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COMPARISON OF RELAPSE RATES IN SYSTEMIC PSORIATIC TREATMENTS

Bhuvaneswari Sapavathu[1]*, Jeffrey B. Travers and Craig A. Rohan

[1]Graduate Student, [2]Dermatologist, Professor and Chair, [3]Dermatologist and Assistant Professor

Department of Pharmacology and Toxicology, Boonshoft School of Medicine at Wright State University, Dayton, Ohio.

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***Corresponding Author**
Dr. Bhuvaneswari Sapavathu
Graduate Student, Department of Pharmacology and Toxicology, Boonshoft School Of Medicine at Wright State University, Dayton, Ohio.

ABSTRACT

Psoriasis is an autoimmune skin disease which affects approximately 100 million people worldwide. The treatment of psoriasis has been revolutionized using biologic medications which target key pathologic cytokines. Though effective, lapses in all types of therapies can often result in skin disease relapse. In this review, data is presented comparing the time of relapse following stopping of common psoriatic therapies. Findings from the literature indicate that the therapeutics which target IL-23 has been associated to the longest period of relapse. The likely mechanisms for time of relapse including half-life of the drug are addressed. Finally, potential interventions that can modulate the time of therapeutic relapse including topical agents as well as oral vitamin D are discussed. An enhanced understanding of the time of relapse of therapeutics used for psoriasis as well as strategies to extend the relapse can result in improved treatments for people suffering with psoriasis.

KEYWORDS: psoriasis, relapse, autoimmune, proinflammatory cytokine, IL-23, PGA, PASI, remission.

INTRODUCTION

Psoriasis is a consistently reoccurring, autoimmune skin condition, that causes scaly plaques on the skin as shown in the fig: 1, most frequently on the knees, elbows, trunk, and scalp. As per the World Health Organization (WHO) reports, it affects approximately 100 million

people worldwide. Plaque psoriasis is the most common form of psoriasis, affecting roughly 85% of people. Psoriasis can happen because of proinflammatory cytokine activation, which has a significant impact in disease severity,[2] this activation can be caused by genetic factors as well as environmental stressors such as alcohol consumption, cigarette smoking, medications, infections, and hormonal changes.[1] Diagnosis can be done based on physical findings and biopsy.[2] Compared to the past two decades, treatment of psoriasis has greatly improved. Oral, topical & systemic agents were introduced with the goal of 50% reduction in Psoriasis Area and Severity Index (PASI50) at baseline.[3] and Biologics are recommended as first-line treatment for moderate to severe plaque psoriasis, according to National Psoriasis Foundation standards.[29]

Additionally, modifications in therapeutic approaches brought on by toxicity worries, particularly with regards to conventional medicines, might lead to recurrent cycles of remission and relapse.[4]

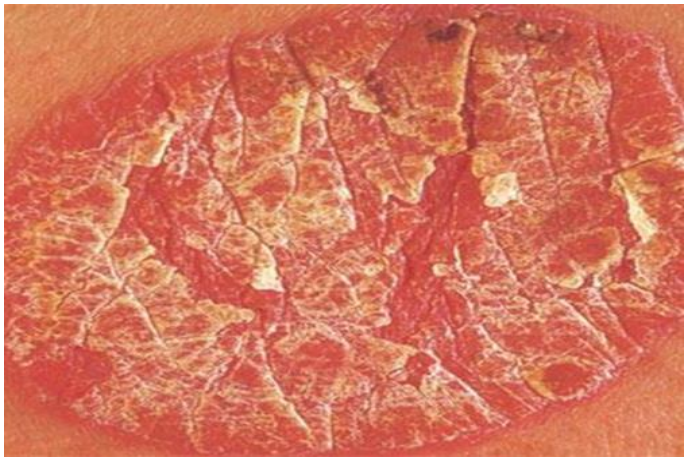

Figure 1: Plaque Psoriasis in its typical form; Source: Dr. Rohan.

