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Newly discovered biologic agent used for psoriasis treatment

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Abstract---Psoriasis is an autoimmune inflammatory skin disorder that affects 2–3% of the world's population. It has distinct features, such as accelerated keratinocyte proliferation and proinflammatory cytokines secretion. Topical, systemic, phototherapy, and biologic therapies are used in the treatment. Topical therapies are preferred over systemic medicines for mild to moderate psoriasis. Systemic therapies are best for severe pathological conditions. Immunosuppressants, biological agents, and recently licensed phosphodiesterase-4 (PDE4) inhibitors are some of the systemic therapies. Present therapies have a lot of drawbacks, and new discoveries in the pathogenesis of psoriasis are opening the way for novel therapeutics that target the disease at the molecular level. Multiple small molecules, PDE-4 inhibitors, biologics, and immunomodulators, as well as newly discovered Janus kinases (JAK) inhibitors, were found to be effective. This article focuses on many emerging treatments as well as presently approved psoriasis medications.

Keywords---psoriasis, traditional therapy and biologic agents, interleukin, tumour necrosis factor-α.

Introduction

Psoriasis is an inflammatory skin disease characterised by silver scaly plaques and skin sores. Psoriasis affects around 1.5-2.0 of the global population.[1] Males are affected two times more than females in India, with a prevalence of 0.44-2.8%.[2] Psoriasis has a significant impact on the patient's lifestyle, causing significant mental, physical, and social distress.[3] The skin's life cycle is decreased to 1.5–3 days in psoriasis, compared to 30 days in normal skin. Psoriasis diseases typically affect the skin and nails. It also encompasses psoriasis arthritis, diabetes, obesity, cardiovascular disease, and metabolic syndrome, among other comorbidities. Because it is caused by a T-cell mediated reaction, it is also known as T-cell mediated autoimmune condition .[4]

Pathophysiology

Although the actual cause of psoriasis is unknown, various factors such as genetic susceptibility, environmental factors, and immune system dysregulation have been suggested as possible causes . Psoriasis is a type of autoimmune disease that is brought on by the activation of the cellular immune system. Dendritic cells, T cells, macrophages, and keratinocytes have all been implicated in the treatment of psoriasis in recent investigations. T-cells, which are found in the immune system, are triggered by a variety of stimuli and subsequently accumulate in the skin and other organs that are impacted. In addition, keratinocytes are stimulated, releasing a variety of chemical mediators such as chemokines and inflammatory cascades. The lesion skin contained Th17 cells that released cytokines such as IL-22 and IL-17 cross-talking with the IL-23/IL-12 axis in his initial flare. Dendritic cells travel between the adaptive and innate immune systems. Which could cause a psoriatic lesion to worsen . [5] Targeted immunotherapy and PUVA (ultra violet) therapy are two methods that can lower the number of dendritic cells.

Triggered dendritic cells secrete cytokine mediators such as IL-23 and IL-12 and operate as antigen-presenting cells. In epithelial immune surveillance, Th-17 cells play a key role .[6] Th-17 cells that have been activated produce cytokines such as IL-17F, IL-17, and IL-17A. Mast cells, innate lymphoid cells, and other T-lymphocytes such as CD8 positive Tc 17 cells and gamma-delta T-cells all produce IL-17. TNF-alpha and IFN-gamma activate keratinocytes in the Th-17 route. While IL-17A, IL-17F, and IL-22 activate TNF-alpha and IFN-gamma in the Th1 pathway. These pathways control keratinocyte proliferation and the production of cytokines, antimicrobial peptides, and chemokines. The inflammatory process is aided by a positive feedback loop that attracts other natural and suitable immune cells. Inflammatory cascades operate as angiogenesis activators and also increase endothelial adhesion molecules, which may drive immune cell migration into psoriatic lesions . [7]

Treatment strategies for management of psoriasis

Due to unknown etiology, psoriasis is not a curable ailment, but it can be treated with a variety of medicines to alleviate the signs and symptoms. The following alternative treatments are used to treat the diseases i.e. topical therapies,

systemic therapies, phototherapy, and biologics application .[8] Topical therapy is most effective for the treatment of moderate psoriasis (body affected area less than 10%). Systemic medication, such as PDE-4, biological agents, and immunosuppressants inhibitors, are more effective in the treatment of psoriasis in moderate to severe disease conditions. Vitamin D3 analogues, corticosteroids, calcineurin inhibitors, and retinoids, among other topical treatments, could be used to treat psoriasis. Adjuvant phototherapy, such as narrow band ultraviolet B, broadband ultraviolet B, and psoralen plus ultraviolet, is combined with topical therapy in cases of severe psoriasis. Immunomodulators (cyclosporine), retinoids (acitretin), and other drugs such as methotrexate and fumaric acid esters are examples of traditional systemic therapy . [9]

