Biologics and Biosimilars as Treatment Options for Psoriasis

By

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Declaration

It is hereby declared that

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2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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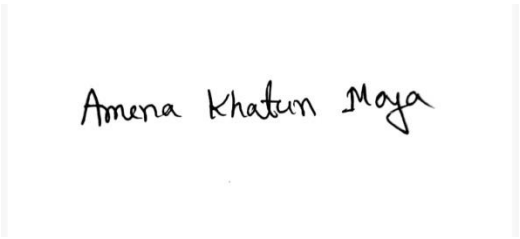

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Approval

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Ethics Statement

This study does not involve any human or animal trial.

Abstract

Psoriasis is a common chronic skin disease stemming from a systemic inflammatory disorder. It affects more than 7.5 million people in the United States and an estimated 125 million people worldwide. It is an immune-mediated disease that causes indurated, erythematous, scaly, pruritic, and often painful skin plaques. Current treatments for psoriasis include topical agents, standard systemic phototherapy, as well as phototherapy combined with psoralen and ultraviolet A radiation. However, these treatments were not always effective which led to the discovery of biologics and biosimilars. Biologics such as T-Cell Targeted biologics (Alefacept, Efalizumab) tumor necrosis factor inhibitors (Infliximab, Adalimumab, Etanercept), IL17 inhibitors (Secukinumab, Ixekizumab) and IL 12/IL 23 inhibitors (Ustekinumab) have been successfully used to treat psoriasis. This was later followed by the introduction of safe and effective biosimilars that increased access to these highly effective medications.

Keywords: Biologics; Biosimilars; Psoriasis; Inflammation; Treatment

Dedication

Dedicated to my beloved parents

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List of Acronyms

BSA	Body Surface Area
IL	Interlleukin
EP	Erythrodermic Psoriasis
UB-UVB	Narrow-band Ultraviolet B
IP	Inverse Psoriasis
mAb	Monoclonal Antibody
FDA	Food and Drug Administration
TB	Tuberculosis
TNF-α	Tumour Necrosis Factor alpha
HZ	Herpes Zoster
mAb	Monoclonal Antibody
Ig	Immunoglobulin
HS	Hidradentitis Suppurativa
Th	T helper
DCs	Dendritic Cells
PsA	Psoriatic Arthritis
PASI	Psoriasis Area and Severity Index
DMARDs	Disease-modifying Antirheumatic Drugs
QOL	Quality of life

Chapter 1

Introduction

1.1 What is Psoriasis

Psoriasis is considered as a systemic inflammatory disease linked to several co-morbidities, including cardiovascular disease and cancer (Kim, 2017). It is multisystem inflammatory disease which mostly affects the joints and skin. It is a disease with elevated levels of circulating proinflammatory cytokines which affects both the skin and the body as a whole. It has a severe psychosocial and emotional impact on patients, impairment social functioning and person to person interactions along with the physical features of the disease. Its systemic nature is reflected in the fact that it coexists with a variety of other conditions, including depression, metabolic syndrome and its components (Samotij et al., 2020). Psoriasis can occur at any age. However, disease opening seems to be bimodal, peaking around twenty to thirty years of age then again around fifty to sixty years of age. Genetic predisposition plays a role in psoriasis. It is common to have a family history of the disease. Individuals with relatives suffering from psoriasis have a higher risk of psoriasis than those without psoriasis patients in the immediate and extended family (Kimmel & Lebwohl, 2018). Studies have reported the different levels of severity of psoriasis in patients, along with the associated disorders such as depression, anxiety, asthma, liver disease, and diabetes, that affects the standard of life (Kim, 2017; Mathew & Chandran, 2020).

1.2 Signs and Symptoms

Psoriasis is a chronic disease identified by erythema, pruritus, scaling and pain on the skin, which has a psychological impact and a lower quality of life. Its symptoms include itching, pain, burning, stinging, burning and skin tightness, as well as skin dryness, scaling, cracking,

shedding or faking, redness and bleeding (Armstrong et al., 2019). Plaque psoriasis is distinguished by red, scaly, itchy and painful plaques that are most commonly found on the scalp, knees and elbows (Rentz et al., 2017). The classic clinical manifestations of plaque psoriasis are pruritic plaques covered in silvery scales, erythematous (Rendon & Schäkel, 2019). Nail psoriasis can manifest in a variety of clinical manifestations depending on the structure intricate in the nail. All over the symptoms of this type of psoriasis are non-particular as well as can be established in a variety of other nail conditions. As a result, microanatomy of involved tissue is the gold standard for nail psoriasis diagnosis; however, in most cases, nail psoriasis can be diagnosed clinically using pattern recognition. Pitting, red spots of the lunula, leukonychia, 'Beau's lines' along with crumbling of the nail plate can occur when it is present in the nail-forming part. Splinter hemorrhages involving the distal third of the nail plate, oil-drop discoloration, hyperkeratosis, and/or nail plate detachment from the nail bed are all symptoms of onycholysis. It can also affect periungual area, causing paronychia (psoriatic) (Pasch, 2016). In guttate psoriasis, the trunk is the most commonly affected site. This type of psoriasis involves sites, extent and accompanying symptoms following upper and lower extremities, elbows, knees, scalp, face, hands and feet and nails (Ko, Jwa, Song, Kim, & Kwon, 2010). In pustular psoriasis, patients develop red and painful lesions on the palm, as well as purulent inflammation of the same fingers affected by cyanosis. This inflammation begins in the nail matrix. Months later, the patient's toe nails turn red, and whitish islets with polycyclic borders appear on the nail, indicating subungual pus. As a result, patients lose several toenails and the periungual tissues become inflamed. The disease then spreads to cover the entire body in sheets of pustules, which only go away after 6 months (Navarini et al., 2017).

1.3. Types

Five major types of psoriasis are: nail psoriasis, plaque psoriasis, guttate psoriasis, erythrodermic psoriasis and inverse psoriasis, each of them have been briefly described below.

1.3.1 Plaque psoriasis

Psoriasis vulgaris is another name for plaque psoriasis (Kimmel & Lebwohl, 2018). It is a persistent, inflammatory skin condition which causes unsightly and disfiguring skin changes (A Blauvelt et al., 2020). Approximately 90 percent of the cases are persistent plaque-types. The classic clinical indications are plaques that covered in silver colored scales, erythematous. Plaques might clump together as well as cover most areas of skin. The extensor surfaces of the limbs, the trunk and the scalp are all common sites (Rendon & Schäkel, 2019). Lenient to average disease, defined as less than 10% of the body surface area getting involved, accounts for around 80 percent of plaque psoriasis patients. The remaining patients have average to severe disease and may be affected by the majority of the body surface area (Kimmel & Lebwohl, 2018). Psoriatic inflammation develops and persists due to disruptions in the adaptive and innate cutaneous immune reactions. In some patients, innate resistant system activation caused by endogenous signals and cytokines coexisting autoinflammatory perpetuation, while within others, T cell-driven autoimmune responses are present. Therefore, it exhibits immunological disorder characteristics on a (auto) inflammatory scenerio, with not only mechanisms overlapping but also even amplifying one other. Main findings in psoriasis are visible at skin's outermost surface is made up by keratinocytes. The expansions of the plaques, however, are not limited to redness in the epidermal surface although it is structured by the reaction of keratinocytes with a variety of