Types of psoriasis

Only one form of psoriasis can occur at a time, based on the locations and clinical manifestation psoriasis can be classified as below

Plaque psoriasis: Psoriasis vulgaris, the most common kind, can cause irritated skin and scaly, silvery plaques with a visible boundary.[28]

Guttate psoriasis: Seen in 2% of the patients, can cause pink-red spots on skin. Children and adolescents are more susceptible to this form of psoriasis.[5]

Pustular psoriasis: The least common type of psoriasis, usually occurs in adults, causes pus-filled bumps surrounded by red skin, may look infectious, but they are not.

Inverse psoriasis: It is also known as intertriginous psoriasis and can appear in skin folds such as armpits and under the breasts. Candida species, fungal, and bacterial infections can all cause this.5

Erythrodermic psoriasis: The least common, but it is a very serious type of psoriasis that affects most of the body and causes widespread, fiery skin that appears to be burned.

Nail psoriasis: Most common in persons with psoriatic arthritis, which damages the joints.

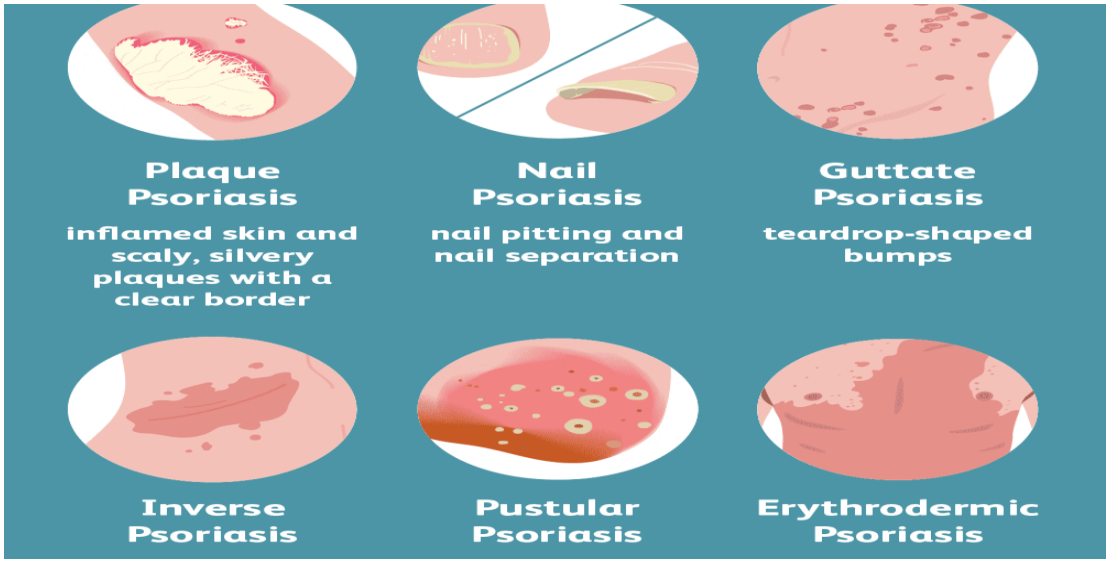

Figure 2: Psoriasis Subtypes and Their clinical presentation. [5]

Pathogenesis

Psoriasis is a complex illness that is thought to be caused by a mix of genetic, environmental, and immune system factors. T-lymphocytes, dendritic cells, keratinocytes, neutrophils, and proinflammatory cytokines are among the immune system components that cause the illness.

Disrupted interaction between immune system components triggers the activation of proinflammatory cytokines, including TNF-alpha. Subsequently, these cytokines activate dendritic cells, which in turn activate Th17 and Th1 at immune axes, as depicted in Figure 3. The activation of these immune cells stimulates the release of IL-17, resulting in increased keratinocyte activation and proliferation. Ultimately, this leads to the development of psoriatic plaques.[6]