Topical Therapy

Topical therapy can be used on the skin to target immune cells, keratinocytes, and irritation. The numerous topical treatments agents listed in Table 1 can be used to treat the skin lesion in psoriasis. Long-term usage of corticosteroids can lead to adverse effects in the skin, such as irritation and atrophy. Combination therapy may be preferred if monotherapy is not found to be more effective. To address these issues, a combination of two or more topical medicines can be used to improve effectiveness and lessen the reaction .[10] Dovobet®, a combination of betamethasone and calcipotriol, showed improved efficacy, less skin irritation, and a faster onset of action. In addition, a novel topical medicine, Icotinib hydrochloride cream, is in clinical phase II for the treatment of mild to moderate psoriasis. Furthermore, ARQ-151 cream 0.15%, and ARQ-151 cream 0.5% are also below phase I/II clinical studies. Moreover, a combination of Halobetasol and Tazarotene (IDP118) lotion for plaque psoriasis (NCT02462122) is in phase III clinical trial. Additionally, Calcipotriol and niacinamide cream's combination has recently passed clinical phase trail II .[11] All of these clinical investigations found that combination therapy is more effective than single-drug therapy.

Biological Therapeutics

Biological agents differ from conventional systemic therapy in that they can specifically target immune mediators involved in a pathophysiologic process. These drugs can be used to treat psoriasis by inhibiting the action of a kind of immune cell known as a T-cell. It may also inhibit proteins such tumour necrosis factor alpha (TNF-) and interleukin (IL) 12,17,23. These proteins play a key role in the development of inflammation and psoriasis symptoms. The first biologics, Alefacept and Efalizumab, were approved by the US Food and Drug Administration (US FDA) in 2003. Although these biologics were taken off the market in 2011 and 2009, respectively, due to post-marketing safety concerns. Biological medicines are classed as TNF-inhibitors, IL-23 and IL-12 inhibitors, IL-23 inhibitors, IL-17 inhibitors, and T-Cell Inhibitors based on the targets and inhibitory activity of inflammatory mediators .[12]

TNF-α inhibitors

TNF-alpha production is increased in the skin in psoriasis and other psoriatic disorders. This causes skin tissue to proliferate at a rapid rate. Blocking TNF-

alpha production can stop the inflammatory cascade that causes psoriasis. Certolizumab pegol, Etanercept, Adalimumab, and Infliximab are some of the biologics utilised to block TNF-α.

- **Certolizumab pegol**- It is also known as CIMZIA, is a humanised fab antibody fragment conjugated to a PEG that inhibits TNF-alpha. It is administered by injection through the subcutaneous method and received FDA approval in 2008 .[13]
- **Etanercept**- Etanercepts brand name is Enbrel. It is a biological therapeutic product which is used to treat autoimmune disorders with interfering with TNF. Etanercept reduces the effect of TNF or work as a TNF inhibitor. FDA give approval in 2004.[14]
- **Adalimumab-** Humira is the brand name for adalimumab. It also has anti-TNF properties. In April 2004, adalimumab was approved for the treatment of plaque psoriasis. It is administered subcutaneously, and FDA approval was granted in 2002.[15]
- **Infliximab**- Emicade is another brand name for infliximab. It binds to TNF-alpha and neutralises it. Subcutaneous administration of infliximab is used and was approved by the FDA in 2006.[16]

IL-23 and IL-12 Inhibitors

It is a biological drug that suppresses the production of IL-23 and IL-12 by specifically targeting proteins/cytokines. Psoriatic inflammation is linked to IL12/23. Tildrakizumab and Risankizumab are IL-23 inhibitors that are used to reduce the symptoms and progression of psoriasis illness.

- **Tildrakizumab-** It is marketed under the brand name Iiumya. It's a monoclonal antibody that's used to treat immunologically-mediated diseases. It inhibits the IL-23 receptor and received FDA approval in 2018.[17]
- **Risankizumab**- Skyrizi is the brand name for the drug Risankizumab. It acts as an IL-23 inhibitor and is administered subcutaneously. Risankizumab is still in clinical phase III and is expected to be approved by the FDA in 2019 .[18]

IL-17 inhibitors

he USFDA recently approved Secukinumab (2015), Ixekizumab (2016), and Brodalumab (2017) Guselkumab, among other biological medicines. These drugs work as inhibitors, preventing the generation of IL-17, which is linked to inflammation in psoriasis.