cell types for example: adaptive and innate cells, vasculature spanning the dermal surface of the skin (Rendon & Schäkel, 2019). Topical treatments are well established in the front-line therapy of psoriatic plaques because they provide very fast relief of skin indications in patients, as well as these symptoms are feasible with topical therapy alone (approximately 80 percent) or with the combination of systemic therapy. Nonetheless, because psoriasis is a chronic disease, long-term control of the signs and symptoms is recommended (Carrascosa, Theng, & Thaçi, 2020). Atopic dermatitis, nummular dermatitis, lichen simplex chronicus, tinea and pityriasis rubra pilaris are very ordinary conditions on the distinguishing diagnosis for plaque psoriasis. In this case, a biopsy would be useful if the diagnosis is unclear. Drug interactions can also cause erythemato-papulosquamous psoriasis-like emissions. This taking into account, the appearence of red bruis with acute pruritus and eosinophilia suggests a drug emission. Since inflammatory papulosquamous bruises Mycosis fungoides might also be manifested which can be mistaken for psoriasis (Kimmel & Lebwohl, 2018). Guselkumab is an IL- 23 mAb that is demonstrated very good and long-term efficacy in average to severe plaque psoriasis (Chiang & Tsai, 2021).

1.3.2 Guttate Psoriasis

Guttate psoriasis is a subset of cutaneous psoriasis characterized by its clinical menifestations which is the sudden opening of small, erythematous, squamous and monomorphic or papules macules that appear as droplets, primarily broaden over the limbs and trunk (Maruani et al., 2019). This is more common in young adults and children and accounts for beneath 2 percent of psoriasis patients (Kimmel & Lebwohl, 2018). It is a type of psoriasis that has an dreadful opening of little erythematous plaques. More or less one-third of cases with this genre of psoriasis can develop plaque-type psoriasis during their adulthood (Rendon & Schäkel, 2019). It can aggravate pre-existing, often mild, chronic plaque psoriasis (guttate flare of chronic psoriasis) or it can occur on its own (acute guttate psoriasis) (Chalmers,

Sullivan, Cm, & Cem, 2019). Treatments for this type of psoriasis include phototherapy (i.e., ultraviolet light therapy), topical or oral medications; and biological medicines. It is unknown which of these treatments is most effective at clearing lesions in guttate psoriasis, as well as whether they are safe (Maruani et al., 2019).

1.3.3 Nail Psoriasis

Psoriasis is a skin disease where nails are most commonly affected. Different clinical nail alterations can be noticed dependant upon the specific nail shape involved (Haneke, 2017). It is a common complication of skin psoriasis, causing not only cosmetic but also functional problems. The disease is a notable burden that reduces patients' quality of life (Bardazzi et al., 2019). Individual patients can suffer greatly from nail psoriasis. According to a recent survey, 47 percent of cases with nail psoriasis usually like to be treated for the condition. Conventional systemic treatments for nail psoriasis, such as cyclosporine, methotrexate, apremilast and acitretin, along with intralesional corticosteroids, might be fruitful. Topical therapies such as calcipotriol, corticosteroids, tazarotene and tacrolimus have also been depicted effective in the therapy, especially in lenient patients. Eventually, non-pharmacological therapy options such as laser therapy, photodynamic, phototherapy and several radiotherapeutic options are discussed but will not be recommended as front-line treatments (Pasch, 2016). Although biologic therapies have been introduced as a treatment option for nail psoriasis, it is still unclear which is the most effective in treating this specific psoriatic localization (Bardazzi et al., 2019)

1.3.4 Inverse Psoriasis

Around more than one-third of psoriasis cases, genital and IP can occur. In these areas, psoriatic lesions can be flat and not scaly and genital positioning might cause sexual dysfunctions as well as debilitating emotional and physical distress. Despite it only affects a small portion of the BSA, this type of psoriasis is realted with a low standard of life as well as

a significant amount of stress. Although men are more likely to have it, women have more severe symptoms (J. J. Hong, Mosca, Hadeler, & Brownstone, 2021). Inverse psoriasis, also callled flexural or intertriginous psoriasis, affects three to seven percent of psoriasis cases. This affects the demi-span like genital regions, axillae as well as the inguinal and inframammary creases. The face can also be associated. There is no histological contrast between IP and plaque psoriasis, so these two are distinguished based solely on remote manifestation (Kimmel & Lebwohl, 2018). Patients have significantly higher levels of embody stigma and disablements in interpersonal relationships. Treatments extensively used to treat plaque psoriasis in usual areas might not always be an good choice for treating bruises in the intertriginous areas (J. J. Hong et al., 2021). Although IP(Inverse Psoriasis) affects only a little percentage of BSA, it can show a very significant change on status of life, mostly sexual function. It has also been proposed that the sudden opening of IP in adults could be a sign of HIV (Dermatology et al., 2019). The treatment of genital and IP requires extra caution because the skin is very thin and vulnerable to the complications of certain therapies. Vitamin D analogs and corticosteroids inhibitors are front-line recommended therapies. Topical coaltar compositions as well as topical PDE-4 hindrances are the second-line recommendations. Biologics, other systemic treatments are suggested for severe cases or recalcitrants of genital psoriasis, with the most available data for ixekizumab (J. J. Hong et al., 2021).

1.3.5 Erythrodermic Psoriasis

Erythroderma is a scarce and possibly fatal form that can be triggered by medication reactions (Foss, Nyckowski, & Steffes, 2021). Erythema, pruritus, edema, hair loss, scaling, occasionally exudative bruises and diffuse desquamation characterize EP (Erythrodermic Psoriasis). In EP, changes in nails are very usual and can span from lenient to chronic onychodystrophy, with fingernails being commonly affected than toenails (Ucmak &

Brodsky, 2016). It is clinically defined as widespread scaling and erythema that affects at least 75–90 percent of the BSA. The patients may experience systemic indications such as fever, chills, pruritus, arthralgia, dehydration and lymphadenopathy for the large cutaneous participation. Several triggers for EP have been identified, including systemic corticosteroid administration, infection, medication withdrawal, preceding illness and severe emotional stress (Lo & Tsai, 2021). The patients may also experience systemic symptoms such as fatigue, dehydration, staphylococcal infection, weight changes, insomnia, electrolyte abnormalities and cachexia due to extensive and severe skin barrier defects. The onset can be gradual or sudden, activated by a variation of componets such as sunburns, emotional stress, drug or infections. The abrupt discontinuation of plaque psoriasis treatments, such as cyclosporin, steroids and methotrexate is a common cause of EP (Chen, Li, Xu, & Yang, 2018). Erythroderma might appear on a part of psoriasis which necessitates immediate therapy (Rendon & Schäkel, 2019). It is a rare psoriasis variant. For this reason, there is little proof to support its treatment. When compared to cases with plaque psoriasis, cases with EP sometimes react less to tradiational therapy having less biologic drug remainders (Chiang & Tsai, 2021). EP treatment is frequently difficult because several factors, such as treatment default or potential complexes, may limit successful results with conventional medications. It is suggested by recent evidence that several biological drugs, for example anti-TNF α and ustekinumab, could help improve EP management (Stinco & Errichetti, 2015). . Because of the severity and high risk of comorbidities in EP, primary management must include a full medical assessment, including an assessment for infection given the expanded risk of sepsis and bacteremia; correction of body fluid, electrolyte abnormalities, protein; and skin barrier restoration. In conjunction with systemic therapy, topicals such as vitamin D analogs, medium-to-high potency steroids and emollients may be beneficial (Chen et al., 2018).