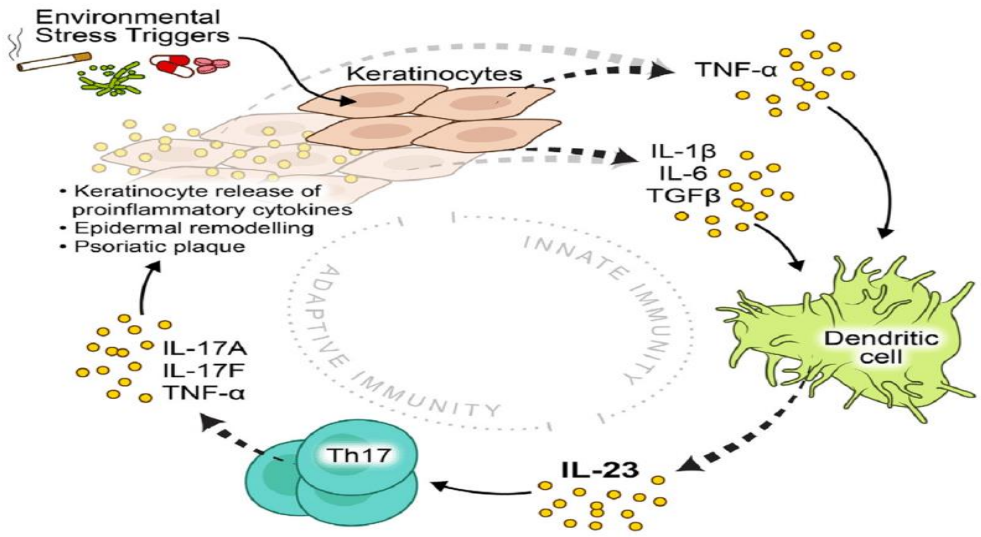

Figure 3: The inflammatory cascade in psoriasis; Source: Dr. Travers.

Another important feature of psoriasis pathophysiology is the creation of new blood vessels, commonly known as angiogenesis. This is due to an increase in the production of VEGF, which is stimulated by pro-inflammatory cytokines. New blood vessel growth contributes to the red, inflammatory appearance of psoriasis lesions.[7]

The critical cytokines implicated in psoriasis pathogenesis include TNF-alpha, IL-23, and IL-17.[27] These small proteins are integral in immune system communication and stimulation by facilitating cell signaling.

TNF-alpha is produced by immune cells such as macrophages, dendritic cells, and T cells. It plays a crucial role in attacking foreign invaders by stimulating immune cells. Yet, excessive TNF-alpha production can result in tissue damage and persistent inflammation.

Dendritic cells and other immune cells produce the cytokine IL-23 (interleukin-23) in response to an infection or inflammation. It promotes the activation of T cells involved in the immunological response and the generation of other pro-inflammatory cytokines such as IL-17. IL-23 is thought to have a key role in the initiation and maintenance of psoriasis by enhancing the proliferation and activation of immune cells in the skin.

Psoriasis assessment tools

Psoriasis Area and Severity Index (PASI) and Physician Global evaluation (PGA) are two commonly used evaluation techniques for determining the severity of psoriasis.

Psoriasis Area and Severity Index (PASI) Although it has certain drawbacks, it is often recognized as the gold standard for assessing psoriasis severity. One criticism is that PASI can be difficult to utilize and interpret. This index is based on the evaluation of three key plaque features, namely erythema (redness), thickness, and scaling, as illustrated in Figure 4.