- **Secukinumab** – Cosentyx is the brand name for Secukinumab. It binds to IL-17A and is utilised in the treatment of psoriasis. Secukinumab is a subcutaneous immunoglobulin that was approved by the FDA in 2015.[19]
- **Ixekizumab** – Ixekizumab acts as binding IL-17A and neutralizing. It gives via subcutaneous route by injection and gets FDA approval in 2006.[20]

T-Cell Inhibitors

T-cells in the immunological system are marked by Abatacept. T-cells are a type of white blood cell that is involved in the irritation process. As a result, Abatacept can reduce inflammation by preventing T-cell stimulation. Table 1 summarizes some new biologics and topical therapies for the treatment of psoriasis. Furthermore, biosimilar medications can be used to treat psoriasis. It is a sort of biological agent that can be given as an injection. The USFDA recently approved Inflectra (2016), Renflexis (2017), and Erelzi as biosimilars for the treatment of psoriasis (2017). Biologics are a type of advanced therapy used to treat psoriasis. They work by suppressing the immune system's overactive reaction. Aside from these advantages, long-term use of biologics may cause immune system tolerance and an increased risk of infection. Furthermore, the high cost, parenteral delivery route, and inter-subject heterogeneity in response are key tests for biologics as the best psoriasis treatment options. Figure 1 depicts the mechanism of biologics and their inhibitory effects.

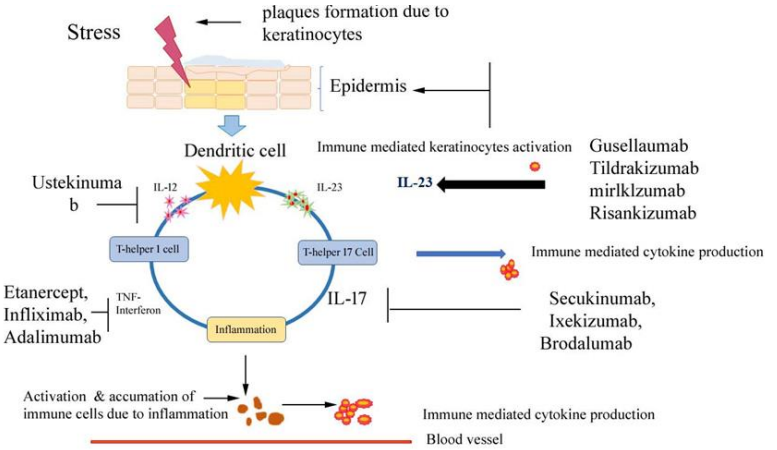

Fig.1: Mechanism and Inhibitory effects of biologics

Small molecular therapy

Small molecules treatment has recently been employed as an advanced therapy for psoriasis, and it has the potential to play a key role in preventing irritation. Apremilast, a phosphodiesterase 4 (PDE-4) inhibitor intended to treat psoriasis inflammation, is one of the newest medications in systemic psoriasis therapy .[21] Phosphodiesterase-4 degrades cAMP and converts it to 5'AMP. The specific inhibition of PDE-4 raises the amount of cAMP and has anti-inflammatory effects. Furthermore, because cAMP is a vasoconstrictor, it lowers blood flow at the site of inflammation, reducing macrophage accretion. Crisaborole, an approved atopic dermatitis therapy, is another PDE-4 inhibitor. It is still undergoing phase II clinical trials and is particularly effective in the treatment of psoriasis .[22]

Furthermore, numerous other immunosuppressant classes (JAK inhibitors) are being investigated for use as oral treatment. JAK receptors are found mostly in lymphocytes and play an important role in wave transmission. JAK receptors bind to cytokines and activate JAK via autophosphorylation in this method. Immune

activation causes STAT to be phosphorylated by signal transmission, resulting in dimerization of transcription and translocation into the nucleus to regulate gene expression and nucleus.[23] Various medicines, such as Baricitinib, Tofacitinib, and Ruxolitinib, act on the Janus kinases receptor and inhibit the provocative mediator, making them a safer target for psoriasis treatment.

Constraint and prospects of current treatments in psoriasis

Topical therapies are frequently used for the management of psoriasis, but it is having various adverse effects such as skin irritation, wasting and skin cancer due to phototherapy. The strategy of adjoining two or more therapeutic agents with nanocarriers might be improved the effectiveness of active constituents, due to improve permeation of nano formulations via scaly plaques are diminishes the negative effects related with standard treatment. Immunosuppressants are effective in the treatment of normal to serious psoriasis condition and they are also a type of oral medicine agent. Currently the biologics are the future of oral medicinal agents which have very high therapeutic ability to treat serious condition of disease Merely the biologics are good oral medicine which may reduce disease seriousness in large amount. End of biological therapies topical agents are best agent in severe psoriasis condition. Novel studies in tropical medicine drugs such as ARQ-151 cream, PDE-4 inhibitors, and novel mixture of present medicinal drugs may additionally enhance the topical treatment strategy in normal to serious psoriasis condition.