1.4 Rationale

Psoriasis affects people from all over the world at all ages. This condition can have a huge negative impact on people's lives since it is a chronic disease and requires long term treatment. It has very complex pathogenesis. There are five different types of psoriasis according to the affected location in the body. Though several conventional therapies have been used to treat psoriasis for years, they all have serious limitations. To overcome these limitations, considerable effort went into developing biologic-based alternate treatment options. Biologics show significantly better efficacy than conventional therapies in the treatment of lenient to chronic psoriasis. Therefore, biologics are now primarily used to treat psoriasis. However, very few biosimilars have been approved till date to treat psoriasis. This is an area that deserves attention because development of biosimilars will make these treatment options more economic and accessible to a larger audience. This paper aims to discuss how biologics and biosimilars are being developed as successful treatment options for psoriasis and explore challenges and opportunities in this field.

Chapter 2

Etiology and Treatment Modalities of Psoriasis

The etiology of psoriasis has been extensively studied, since the prevalence is found to be increasing worldwide.

2.1 Etiology of Psoriasis

Psoriasis and the related co-morbidities have a complicated etiology that is the effect of complex realtion between immune system, disease-associated susceptibility loci the skin and multiple environmental triggers (Hawkes, Adalsteinsson, Gudjonsson, & Ward, 2018). It is a severe skin disorder, and T-cells with Th1 and Th17 dispersion are abundant within psoriatic bruises. Because psoriasis is thought to be primarily arbitrated by T-cells dispersed to a Th17 fate, any of the factors that influence T-cell expansion may provide to its etiology (Mei et al., 2018). This disease's harmful inflammatory event is not bound to the skin surface and is responsible for an increased rate of co-morbid conditions, for example stroke, cardiometabolic disease, obesity, dyslipidemia, diabetes, gastrointestinal disease, chronic kidney problems, mood dysfunction. These co-morbidities contribute to the increased death seen in psoriasis cases which have significant hints for disease management (Hawkes, Chan, & Krueger, 2018). While the exact cause of psoriasis is unknown, genetic factors are known to influence susceptibility to the disease. Pedigree analysis has revealed that children have a 20 percent chance of developing psoriasis if one parent has the disease; the chance is approximately three times higher if both parents are afflicted. According to twin studies, the disease concordance of psoriasis is two to three times more in monozygotic than dizygotic twins (Tseng, Chang, Huang, Hsu, & Chuang, 2021). Erythrodermic psoriasis must be distinguished from other reasons of generalized erythroderma, such as drug reactions,

congenital ichthyosis, cutaneous T cell lymphoma, atopic dermatitis, bullous dermatoses. A previous personal or bloodline of psoriasis can be very helpful if present. It is difficult to determine the underlying cause of erythro-derma, and in many cases, even with biopsies and other tests, the cause is never determined (Kimmel & Lebwohl, 2018).

2.2 Treatment Modalities

Psoriasis is a relapsing severe disease that often needs long term therapy (Rendon & Schäkel, 2019). Moreover, the extent as well as clinical severity of the cutaneous involvement, several factors should be considered while choosing therapy. Psoriasis phenotype and previous treatment history, presence of psoriatic arthritis and other comorbidities, clinical severity and psychosocial impact, concomitant medications, conception plans, individual preferences and treatment goals are all considered (Reid & Griffiths, 2020). The cases are usually divided into 2 groups based on the percentage of how much body surface is affected, clinical severity of the lesions and patient standard of life: lenient or average to severe (Rendon & Schäkel, 2019). An effective treatment approach is integrated, recognizing the disease's multifaceted nature and should be adaptable as this chronic disease evolves and patient demands change with time (Reid & Griffiths, 2020).

2.2.1 Topical Treatment

Topical drugs are the first-line treatment for mild-to-moderate psoriasis, although the patient adherence is very low (around 50–70 percent), which is a obstacle to treatment success (Svendsen, Feldman, Möller, Kongstad, & Andersen, 2021; Thaçi et al., 2020). In patients with psoriasis that affects 10 percent of their BSA, topical therapy is the preferred treatment (mild psoriasis). It can also be used to treat psoriasis in sensitive areas like the face, genitals and flexures (Torsekar & Gautam, 2017). In clinical practice, the topical treatment modality is used for all cases with plaque psoriasis, notwithstanding disease constancy Approximately 80 percent of psoriasis cases have localized disease that can be managed by topical therapies

(Thaçi et al., 2020). TCS, salicylic acid, Vitamin D analogs, coal tar and anthralin are all topical therapies for scalp psoriasis that come in a variety of formulations such as foams, solutions and shampoos. Moreover, vitamin D analogs, TCS and tazarotene are all effective treatments for nail psoriasis (Torsekar & Gautam, 2017). In a 12-week multicenter study rating the evaluating and efficacy of Cal/BD gel implimented to scalp following complete remission, biweekly use of Cal/BD gel has shown more efficacy as well as related to a lower rate of recurrence of the indications of psoriasis against on-demand therapy (Carrascosa et al., 2020). Moisturizers contribute to the normalization of differentiation, hyperproliferation and apoptosis. They have anti-inflammatory properties as well as improving barrier activity. This aids in the treatment of the Koebner's phenomenon and skin stresses. Emollients are the foundation of psoriasis treatment. Because dry skin is usual in this disease and contributes to its irritability, they are an excellent first-line treatment. Emollients, as a result, reduce scaling, soften cracks, moisturize dry skin, relieve itching and improve the spread of other agents. They might also lessen the rate of epidermal change. These serve as extra to topical or systemic treatment rather than as a stand-alone treatment (Torsekar & Gautam, 2017). Psoriasis frequently affects the scalp, necessitating the use of gels, solutions or foams that are less messy than creams and ointments. In other cases, patients may prefer a less greasy preparation, for example a cream, during the day and an ointment that is more efficient but less cosmetically likable at night (Torsekar & Gautam, 2017). Although there is lacking in putting labels, this therapy continues to play a vital role in psoriasis therapy, as well as current recommendations suggest a psoriasis control regimen. Proactive relapse management and adherence optimization may be important factors in achieving clinical effects in topical long-term management. The only topical formulation is Calcipotriol/betamethasone dipropionate foam with long-term data as a biweekly active therapy perspective for chronic plaque psoriasis for up to 52 weeks (Carrascosa et al., 2020).