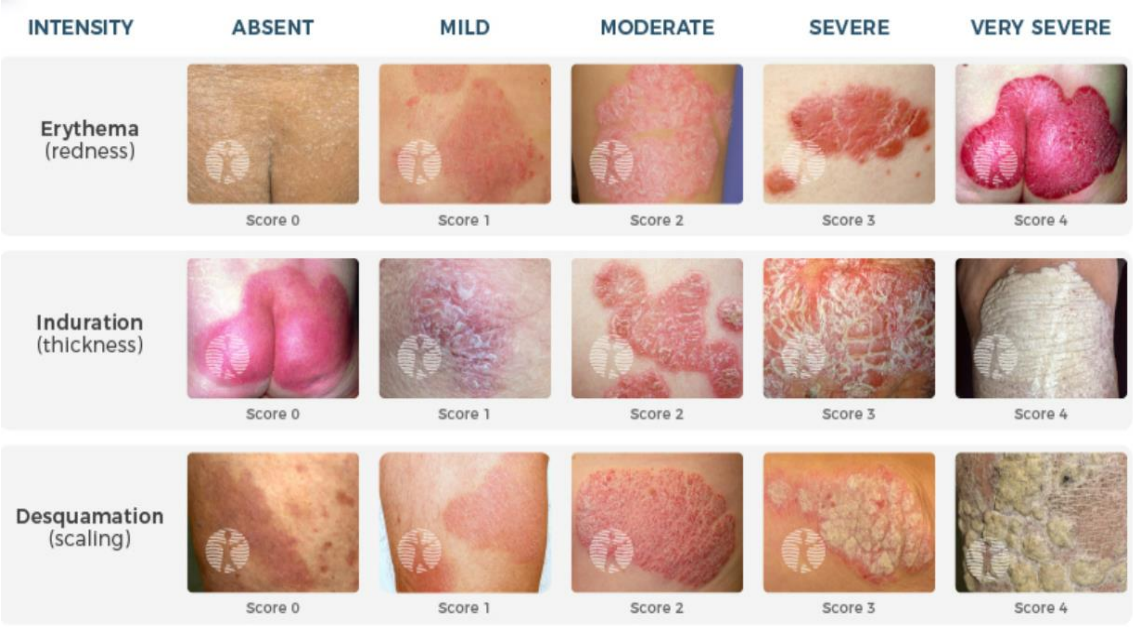

Figure 4: PASI Score to monitor psoriasis progression.[8] Scoring ranges from 0 to 4 depending on how severe the redness, thickness, and scaling of the psoriatic plaques are. Score 0 indicates a normal condition, whereas score 4 indicates a serious condition.

The use of PASI alone as an effective endpoint for psoriasis therapies is not appropriate, according to the US Food and Drug Administration (FDA). Instead, a fixed Physician Global Assessment (PGA) is used.[8]

Physician Global Assessment (PGA) used to evaluate solely the plaque qualities because they average the body's erythema, induration, and desquamation levels because the majority of PGA instruments do not account Body Surface Area (BSA), they cannot provide an overall assessment of psoriasis severity.[8]

Treatment

Psoriasis therapy has evolved over time, and it was formerly assumed to be largely treated as a cosmetic skin condition. As a result, patients are frequently given the choice of their own treatment. Under treatment has frequently been a result of ignorance regarding the nature of

the illness, its pathophysiology, and the systemic inflammation that affects more than just the skin.[9]

Psoralens, topical and systemic corticosteroids, sulfur, tar, arsenic, salicylic acid, X-ray, anthralin, UV radiation, and later methotrexate, retinoids, cyclosporine, and calcipotriol have all been used in traditional psoriasis treatment. Although many individuals have benefited from these medications, there is a lack of anti-psoriatic activity and treatment efficacy.[9]

Biologics are recommended as first-line treatment for moderate to severe plaque psoriasis, according to American Academy of Dermatology-National Psoriasis Foundation guidelines.[30]

Some other medications that are involved to treat psoriasis include.
Oral: methotrexate, acitretin, cyclosporine and apremilast.
TNF-α inhibitors: etanercept, adalimumab.
Other biologics inhibit cytokines: IL-12/IL-23 (ustekinumab), IL-17 (secukinumab, Ixekizumab), IL-23 (guselkumab, risankizumab) and IL-36 inhibitors.
Light therapy: narrowband UV-B phototherapy.

