 mg of methotrexate were able to obtain a PASI-75 score.[40]

When treating severe psoriasis, methotrexate dosages range from 7.5 to 25 mg once weekly. Additionally, patients should take a 1–5 mg folate supplement daily, excluding the day they take methotrexate. The purpose of folate is to guard against methotrexate-related liver toxicity, bone marrow suppression, and gastrointestinal adverse effects.

Methotrexate can also cause stomatitis and lung fibrosis as side effects. Methotrexate use is contraindicated in the following conditions: pregnancy, lactation, alcoholism, chronic liver illness, immunodeficiency syndromes, bone-marrow hypoplasia, leukopenia, thrombocytopenia, anemia, and methotrexate hypersensitivity.

The 2009 guidelines for the use of methotrexate in the treatment of psoriasis by the National Psoriasis Foundation recommend that a complete blood cell count with platelets, blood urea nitrogen, creatinine, and liver function tests be done at baseline and at 1- to 3-month intervals thereafter.

In the past, liver biopsies were advised for patients on long-term methotrexate when the total dosage reached 1.5 This suggestion has been updated, nonetheless, in light of the invasive nature of the liver biopsy technique and the low frequency of methotrexate-induced hepatotoxicity.

When a cumulative dose of 3.5 to 4.0 g of methotrexate is reached, liver biopsy should be considered in patients with normal liver function tests and no significant risk factors for hepatic toxicity (such as obesity, diabetes, hyperlipidemia, hepatitis, or history or current alcohol use). Other options include monitoring the patient without a liver biopsy or, if feasible, switching to an alternative medication.[43]

A liver biopsy should be considered shortly after beginning methotrexate and repeated every 1.0 to 1.5 g, and patients at high risk should be closely watched.

In the United States, there are currently no established noninvasive methods for assessing liver fibrosis. The risk of liver fibrosis has been linked to serial measures of blood type III procollagen aminopeptide; however, this test is only easily accessible in Europe.[44]

Cyclosporine

Psoriasis, especially erythrodermic psoriasis, can be effectively treated with cyclosporine (Gengraf, Neoral, Sandimmune). Because of its quick start and the risk of glomerulosclerosis associated with long-term therapy (three to five years), it is frequently only used temporarily or as a bridge to other maintenance therapies.[45]

By binding to cyclophilin and inhibiting the transcription of calcineurin and nuclear factor of activated T cells, cyclosporine reduces T-cell activation. Up to 80% to 90% of psoriatic individuals have demonstrated quick improvement while using cyclosporine at doses of 2.5 to 5 mg/kg/day.[53]

Cyclosporine is typically prescribed at an initial dose of 2.5 to 3 mg/kg/day in two divided doses. This dose is maintained for 4 weeks, after which it is raised by 0.5 mg/kg/day until the disease stabilizes.[36]

The two most dangerous side effects of cyclosporine are nephrotoxicity and hypertension. After baseline, blood urea nitrogen, creatinine, and blood pressure should be checked twice a month for the first three months, and then once a month after that. Monthly checks should also be performed for potassium, magnesium, uric acid, lipid profiles, liver function tests, and complete blood cell counts.

Additionally, cyclosporine raises the risk of cutaneous squamous cell carcinoma, particularly in patients who have had psoralen plus UVA therapy. Cyclosporine should not be administered to patients who have a history of systemic malignancy, renal insufficiency, a history of chronic infection (such as tuberculosis, hepatitis B, or hepatitis C), or cyclosporine hypersensitivity.[36]

Acitretin

For many years, psoriasis has been treated with the oral retinoid acitrin. Its effects are dose-dependent, and its onset is gradual, usually lasting three to six months. It works best as a maintenance treatment, typically in conjunction with other therapies like phototherapy or after the illness has been stabilized by medications like cyclosporine.[36] Patients with pustular psoriasis have demonstrated efficacy with acitretin.[54] Acitretin has not been demonstrated to produce notable cumulative toxicities and does not change the immune system. Given that acitretin can result in hypertriglyceridemia, serum triglycerides are regularly checked.