2.2.2 Phototherapy

Phototherapy is the therapy option for those who do not react to topical therapy (Narbutt et al., 2021). Over the last several decades, numerous classes of phototherapy have been established and used to manage psoriasis. BB-UVB, 290-320 nm had been the initial to be grown although it was later substituted by NB-UVB, 311 nm because it is more fruitful (Zhang & Wu, 2018). Phototherapy with blue LED light is a highly effective and safe method of treating psoriasis (Lesiak, Bednarski, & Narbutt, 2021). This treatment usually necessitates often visits to a hospital that can provide UV light, which can not only be financially but also be logistically difficult for the cases. As demonstrated in a study report, NB-UVB phototherapy might not be useful as a monotherapy for critical patients. Blistering, pruritus and folliculitis are some of the side effects. Long-term complications include non-melanoma and an expanded risk of skin cancers. Phototherapy must not be an option in cases with photosensitive diseases; for example xeroderma pigmentosa and used cautiously in patients with regular oral herpes simplex virus infection. It is worth noting that NB-UVB phototherapy is often regarded as secure in cases who take photosensitizing drugs (Menter, Strober, et al., 2019). Aside from the problems mentioned, this is an important option to consider for psoriatic skin toxicity from ICIs, particularly for those who cannot tolerate or have been recalcitrant to steroid treatment (Ma et al., 2020).

2.2.3 Systemic Therapy

Systemic therapy has been important, safe and effective treatment option (Bellinato, Gisondi, & Girolomoni, 2021). Use of adalimumab, methotrexate, etanercept, ixekizumab and infliximab are used in cases with average to serious (Korman, 2020). Cyclosporine, methotrexate, cyclosporin, acitretin, biologics and phototherapy are primarily used in the juvenile population with average to serious psoriasis. This is recommended that systemic medication be stopped after the severity of the condition has been controlled (Aslam, Saleem,

Murtazaliev, Quazi, & Khan, 2020). The reduced mortality risk linked with systemic medicines should be taken into account while making psoriasis treatment decisions (Langley, Poulin, Srivastava, & Augustin, 2020). However, pediatric psoriasis patients are treated with the traditional systemic medicines cyclosporine (for short-term usage only) and methotrexate. Psoriasis patients with type 2 diabetes and/or insulin resistance can benefit from any of the systemic therapies evaluated (Lambert et al., 2020).

2.3.4 Combination Therapy

Nonetheless, multiple therapies exist, yet more have been suggested, no one treatment for psoriasis provides a complete and acceptable cure, along with most of them having adverse effects (Iriventi, Gupta, Osmani, & Balamuralidhara, 2020). A combination of medicines may offer a better therapeutic choice, with a faster onset of action while reducing the total amount of dose and safety issues associated with larger mono-therapy doses. Despite the fact that such a combination has been explored in psoriatic arthritis and rheumatoid arthritis, there are few randomized controlled trials examining the safety and efficacy of MTX plus CsA in persistent plaque psoriasis. This was mostly owing to concerns that both medications might raise each other's blood levels and reduce elimination (Singh & Singnarpi, 2021). For psoriasis, a combination of betamethasone dipropionate and calcipotriol is found to be more efficacious than either monotherapy. The combination gel is well accepted which can be used once a day, with the exception of the genital, face and flexural areas (Kim, 2017). When curcumin was combined with an anti-inflammatory medicine like caffeine, it had a stronger antipsoriatic effect and reduced the time it took to treat psoriasis (Iriventi et al., 2020).

Chapter 3

Biologics and Biosimilars

Traditional treatment options for psoriasis have their limitations, which led to the search for alternate treatment options such as biologics and biosimilars. Biologics are complex macromolecular substances produced by living systems, and its biosimilars are mandated to demonstrate high resemblance to their authorized originator biologics in subject to their biological, biochemical, safety and immunological properties (Kabir, Moreino, Kawsar, & Siam, 2019).

A greater understanding of the pathophysiology of psoriasis has permitted the expansion of a growing variety of useful and safe therapies in recent years, for example biologicals for average to serious psoriasis patients. TNF-α (etanercept, infliximab, adalimumab and certolizumabpegol), IL-17 (secukinumab, brodalumab, ixekizumab), IL-12/23 (ustekinumab) and IL-23 (risankizumab, tildrakizumab and guselkumab) inhibitors have already been approved (Bellinato et al., 2021). By mid-2020, the FDA had approved more than 14 biologics for adult psoriasis (TNF-α blockers, interleukin-17 inhibitors and interleukin-12/23 inhibitors). Only ustekinumab and etanercept have been approved for pediatric psoriasis, despite the fact that numerous additional medicines are used off-label (Aslam et al., 2020). Ustekinumab has been indicated to treat psoriasis patients over age 12. The biological medications etanercept, adalimumab, infliximab and ustekinumab are recommended for young persons with psoriasis because of their safety and efficacy. The biological medications certolizumabpegol, adalimumab, etanercept and infliximab; ixekizumab, brodalumab and secukinumab; guselkumab, ustekinumab, tildrakizumab, risankizumab, tildrakizumab; and the synthetic drug apremilast are proposed for geriatric psoriasis patients (Lambert et al., 2020). Based on the available proof of pregnancy outcomes and placental transfer, using the

Fc-free biological drug certolizumabpegol as first-line treatment for female psoriasis patients are recommended who want to conceive or who may be pregnant and need treatment, followed by either etanercept or adalimumab. Adalimumab, Enbrel, Cimzia and Infliximab should only be administered during pregnancy if absolutely necessary (Ghalandari & Laan, 2020; Lambert et al., 2020). Depression, suicidal ideation behavior (SIB), anxiety, lack of confidence, poor quality of life (QOL) and sleeplessness are more common in psoriasis patients and these symptoms can be alleviated with adequate treatment (Lambert et al., 2020). The effect of biologics on who have depression disorder in psoriasis cases has proven promising. In patients with for average to serious psoriasis, uncertained controlled trials with etanercept, adalimumab and ustekinumab are linked to a statistically significant reduction in depressed symptom scores on several scales (Mathew & Chandran, 2020). Amgevita, Cyltezo, Solymbic, Imraldi, Erelzi, Benepali, Flixabi, Remsima and Inflectra are among the nine biosimilars that approved by the European Medicines Agency (EMA) for hidradenitis suppurativa and plaque psoriasis; the number is growing. Ustekinumab is a mAb that is useful in the treatment of psoriasis, however no biosimilars for individuals have been licensed (Constantin et al., 2019).

3.1 Currently Available Biologic Therapy

Several approved biologics and their biosimilars have been approved for use in patients with psoriasis according to the age groups (Tables 1 and 2).

3.1.1T-Cell Targeted Biologics

T cells have been linked to the pathogenesis of psoriasis for over 50 years, according to extensive scientific study (Hu et al., 2021). Psoriasis is a T-cell-mediated illness, according to research on the mechanism of action of ciclosporin in controlling it, and subsequent mouse models added to the theory that immune cells are the major effector cells in driving the

disease. As a result the first biologics to treat psoriasis were designed for targeting T cells (Reid & Griffiths, 2020). The importance of T-cells in the development of psoriasis cannot be overstated (Hawkes, Chan, et al., 2018). Alefacept was taken off the market in 2011 because it became obvious that more effective and cost-efficient alternatives had become available. In 2009, the drug efalizumab was also taken off the market. This emphasizes the significance of post-marketing drug safety monitoring (Reid & Griffiths, 2020).