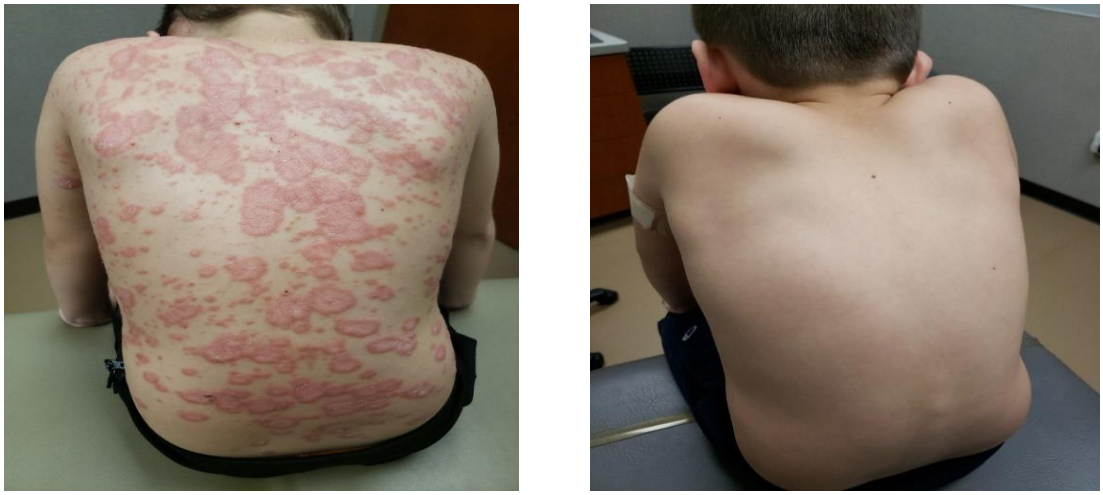

Figure 5: Before and after pictures of patient treated with Ixekizumab; Source: Dr. Rohan

Time of relapse

In general, a psoriasis relapse refers to the return of psoriatic symptoms in a specific individual following the improvement of the psoriasis condition, also known as remission of the illness. Psoriasis relapse is defined by the National Psoriasis Foundation Medical Advisory Board as a 50% deterioration from baseline.[10]

As a result, the time to relapse can be defined as the duration of time following the discontinuation of medication until patients experience a 50% worsening from baseline or reach PGA≥3.[11]

Mechanism of relapse in psoriasis

Psoriasis relapse can be caused by a variety of causes, including seasonal changes, stress, medications, alcohol, and cigarette smoking. However, there is no known cure for psoriasis with currently available drugs, recurring cycles of remission and relapse may also happen because of changes in treatment strategies, particularly with older therapies. Relapse occurs as a result of discontinuing psoriatic disease treatment.[10]

Remission normally lasts between one to twelve months after standard medicines are discontinued, however this can vary depending on the disease's natural course.[10]

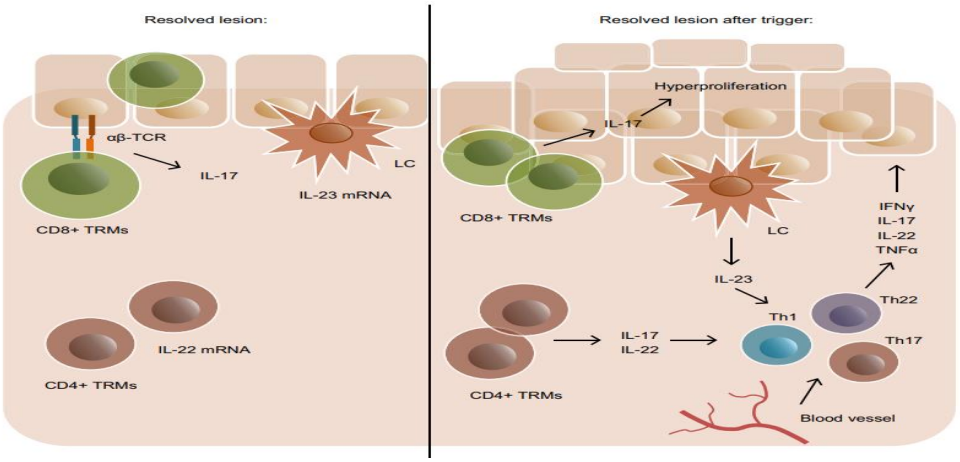

Figure 6: Mechanism of psoriasis recurrence. *[25]*

CD8+TRM (resident memory T cells) and T cells are responsible for the recurrence of psoriatic symptoms. Though the mechanism is not fully understood, according to some studies they may cause inflammation and damage to the tissue which can result psoriatic plaques.[11]