Because they fall under pregnancy category X, all retinoids, including acitretin, should be avoided when pregnant. Despite having a short half-life of 49 hours, acitretin can change into etretinate on its own or when alcohol is consumed. The half-life of etretinate is 168 days, and it may take up to three years for the body to get rid of it. Consequently, women who intend to get pregnant or who refuse to use appropriate contraception for three years following the drug's discontinuation should not use acitretin.[36]

FOR ERYTHRODERMIC PSORIASIS:

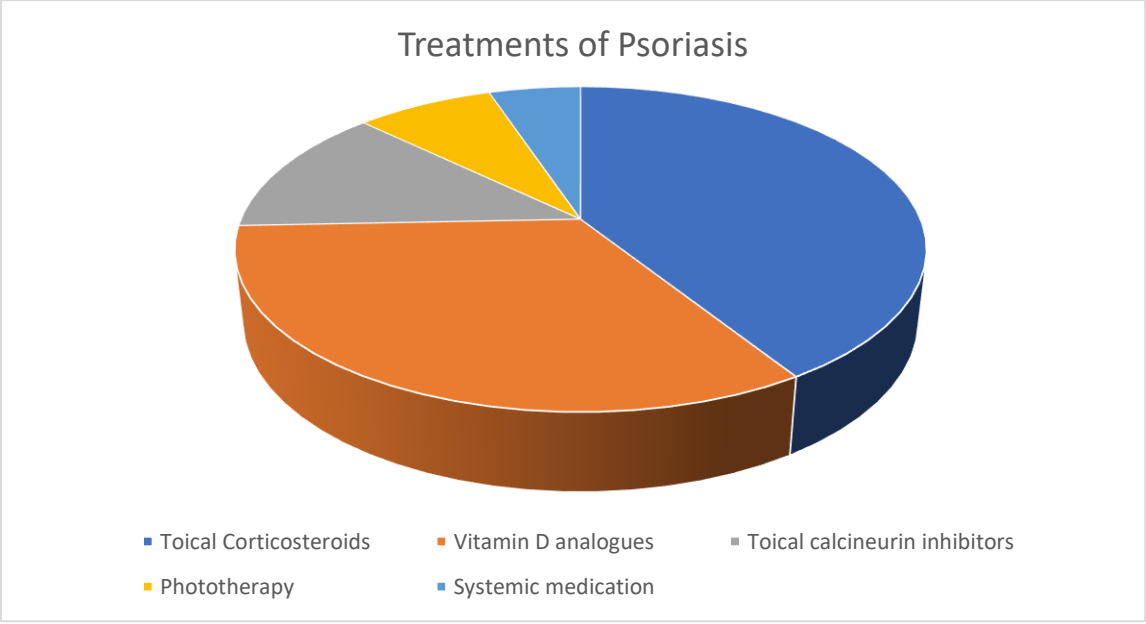
medications that act promptly

Because erythrodermic psoriatic patients also have systemic symptoms, their therapy differs from that of typical psoriatic patients. Sepsis is a known cause of erythrodermic psoriasis, so it is important to rule it out.[55]

It is advised to use systemic drugs with a rapid onset, like oral cyclosporine. The quick start of infliximab has also been said to be advantageous.[55]

SUMMARY

With its vast range of clinical manifestations and related comorbidities, psoriasis continues to pose a serious threat to global health, affecting millions of people worldwide. This review covered the delicate relationship between immunological dysregulation, environmental factors, and genetic predisposition in the etiology of this chronic inflammatory skin disease. Significant progress in comprehending the illness mechanisms has resulted in the creation of numerous efficacious therapy approaches, even though a full cure is still elusive. Clinicians have a variety of methods to treat milder types of the disease, ranging from phototherapy and conventional systemic medicines like methotrexate and cyclosporine to standard topical medications like corticosteroids and vitamin D analogs. The therapy of moderate-to-severe psoriasis has been transformed by the introduction of biologic medicines that target particular immune pathways, such as TNF-α, IL-17, IL-12/23, and IL-23. For many patients, these therapies have improved efficacy and safety profiles. Furthermore, the significance of treating related comorbidities, such as psoriatic arthritis, cardiovascular disease, metabolic syndrome, and mental health disorders, using a multidisciplinary approach has been highlighted by the growing knowledge of psoriasis as a systemic illness. Not with standing these developments, there are still issues with treatment accessibility and cost, biologics' long-term safety, and the requirement for individualized treatment plans based on patient traits and disease phenotypes. Future studies that concentrate on finding new therapeutic targets, creating more individualized and targeted treatments, and advancing early detection and prevention techniques have the potential to improve patient outcomes and, eventually, the quality of life for those who have psoriasis.



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