3.1.1.1 Alefacept

In 2003, the first biologic agent alefacet was approved to treat medium to high severity of chronic plaque psoriasis by the FDA and it has been used successfully in a patient with palmoplantar psoriasis and EP. This medication was phased out in 2011 (Chen et al., 2018). Alefacept's introduction was the turn of the century, biological therapy for psoriasis became available. It is a fusion protein of the immunoglobulin (Ig) 1 and the human lymphocyte function-associated antigen (LFA)-3. On activated T cells' surface, it interacts with CD2 molecules, preventing T-cell co-stimulation by the antigen-presenting cell (APC). Furthermore, it selectively targets memory T-cells, inhibiting T-cell activation while depleting memory effector T-cells. Because of the mechanism of action of alefacept, the drug was expected to provide a relatively long-term remission even in the absence of treatment (Rønholt & Iversen, 2017). As a result of their significant adverse effects, T-cell inhibitors like efalixumab and alefacept are poorly used. There have been no published studies evaluating the efficacy of these drugs in nail psoriasis (Haneke, 2017).

3.1.1.2 Efalizumab

In 2003, Efalizumab became the first biologic to be approved in the United Kingdom for the treatment of psoriasis (Reid & Griffiths, 2020). The medication is a monoclonal IgG1 antibody (humanised) guided against CD11a, the LFA-1 -subunit. It inhibits the interaction

between Intercellular Adhesion Molecule 1 (ICAM-1) and LFA-1, which, like alefacept, interposes with T-cell co-stimulation when contacted by the APC. Because ICAM-1 is expressed in different tissues, the sites of action for efalizumab are more numerous than alefacept. Efalizumab inhibits the extravasation of circulating lymphocytes as well as the interaction of activated T cells with keratinocytes (Rønholt & Iversen, 2017). Because of its significant adverse effect profile, efalizumab is not widely used (Haneke, 2017). Long-term efalizumab treatment was linked to progressive multifocal leukoencephalopathy, a infrequent yet life-risky infection of the CNS, according to post-marketing drug surveillance. As a result, in 2009, this medication had been withdrawn from market (Reid & Griffiths, 2020).

3.1.2 Tumor-Necrosis-Factor (TNF)-α Inhibitors

TNF is known to have widespread and profound effects on the activation and proliferation of various immune cell subsets in a variety of disease states (Holbrook, Lara-reyna, Jarosz-griffiths, & Mcdermott, 2019). TNF-α is a cytokine that has pleiotropic effects on a difference of cell types. It has been identified as a major regulator of inflammatory responses and has been linked to the pathogenesis of several inflammatory and autoimmune diseases. It is known to activate a variety of inflammatory molecules, including other cytokines and chemokines. TNF-α is available in both soluble and transmembrane forms (Jang et al., 2021). Many TNF antagonists' clinical efficacy (for example: adalimumab, infliximab, and etanercept) emphasized the role of TNF-a to promote and maintain psoriatic skin bruises, although the share of patients tolerating remarkable betterment in their skin lesions is successfully less than that found with novel IL-23 and IL-17 antagonists (Hawkes, Chan, et al., 2018). Infliximab and adalimumab both outranked the standard systemic agent methotrexate in terms of treatment outcomes. The most effective TNF-α inhibitor is infliximab, which is followed by adalimumab and etanercept. However, these are well-known

risk factors for serious infections such as skin, lower respiratory tract and soft tissue infections such as cellulitis and pneumonia (Lynn, 2020).

3.1.2.1 Etanercept

In 2004, the FDA authorized etanercept as the foremost TNF-a inhibitor to treat psoriasis. It is a fusion protein for human TNF-A receptor that is recombinant. It is made up of two extracellular domains of human soluble TNF receptor units that bind both membrane-bound and soluble TNF, as well as a human IgG Fc fragment that stabilizes the molecule. It may bind two TNF-α molecules as a dimeric molecule and function as a competitive inhibitor of endogenous TNF-α. Dendritic cells, Th22-, Th17 and Th1- cells, keratinocytes as well as macrophages all release TNF-α, which has several targets in psoriasis pathogenesis. In comparison to second-generation biologics, TNF-α antagonists are thus contemplated targeted treatment with broad target (Rønholt & Iversen, 2017). . It is presently approved to treat average to serious plaque psoriasis in adults and children, as well as psoriatic arthritis, juvenile rheumatoid arthritis, rheumatoid arthritis and ankylosing spondylitis. In psoriasis, the recommended dose of etanercept is 50 mg twice weekly for the first 12 weeks, then 50 mg once weekly after that. After efalizumab (Raptiva®) was pulled from the market due to its link to progressive multifocal leukoencephalopathy caused by the JC virus, etanercept became the obvious market leader. By week 12, 49 percent of patients had attained PASI 75 during the first three months of therapy, when etanercept was allowed to be administered twice a week. This twice-weekly dose, however, was permitted. Moreover, this twice-weekly dose was only allowed for the first three months; after that, etanercept injections are only allowed once a week (J. Hong & Bhutani, 2021). It is best to use it when the patient is at least six years old. In average to serious plaque psoriasis, erythrodermic psoriasis, palmoplantar psoriasis, pustular psoriasis several case reports revealed its potency as a adjuvant therapy

with other conventional regimes in 22-month-old children (Aslam et al., 2020). However, etanercept is still useful for certain subpopulations today. Etanercept, for example, has one of the most favorable safety profiles for treatment in older individuals with severe psoriasis. The FDA package insert claims that senior people have no higher risk of adverse effects when compared to younger patients under the geriatric statement section. Furthermore, it was the first biologic treatment for psoriasis to be licensed for pediatric usage down to 4 years old, owing to its excellent safety record of more than 20 years. When compared to other TNF-α agents (infliximab and adalimumab), etanercept has a lower risk of TB (J. Hong & Bhutani, 2021).

3.1.2.2 Infliximab

Infliximab was licensed to treat Crohn's disease in the United States in 1998. Its indications were broadened after that and it became available for the treatment of PsA in 2005/2006 (Pasch, 2016). Because of its quick onset, infliximab is considered a first-line biologic for EP (Lo & Tsai, 2021). Infliximab treatment has been shown to increase the polyclonality of CD4+, CD25+ TReg cells in psoriasis patients (Samotij et al., 2020). . This is a chimerical mAb which binds to both transmembrane as well as soluble TNF-alpha molecules and balances them. It is made up variable region of a mouse and a human IgG1-alpha constant region. It is used to treat psoriasis, rheumatoid arthritis, PsA as well as ankylosing spondylitis in adults. It is also licensed to treat both children and adults who are suffering from ulcerative colitis and Crohn’s disease (J. Hong & Bhutani, 2021). Its chimeric nature may lead to a larger production of neutralizing antibodies than fully human(-ized) antibodies. The decreasing efficacy of infliximab over time, which may necessitate increasing infusion frequencies, infusion responses and higher doses, which occur in 16 percent of infliximab-treated patients, are all concerns related to the formation of these antibodies. Chills,

headache, fever, flushing, myalgia, urticaria, arthralgia, dyspnea, nausea and hypotension are some of the symptoms that can occur (Pasch, 2016). 5 mg per kg is given as IV dose at weeks 0, 2, and 6 to treat severe plaque psoriasis, with maintenance dose every 8 weeks after that. It has a similar beginning of action as cyclosporine due to its mode of administration. As a result, experts agree that the medicine need to be considered as a second-line treatment for EP patients who are in a stable state. Infliximab is a single therapy option which has been supported by multiple case reports and series in, as well as one multicenter clinical trial. Other systemic medicines, such as acitretin and methotrexate, have been successfully used with infliximab, with great clinical effects (Ucmak & Brodsky, 2016). Infection, such as nasopharyngitis, staphylococcus aureus septicemia and erysipelas, is the most prevalent side effect. In addition, infliximab has been linked to delayed infusion responses, suicide attempts, myocardial infarction and immunoallergic shock (Lo & Tsai, 2021). Among TNF-α inhibitors, infliximab has the highest risk for HZ, albeit there is no statistical significance when compared to adalimumab. The risk of HZ in individuals receiving ustekinumab, an interleukin-12/23 inhibitor, is strikingly similar to that of infliximab (Tang, Shen, & Chen, 2021).