Unlike all T cells that circulate in blood, these resident memory T cells will retain in tissue and respond quickly to pathogen re-infection and produce cytokines. After resolution of inflammation, $CD8^{+}T_{RM}$ and γδT cells remain in resolved skin. Triggers reactivates gene expression in epithelial stem cells (EpSCs), CD8+TRM and γδT cells to produce IL-17A and

other inflammatory cytokines, thus reinitiating inflammation in the skin and triggering psoriasis relapse.

Relapse comparison between Biologics and Oral drugs

The need for long-term maintenance therapy is necessary to prevent the recurrence of psoriatic symptoms. Relapse rates can vary from person to person; some people may experience early relapses while others may not experience any until years after stopping medication.[12]

Biological agents treated as first line choice for psoriasis as they have excellent disease control and have After more than 5 years of treatment, there was no significant increase in major infections, cancer, or mortality. Although discontinued biological treatment can cause relapse, but it is still considered as a first line treatment due to the number of reasons like less burden of therapy, unaffordable medical expenses, the development of adverse events, and particular situations like pregnancy.[13]

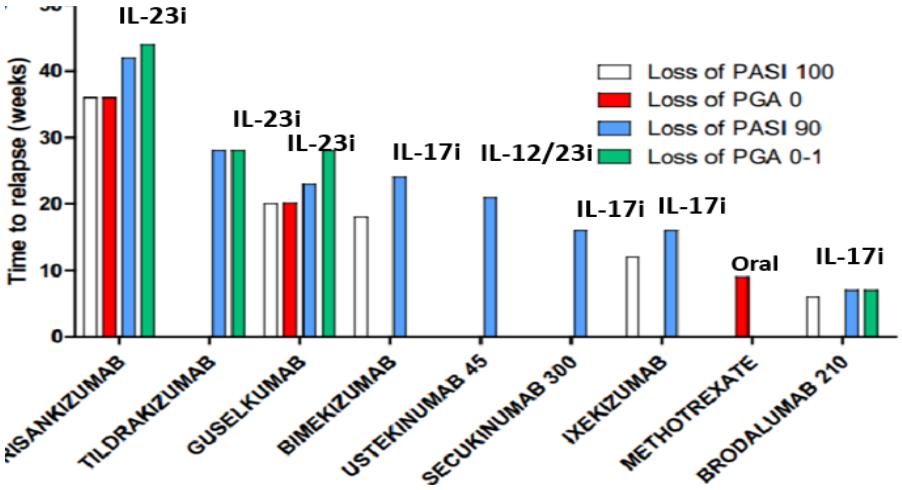

Figure 7: Relapse Rates-Biologicals Vs Orals. [13]

For systemic oral agents like methotrexate (in general it acts as an anti-metabolite, it is most frequently used in cancers and in autoimmune diseases which acts as an immunosuppressant) and cyclosporine It took an average of 4 weeks to lose 50% of the maximal PASI improvement, and according to the above graph comparison to oral systemic treatment, observed a prolonged period of sustained reaction after biological agent withdrawal.

In addition, compared to IL-17 and TNF antagonists, therapy with IL-12/23 and IL-23 antagonists resulted in a longer time to relapse in fig: 7. It's unknown whether stopping after a long period of remission will yield the same outcomes.[13]