Table 1
Some new biologics and topical therapeutics used for the treatment of psoriasis

Drugs	Other name	Administration route	Molecular targets and mechanism of action	Clinical status	Year
Anthralin	Dithrocream	Topical	Decreases keratinocyte proliferation, prevents T-cell activation	-	-
Tacrolimus and Pimecrolimus	Prograf	Topical	Calcineurin inhibitors, Prohibit the action of calcineurin phosphatase and also inhibits activation of T cells and restrict the production of inflammatory mediator's	Approved	2006
Vitamin D3 Analogs	Calcipotriene Calcitriol	Topical	Normalizes the genes in epidermal proliferation inflammation.	Approved	-
Topical Corticosteroids	Gluco-corticosteroids &	Topical	Antiproliferative, anti-inflammatory, and	Approved	

	cortisone		immunosuppressive		
Retinoid	Tazarotene	Topical	Selectively binds to beta and gamma retinoic acid with the cell membrane of keratinocytes and altering transcription of genes in keratinocytes	approved	2015
Icotinib hydrochloride cream	Conmana	Topical	Icotinib is a quinazoline derivatives that competitively inhibits the ATP binding site of the EGFR receptor protein.	Clinical Phase II	2015
ARQ-151 cream 0.5%,	Roflumilast	Topical	Type 4 cyclic nucleotide phosphodiesterase inhibitors	Clinical Phase II	2021
IDP-118	Tazarotene	Topical	Retinoids X receptors agonists Steroid receptor agonists	Clinical Phase III	2020
AN2728	Crisaborole	Topical	PDE4 inhibitor	Clinical Phase III	2020
AS101		Topical	Integrin inhibitor	Clinical phase II	
Tofacitinib	Xeljanz	Topical	JAK inhibitor	Clinical Phase II	2017
Ruxolitinib	Jakafi	Topical	JAK inhibitor	Clinical Phase II	2021
Crisaborole	Eucrisa	Topical	PDE4 inhibitor	Clinical Phase IV	2016
Certolizumab pegol	Cimzia	Subcutaneous	TNF-Alfa inhibitor	Approved	2008
Secukinumab	Cosentyx	Subcutaneous	IL-17 inhibitor	Approved	2015
Etanercept	Enbrel	Subcutaneous	TNF inhibitor	Approved	2004
Adalimumab	Humira	Subcutaneous	TNF inhibitor	Approved	2002
Tildrakizumab	Ilumya	Subcutaneous	IL-23 inhibitors	Approved	2018
Mirikizumab	NA	Subcutaneous	IL-23 inhibitors	Clinical phase II	-
Guselkumab	Tremfya	Subcutaneous	IL-23 inhibitors	Approved	2017
Infliximab	Remicade	Subcutaneous	TNF inhibitor	Approved	2006

Brodalumab	Siliq and Kyntheum	Subcutaneous	IL-17 inhibitor	Approved	2017
Ixekizumab	Taltz	Subcutaneous	IL-17 inhibitor	Approved	2017
Risankizumab,	Skyrizi	Subcutaneous	IL-23 inhibitors	Phase III	2019
Ustekinumab	Stelara	Subcutaneous	IL-12/23 inhibitor	Phase III	2009

Conclusion

Treatment of psoriasis is difficult due to the unknown epidemiology, and topical therapies such as emollients and corticosteroids are used. Immunomodulators appeared to be a better therapeutic strategy based on the function of T-cells in the pathogenesis of psoriasis. Long-term use of these drugs, on the other hand, has been linked to immunological suppression, which can lead to serious infections. Existing treatments developed as nanocarriers showed greater efficacy and fewer negative effects. PDE-4 inhibitors and JAK inhibitors have shown promise in the treatment of psoriasis, although further research is needed. The capacity of these novel compounds to target these therapies at the molecular level has increased their efficacy. To develop better treatment options, extensive clinical trials for the delivery of small molecules in both topical and oral therapy are now underway. This can increase efficacy while reducing long-term side effects, which are common with steroids, retinoid compounds, and immunomodulators. Various targeting approaches can be used in treating psoriasis, depending on new findings in the pathophysiology of the illness, which can finally provide a new direction to the dermal clinic.

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