3.1.2.3 Adalimumab

In 2002, the FDA authorized the first entirely human mAb, adalimumab. It is a monoclonal antibody with human light and heavy chain variable domains, as well as human IgG1:k continual regions, that may link to both transmembrane TNF-α and soluble. Biosimilars Amjevita, Imraldi and Cyltezo have been approved to treat plaque psoriasis and hidradenitis suppurativa (Constantin et al., 2019). TNF-α targeting antibody adalimumab is a totally human, recombinant IgG1 mAb. It binds to TNF and disrupts the cytokine's interrelation with the p75 and p55 cell surface TNF receptors, reducing TNF-α related biological processes

(Zhou, Chen, & Bi, 2021). Adalimumab is suggested for psoriasis patients over the age of four, and etanercept is advised for those over the age of six (Lambert et al., 2020). Psoriasis in juvenile idiopathic arthritis, adults, PsA, adult along with pediatric Crohn's disease, adult rheumatoid arthritis, uveitis are among the ten indications for adalimumab. The initial dose of adalimumab for is 80 mg, subsequently 40 mg as SC the following week and at 2-week intervals thereafter. Its efficacy in patients with average to serious psoriasis has been demonstrated in multiple RCTs comparing it to methotrexate, placebo or other biologics (Menter, Cordoro, et al., 2019). With its suppression of joint deterioration and nail psoriasis, it is considered one of the most effective therapies for psoriatic arthritis, even if the patient does not have a global BSA larger than 10 percent. FDA approved it to treat juvenile idiopathic arthritis in children under the age of two and hidradenitis suppurativa (HS) in teenagers. It was recently approved to treat children with extreme persistent plaque-type psoriasis. Its effect appears to fade over time with more injections than the newer medications. Adalimumab is still regarded as one of the most effective first-line treatments for psoriatic arthritis (Brownstone, 2021).

3.1.3 IL-12/IL-23 Inhibitors

The pro-inflammatory cytokine IL-23, which is made up of the two subunits p40 and p19 distriuted with IL-12, is primarily constructed by inflammatory DCs in inflamed skin, with macrophages and keratinocytes contributing as well. The Th17 subsets of T cells are expanded and maintained by IL-23 (Boutet, Nerviani, Gallo Afflitto, & Pitzalis, 2018; Hu et al., 2021). Data from clinical trials have revealed that IL-23 inhibitors have a good safety profile; however, long-term studies suggest that side effects still occur during treatment. Selective interleukin-23 inhibitors necessitate less frequent dosage than interleukin-17 inhibitors and may have a better risk profile, with reduced candidiasis and inflammatory

bowel disease risk (Hu et al., 2021). Ustekinumab is a human mAb that is proven to be successful in treating nail psoriasis. It targets p40 component of both IL-23 and IL-12 (Bardazzi et al., 2019).

3.1.3.1 Ustekinumab

Ustekinumab was the first inflammatory condition for which the FDA granted approval. When TNF-α inhibitors were authorized for psoriasis by the FDA, they were already licensed for the Crohn's disease and/or as variety of rheumatic disorders. It was approved for PsA four years later, in 2013, and for the Crohn's disease in 2016 (Rønholt & Iversen, 2017). It is a human IgG1 mAb which inhibits the function of the IL-12 and IL-23 receptor by targeting the usual protein subunit p40 (Aslam et al., 2020; Rønholt & Iversen, 2017). It blocks the function of these two cytokines, which are released by myeloid dendritic cells after naive T-cells are activated and differentiated into Th17-cells and Th1- . Ustekinumab, unlike previous biologics approved to treat of psoriasis, targeting the IL-23/Th17 and IL-12/Th1 routs, which are critical in the pathophysiology of psoriasis. It set the door for a recent method for psoriasis drug enlargement with its revolutionary outlook of interposing with immune system (Rønholt & Iversen, 2017). For adult and adolescent psoriatic patients, it is advised. In general, it has been established that alternative activated immune-mediated pathways other than interleukin 23 and 12 can cause significant clinical response through partial response. Ustekinumab, in compared to other biological treatments, requires fewer injections, making patient follow-up easier (Aslam et al., 2020). Nasopharyngitis, headache and exhaustion are the most usual side effects of ustekinumab (Rønholt & Iversen, 2017).

3.1.4 IL-17 Inhibitors

It was brought to light that blocking IL-17 outcomes in a total change of the molecular and clinical disease characteristics seen among most of psoriasis cases, putting IL-17-producing T-cells and IL-17 at the core of the current psoriatic disease model (Hawkes, Chan, et al., 2018). IL-17A had been thought primarily to be a "unique" cytokine created solely by T cells in psoriasis. Till now, it is clear that several cells contribute to the majority of IL-17A found in ill-skin, and that so many different isoforms of IL-17 may play a role in psoriasis. IL-17A primarily acts on particularly epithelial cells, non-hematopoietic cell and is consistently involved in preventive immunity at border tissues. In terms of the skin, IL-17A promotes keratinocyte proliferation and abnormal differentiation, as well as contributing to skin barrier disruption by suppressing the expression of molecules involved in keratinocyte differentiation, for example: Fillagrin. Furthermore, it contributes to the expansion and formation of the inflammatory network by boosting the freeing of antimicrobial peptides as well as proinflammatory chemokines/cytokines (Brembilla, Senra, & Boehncke, 2018). Until now, three IL-17 rout inhibitors to treat of psoriatic disease have been approved:, secukinumab, brodalumab and ixekizumab (Hawkes, Chan, et al., 2018).

3.1.4.1 Secukinumab

Secukinumab is an IL-17A-binding human IgG1 monoclonal antibody. Adult plaque psoriasis, ankylosing spondylitis and PsA have all been authorized by the FDA. When it comes to its dosing, multiple RCTs have shown that the 300-mg dose is more useful than the 150-mg dose. The excessive dose appears as secured as the lower one. However, for certain cases, single dose of 150 mg may not be inusfficient. It is also beneficial for psoriasis of the neck, head, nail, erythrodermic, palmoplantar and generalized pustular (Menter, Cordoro, et al., 2019). Furthermore, patients with EP who were treated with secukinumab experienced long-term remission. Its efficacy might be seen as quick as 2^{nd} week to 6^{th} week (Chiang &

Tsai, 2021). When compared to other biologics, it has a rising proportion of cases who obtain PASI 100 and 90 clinical responses. This is linked to higher gains in health-related quality of life metrics. It has also been revealed to be potent in treating of psoriatic arthritis and other kinds of psoriasis (such as GPP and hPPP). In conclusion, secukinumab has the potential to provide a large therapeutic response in both PsA and psoriasis and it should be regarded as a valuable addition to our psoriasis treatment (Frieder, Kivelevitch, & Menter, 2018).