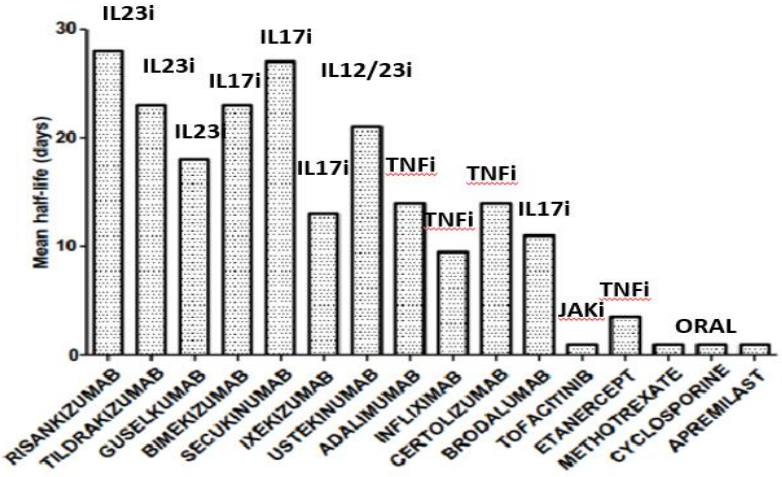

Figure 8: Impact of drugs half-life on relapse rates.[13]

According to pharmacokinetic studies, the sustained response after the average drug half-lives appears to be slightly associated with drug cessation. The drugs with the longest half-lives had the longest time to relapse. The discrepancy in efficacy maintenance between drugs cannot be explained solely by drug half-lives. Additional factors, such as the psoriasis inflammatory cascade's molecular target and site of action, may also play a role.[13]

In Fig: 8 risankizumab (IL23i) has the longest elimination half-life when compared to other drugs, hence it has the longest time of relapse in psoriasis patients.

In 2021, IL-36 inhibitors like bimekizumab received FDA approval in use for severe plaque psoriasis. IL-36 cytokines belong to IL-1 family responsible for homeostasis, they control the innate immune system, and when they are overexpressed and activated, it can lead to pathological inflammatory reactions. There are not many studies on relapse rates for bimekizumab but recently got approval in use of pustular psoriasis.[14]

Potential strategies to enhance the time of relapse

Although psoriasis has no cure, it can be controlled with available treatment options. However, there are some potential mechanisms to enhance time of relapse in psoriasis like.

Lifestyle modifications

There are many studies on altering in lifestyle modifications can be one of the causes of occurring psoriasis, most of the research has demonstrated that obesity and dietary habits play important roles in the etiology of the condition, can cause, or worsen psoriasis symptoms, and can affect how well a treatment works. Moreover, several drugs (lithium, betablockers, synthetic antimalarials, and non-steroidal anti-inflammatory drugs) may act as psoriasis triggers. Skin lesions could become worse because of psychological conditions like depression. It's also important to remember that altered microbiota and protracted infections are thought to be risk factors for the onset of psoriasis. It is hard to emphasize the need of educating patients on good dietary behaviors, nutrition, weight loss, and a healthy lifestyle throughout therapy because these aspects affect the prevalence, severity, and progression of psoriasis.[22]

Combinational therapy

Although monotherapy with topical therapy, phototherapy, traditional systemic medicines, or biologics can be useful for many individuals, other patients continue to have insufficient response even at authorized levels. Although increasing the dosage of monotherapy on a regular basis is one management strategy, it may be limited by concerns about compounded toxicity and cost. The severity of the disease, previous treatment, existing comorbidities, and adverse effects all influence the selection of combination therapy. In properly selected individuals, well-planned combinations may result in improved efficacy while avoiding risk.[19]

Certain monotherapies, such as methotrexate, can have dose-related adverse effects such as bone marrow suppression, immunosuppression, and liver damage. High-dose phototherapy is associated with an increased risk of burning, and long-term use is associated with an increased risk of skin cancer, particularly with UV-A exposure.[19]

Combining oral or biological agents with topical treatment like vitamin D analogs, steroids, Tapinarof and phototherapy can reduce the adverse effects that are caused due to systemic treatment. Topical vitamin D can be considered as first line therapy for mild to moderate psoriasis as they inhibit keratinocytes proliferation into the cells reducing IL-8 production. Topical vitamin D analogs, such as calcipotriol, cause less skin irritation than other forms of analogs, making it the most commonly used topical medicine for sensitive skin diseases such as psoriasis.[15]

Because of their immunosuppressive function, topical corticosteroids can reduce the negative effects of vitamin D analogs such as skin irritation.[16] Though topical corticosteroids are far more effective than topical vitamin D, they can cause tachyphylaxis, which is a prominent side effect of this class of medications. It is therefore preferable to use topical corticosteroids in conjunction with other drugs.[15] Some studies, however, suggest that using topical corticosteroids in conjunction with topical vitamin D can reduce psoriatic symptoms by 84%.[17]

Table 1: Topical treatments in patient with psoriasis.[15] This table contains a list of drugs that can be applied topically to treat psoriasis, as well as their Efficacy and Adverse effects.