3.1.4.2 Ixekizumab

It is a humanized IgG4 mAb which inhibits interaction of IL-17A with IL-17 receptor. Plaque-type psoriasis, psoriatic arthritis and ankylosing spondylitis are among the FDA indications for ixekizumab (Brownstone, 2021). Ixekizumab was approved in March 2016 to control of average to serious plaque-type psoriasis (Hawkes, Chan, et al., 2018). The first dose of this is 160 mg, which is following 80 mg on weeks 2, 4, 6, 8, 10, and 12. After the initial 12 weeks, the maintenance dose of ixekizumab is required 80 mg each four weeks. However, few people may need an 80-mg dose each two weeks to sustain their therapy response (Menter, Cordoro, et al., 2019). There are also other case reports on the potency of ixekizumab to treat of EP, including one instance with human immunodeficiency virus (HIV) infection. It showed a fast response as quickly as week 4 in patients who had previously failed with secukinumab (Lo & Tsai, 2021). Ixekizumab, a high-affinity mAb that targets IL-17A, is currently only medicine whose FDA label includes information on genital psoriasis (grade of recommendation: B). In refractory genital psoriasis patients treated with ixekizumab, several studies have shown considerable improvements in genital bruise presence, sexual health, itch, and QOL (J. J. Hong et al., 2021). According to efficacy data, ixekizumab is the fastest acting biologic. In a confront differentiation, guselkumab had a faster beginning of action in the treatment of plaque psoriasis. Ixekizumab was also better

than adalimumab when both PASI 100 rates and psoriatic arthritis improvement findings were combined. It is a safe and well-tolerated biopharmaceutical with few side effects. There are no black box warnings on it, and there is no proof that it increases the incidence of tuberculosis (Brownstone, 2021).

3.1.4.3 Brodalumab

Brodalumab is a mAb that inhibits the biological activity of IL-17F, IL-17A, IL-17C, and IL-17E by linking to the IL-17 receptor A (IL-17RA) (IL-25). In Japan, it has been approved to treat of all kinds of psoriasis (Chen et al., 2018). It has been approved by the FDA in February 2017. However, it was approved in Japan in 2016, and the European Medical Agency recommended brodalumab approval to the European Commission without reservations in May 2017 (Rønholt & Iversen, 2017). Three phase III studies investigating the effectiveness of brodalumab to treat of average to serious plaque-type psoriasis, all of which were randomized, double-blind and placebo-controlled (Hawkes, Chan, et al., 2018). In a head-to-head comparison, it was more active than ustekinumab. Despite being licensed in the United States and Japan, the clinical trial was stopped due to behavior and suicidal ideation (Haneke, 2017). Brodalumab has also been investigated as a potential EP treatment (Chen et al., 2018). At weeks 0, 1, and 2, a 210 mg loading dosage is given in SC. Then, every two weeks, a maintenance dose of 210 mg SC is given. It is a drug with a high effectiveness and a fast beginning of action. In the Phase III clinical trials, 44 percent of patients attained PASI 100 by week 12 in terms of efficacy (J. Hong & Bhutani, 2021). Upper respiratory infections, nasopharyngitis, headaches, moderate neutropenia, diarrhea, Candida albicansmucocutaneous infections, depression and a risk of suicide have all been reported in clinical trials with brodalumab (Hawkes, Chan, et al., 2018; Tokuyama & Mabuchi, 2020). There is an increased

risk of new or worsening inflammatory bowel illness, as well as a modest increase in the risk of yeast or fungal infections, as with other IL-17 medications (J. Hong & Bhutani, 2021).

Table 1. Biologics for Different Age-Groups of Psoriasis Patients (Adapted from (Aslam et al., 2020; Constantin et al., 2019)

Patient Category	Modality	Biologics
Children below 12 years	TNF-α Inhibitors IL-12/IL-23 Inhibitors	Adalimumab (≥ 6 years) Ustekinumab (≥ 12 years)
Children above 12 years	IL-12/IL-23 Inhibitors	Ustekinumab
Young people	IL-12/IL-23 Inhibitors TNF-α Inhibitors	Ustekinumab Adalimumab, Etanercept, Infliximab
Elderly people	IL-17 Inhibitors TNF-α Inhibitors IL-12/IL-23 Inhibitors	Brodalumab, Ixekizumab Secukinumab Adalimumab, Etanercept Infliximab; Ustekinumab,
Pregnant and Lactating women	TNF-α Inhibitors	Adalimumab, Etanercept

*Table 2. Approved Biosimilars (*Adapted from (Constantin et al., 2019))

Reference Biologic	Biosimilars	Date of authorization
Adalimumab (monoclonal antibody)	Cyltezo (BI 695501)	10/11/2017
	Amgevita and Solymbic (ABP 501)	22/03/2017
	Imraldi (SB5)	24/08/2017
Etanerecept (fusion protein)	Benepali (SB4)	14/01/2016
	Erelzi (GP2015)	23/06/2017
Infliximab (monoclonal antibody)	Flixabi (SB2)	26/05/2016
	Inflectra and Remsima(CT-P13)	10/09/2013

3.2 Safety and Efficacy

In individuals with moderate to severe psoriasis, biologic therapy was linked to a lower risk of death regardless of treatment duration; methotrexate was only linked to a lower risk when used for a year or longer (Langley et al., 2020). Biologics differ from systemic medications in that they target particular inflammatory routs as well as are given on a weekly basis subcutaneously (s.c.) (or intravenously, in the case of infliximab). Biologics now target the IL-23/Th17 axis as well as TNF-α signaling pathways, which are both important in chronicity and the formation of psoriatic plaque (Rendon & Schäkel, 2019).

Even if there is still a medical demand for novel medications that allow for greater durability and cutaneous clearance, the introduction of recent biologics has put up the bar of safety, efficacy in treating psoriasis (Bellinato et al., 2021). During the drug's pre-authorization clinical studies, patients must be examined for anti-biosimilar antibodies. Immunogenicity is a crucial aspect of post-authorization pharmacovigilance and must be incorporated in the risk management plan. Because it is possible to duplicate biologics perfectly, group-to-group variation has been expected. When it comes to biosimilar safety, immunogenicity is essential. Diminishing of the innate counterpart, loss of efficacy and usual immune system impacts are all possible clinical symptoms of antibodies (Constantin et al., 2019).