Drugs	Advantages	Disadvantages
Vitamin D analogs (calcipotriol)	Effective	Short duration of remission necessitates constant treatment. Irritant, hypercalcemia.
Corticosteroids	Effective	Short duration of remission. Risk of cutaneous atrophy and rebound of psoriasis on discontinuation. myelosuppression, alopecia,teratogenic.
Dithranol (anthralin	Effective	Dithranol stains skin, clothing and skin Irritation.
Tar (crude coal tar)	Effective	long contact time required. Irritation, unpleasant odor, folliculitis, possible carcinogen.
Retinoids (tazarotene)	Effective	Irritant, teratogenic, Pruritis.
Calcineurin inhibitors (tacrolimus)	Effective only on thin plaques (face and flexures)	Should not be used with phototherapy or sun exposure. transient burning sensation

Apart from this, there are some novel medications in the psoriasis treatment pipeline, such as topical treatments like tapinarof and roflumilast, which according to the studies suggested that they may have a significant influence on psoriasis therapy.[18]

Phototherapy

Phototherapy can be combined with biological and oral agents and is a recommended treatment option for patients who are not responding to monotherapy of biological agents or topical treatment in psoriasis. According to studies, the combination of biologics with phototherapy has greater efficacy than monotherapy alone.[19]

Combining NB-UVB with etanercept (ETN) enhanced efficacy in patients with moderate to severe psoriasis, according to observational research. It was also shown that this combination lowered the length of ETN usage, resulting in a lower burden on treatment costs.[20]

There is insufficient information accessible in the event of a relapse, even though all existing psoriasis treatment options are the fastest and most effective during remission.[21]

Future perspectives

Precision medicine is one of the most intriguing areas of research in psoriasis. This can tailor's treatment to the individual patient based on their unique genetic and environmental characteristics. With improvements in genetics and biomarker studies, it is now possible to identify individuals who are likely to respond to specific treatments and prevent unneeded medications or therapies that may be useless, by this we can minimize the risk of adverse effects with various treatment options.[23] Although genuinely personalized medicine in psoriasis treatment is not yet practicable, a tiered approach to therapy selection may offer a solution. One of the difficulties in establishing a consistent strategy to classify patients in a way that can predict reactions to different therapies is the difficulty in assessing response to therapy.[26]

Nonetheless, it is expected that a more complete and accurate understanding of the molecular and clinical data in psoriasis may give potential for precision medicine to enhance patient outcomes and reduce disease burden.[24]

CONCLUSIONS

Relapses are common with psoriasis, and maintenance medication may be required. Observational research found that remission lasted from 2 weeks to 9 years, with 4% of patients never experiencing any remission. Patients who got cyclosporine had a relapse within six months after ceasing their medicine, whereas methotrexate patients had a higher likelihood of relapse when abrupt medication discontinuation was employed instead of a low dose. After 5 months, ixekizumab relapsed, whereas etanercept relapsed 6 months after treatment was terminated. However, other factors, such as the molecular target and site of action in psoriasis inflammation, play a significant part in this cascade.

This therapy withdrawal may be induced by life events such as pregnancy or concomitant disease, as well as to reduce treatment burden or expenditures. According to the compression, most biological agents have a longer time to relapse than oral systemic drugs. Risankizumab (IL23i) has the longest time to relapse among biologicals, but apremilast (PDE4 inhibitor) has the shortest time to relapse in psoriasis.

Disclosure statement

ACKNOWLEDGMENTS

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