3.3 Challenges

To date, psoriasis can only be controlled, not cured. However, multiple treatment methods may provide consistent control of disease symptoms (Lynn, 2020). It has also been reported that the biological medications infliximab, ustekinumab, adalimumab and etanercept, as well as most conventional treatments, require higher dose in obese psoriatic patients than in healthy-weight patients (Lambert et al., 2020). A first-in-class IL-17A mAb, Secukinumab having a favorable safety profile, has been licensed for the management of patients with PsA, average to serious plaque psoriasis (Andrew Blauvelt, Reich, Tsai, & Tyring, 2016). Ustekinumab’s efficacy within many intractable instances and its higher response rate than other biological treatments, highlight the worth of the IL-23/Th17 and interleukin-12/Th1 inflammatory pathways in EP pathogenesis (Stinco & Errichetti, 2015). Due to greater documented rates of malignancies associated with infliximab usage in pediatric psoriasis patients compared to the general pediatric population, infliximab use is not recommended. Due to inadequate data and a lack of licensing for use in apremilast, children, the TNF inhibitor certolizumabpegol, the IL17 inhibitors ixekizumab, brodalumab and secukinumab,

and the IL23/p19 inhibitors risankizumab, guselkumab and tildrakizumab, cannot presently be recommended in young patients (Lambert et al., 2020). Anti-IL-23 as well as anti-IL-17 drugs show raising cutaneous reaction rates than anti-IL -12/23 agents and anti-TNF-therapies across several outcomes and over short and long-term look into, in accordance with a newer network analysis with confront distinctions. TNF-α inhibitors and IL-17 are also a front-line biological therapy for PsA, especially when the tendons, axial and entheses domains are involved (Bellinato et al., 2021). Large trials have shown that biologics have a long-term advantage in lowering antidepressant use in psoriasis patients. With ongoing treatment, the positive effect was more pronounced. Biological therapies appear to be more successful than DMARDs in lowering depression and sleeplessness. However, there is a scarcity of reliable comparative data among the many biological drugs. Although adalimumab, etanercept, and ustekinumab were all linked to a statistically significant reduction in depression symptoms, due to the varied rating scales employed, comparisons between the medicines were impossible. In one trial, guselkumab outperformed adalimumab in terms of depression and anxiety. Ixekizumab and IL-17 antagonists, secukinumab have been found to increase patients' QOL and reduce depression in 40 percent of patients, respectively. Fumarates have also been demonstrated to help patients with depression symptoms (Lambert et al., 2020).

Chapter 4

Discussion

Over the last 16 years, the introduction of anti-psoriatic biologic medicines has raised the bar for psoriasis treatment outcomes and is meeting the unmet needs of hundreds of thousands of psoriasis patients. Biologics are frequently utilized as a front-line treatment for average to serious psoriasis, as well as in cases of significant side effects, treatment failure with one or more standard systemic therapies or patients with numerous co-morbidities (Frieder et al., 2018). Patients with average to serious psoriatic illness who are candidates for systemic therapy or phototherapy should use biologics developed for psoriasis. Some biologics have also been authorized for the management of PsA. Only a few head-to-head trials have been done on recent biologics advanced for psoriasis and the majority of outcomes are according to some haphazard studies with placebo as the control arm. In addition, long-term safety and efficacy data are necessary, which cannot be obtained via the relatively short-term clinical trials are needed for drug authorization. As a result, it is now impossible to draw conclusions about the most advantageous medicine among the newer, highly targeted biologics (Rønholt & Iversen, 2017). Because of biologics, the treatment of psoriasis has changed dramatically. On the other hand, eradicating risk factors is crucial for disease control (Kamiya, Kishimoto, Sugai, Komine, & Ohtsuki, 2019). Patients with psoriasis have seen significant improvements in their treatment outcomes thanks to biologic drugs targeting tumor necrosis factor-a or interleukins, such as monoclonal antibodies and receptor fusion proteins. Despite the fact that biologic drugs are significantly more effective than traditional systemic therapy, their high cost has limited their use and contributed to disparities in psoriasis treatment in many countries (Cohen et al., 2020). Biologics have transformed the treatment of plaque-type psoriasis and have shown efficacy in the treatment of EP. Anti-TNF agents, such as etanercept and infliximab, can be combined with traditional immunosuppressive agents for improved efficacy, whereas anti-IL12/23 agents anti-IL17 agents and anti-IL12/23 agents such as secukinumab, ustekinumab, ixekizumab, brodalumab and guselkumab are usually

given as single dose therapy for EP for their high potency and are anti-IL17 medications, for example, can reduce EP symptoms in a matter of weeks, making them a viable option for patients who require immediate relief. Despite tremendous advances in the growth of biologics for psoriasis, study on EP effectiveness is still scarce (Lo & Tsai, 2021). Biological therapies have been frequently employed in dermatology in recent years, particularly in patients with persistent psoriasis. Biological treatments have been proved in numerous clinical trials to effectively control sickness and improve quality of life. In the meanwhile, dermatologists are concerned about the safety of biological agents. As a result, the short-term therapeutic efficacy and safety of IL-12/23, IL-17 and IL-23 biological agents are reviewed and assessed in the treatment of average to serious plaque-type psoriasis (Efficacy et al., 2019). None of biopharmaceutical products, whether biosimilar or original, is safe, but while accepting biosimilars marketing authorization in a highly-regulated region such as the European Union, the authorization is founded on a solid science-based growing process that ensures a equivalent risk-to-benefit balance (Mora, 2015).

Chapter 5

Future prospects

Biologics and biosimilars have made a significant difference in the treatment of psoriasis, competing with the traditional “small molecules" and their generics in terms of price and market share. Researchers have uncovered a huge number of variations linked to psoriasis susceptibility because of advances in genome sequencing methods (Ogawa & Okada, 2020). In comparison to previously approved biologics, novel biologics function through technologies, innovative targets and mechanisms of action. Next-generation biologics, often known as ‘biobetters,’ contain the paired target or mode of activity as formerly approved biologics though they have different structures and formulations. The discussion on the future of biosimilars is not near from over. The rapid advancement of biological therapy and the emergence of biosimilars are significant achievements in the global endeavor to provide modern patient health-care (Constantin et al., 2019). . In psoriasis patients, the type of monobiologic treatment has little effect on the risk of Herpes Zoster. More research is needed in the future to explore Herpes Zoster risk in psoriasis patients on biologics, particularly combined treatment Researchers have been paying close attention to phytopharmaceuticals in recent years, and they are working hard to find something more effective, trustworthy and safe for antipsoriatic therapy. Phytoconstituents (Curcumin, Silymarin, Capsaicin, Quercetin, Berberine, Beta amyrin, and others) may be used to support current therapies in the near future. These phytoconstituents are more effective and have fewer adverse effects. Curcumin is one of the most important phytoconstituents with anti-psoriatic effects (Iriventi et al., 2020). On the other hand, the efficacy of anti-TNF α drugs and ustekinumab supports the relevance of TNF α as well as not only the IL-12/Th1 but also IL-23/Th17 inflammatory routs in EP, despite the fact that the specific pathophysiology of EP is still unknown. Newer/developing anti-psoriatic biologic therapies pointing the IL-23/Th17 rout, like anti-IL17A antibodies, anti-IL-23p19 and brodalumab may play a favorable role in EP therapy (Stinco & Errichetti, 2015). Future research into the automatic link between co-morbidities

and genetics and psoriasis can yield knowledge that allows for a more personalized treatment outcome (Rønholt & Iversen, 2017).

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