

# Treatment options for moderate to severe psoriasis

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**UNIVERSITY OF ZAGREB  
SCHOOL OF MEDICINE**

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**Treatment options for moderate to severe  
psoriasis**

**GRADUATE THESIS**



Zagreb, 2022.

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## Abbreviation

AMP – anti microbial peptides

APC- antigen presenting cell

bDMARDs - biologic disease modifying anti rheumatic medicines

BMI- body mass index

BSA- the body surface area

C<sub>max</sub>- maximal plasma concentration

COX- cyclooxygenase

CSF- cerebrospinal fluid

CYP- cytochrome P

DHFR- dihydrofolate reductase

DLQI- dermatology life quality index

DNA – deoxyribonucleic acid

FDA- food and drug administration

GI- gastrointestinal

HIV- human immunodeficiency virus

HLA- human leukocyte antigen

HR QoL- health related quality of life

IFN- interferon

Ig- immunoglobulin

IL- interleukin

IV- intra venous

JAK/STAT- Janus kinase/signal transducer and activator of transcription

LD<sub>50</sub>- "lethal dose". LD<sub>50</sub> is the amount of a material, given all at once, which causes the death of 50% (one half) of a group of test animals.

mDC- myeloid dendritic cells

MHC- major histocompatibility complex

NAD- nicotinamide adenosine dinucleotide

Nb UVB- narrow band ultraviolet B-rays

NF- nuclear factor

PASI- psoriasis area and severity index

P DC- plasmacytoid dendritic cells

pH- potential of hydrogen

PsA- psoriatic arthritis

PSOR - psoriasis susceptibility

PUVA -psoralen + UVA

QALYs- quality adjusted life years

RAR- retinoic acid receptors

TB- tuberculosis

TCR- T-cell receptor

Th- T-helper

TLR- toll like receptor

TNF- tumor necrosis factor

UDPG- uridine diphosphoglucose

UDPGA- uridine diphosphate glucuronic acid

UV- ultraviolet

UVB- ultraviolet B-rays

VAS- visual analogue scale

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## **SUMMARY**

**Title: Treatment options for moderate to severe psoriasis**

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Psoriasis is a T-cell-mediated illness that affects a large percentage of the population. Psoriasis is increasingly recognized as a multi-system inflammatory condition, rather than only a skin disease. In addition, the disease's chronicity has a major psychological impact on the patient's and cares quality of life. To arrest the so-called psoriatic march, proper illness management is crucial.

Because there is no one-size-fits-all treatment for psoriasis, lifestyle changes, comorbidities, and the elimination of disease-modifying medicines must all be included in the treatment plan. There are a variety of treatments available for psoriasis, ranging from topical medicines to phototherapy to systemic therapy and biologics.

The therapeutic module, particularly pharmaceutical selection, can be influenced by a variety of circumstances. The patient's age, risk factor, past therapeutic response, sickness severity and stability, and treatment cost are all aspects to consider. It is not uncommon to find difficult to treat psoriasis patients who have not responded, have not tolerated, or have exhausted all well-established therapeutic choices because to risk factors, side effects, or the high cost of the drugs.

Psoriasis therapy has progressed rapidly over the years, and as a result, patients may now enjoy a great quality of life. This has occurred in concert with our improving understanding of the pathophysiology of the disease. It is deserving of recognition as a shining example of excellent research that demonstrates the importance of research to humanity's future. Directly tackling immunological pathways in order to treat psoriasis with innovative biologics and small molecules has led to the discovery that the most successful patient care approach is a holistic one that acknowledges the biopsychosocial aspect of the condition. Despite everything that has been said, there is still much more to learn, and more research is needed to enhance patient quality of life.

**Key words:** psoriasis, quality of life, pharmaceutical selection, psoriasis therapy, research.

## **SAŽETAK**

**Naslov: Mogućnosti liječenja umjerene do teške psorijaze.**

**Autor: Chen Siboni**

Psorijaza je bolest posredovana T-stanicama koja pogađa veliki postotak svjetske populacije. Psorijaza se sve više prepoznaje kao višesistemsko upalno stanje, a ne kao bolest kože. Osim toga, kronicitet bolesti ima veliki psihološki utjecaj na bolesnikovu kvalitetu života. Za zaustavljanje tzv. psorijatičnog marša ključno je pravovremeno i pravilno liječenje bolesti. Budući da ne postoji jedinstveni način liječenja psorijaze, promjena načina života, liječenja komorbiditeta i izostavljanje lijekova koji mogu utjecati na samu bolest moraju biti uključeni u plan liječenja. Dostupni su različiti načini liječenja psorijaze, od lokalnih lijekova preko fototerapije, sistemske konvencionalne terapije i bioloških lijekova. Na odabir terapije utječu različiti čimbenici: bolesnikova dob, čimbenici rizika, odgovor na prethodno primijenjenu terapiju, težina i stabilnost bolesti, te cijena liječenja. Poseban izazov u liječenju predstavljaju bolesnici sa psorijazom koji nisu primjereno odgovorili na prethodno primijenjenu terapiju, ili je nisu tolerirali ili su iscrpili sve terapijske mogućnosti zbog čimbenika rizika, nuspojava ili visoke cijene lijekova. Kao rezultat boljeg poznavanja patofiziologije psorijaze tijekom proteklih godina značajno je povećana učinkovitost terapije, a kao rezultat takve terapije značajno je poboljšana i kvaliteta života liječenih pacijenata. Upravo istraživanja na području psorijaze zaslužuju priznanje kao primjer istraživanja koja su dovela do dobrobiti pacijenata. Otkriće imunoloških puteva u liječenju psorijaze inovativnim biološkim lijekovima i malim molekulama dovelo je do uspješnog pristupa skrbi o pacijentima uz holistički pristup koji priznaje biopsihosocijalni aspekt stanja. Unatoč navedenom, potrebna su daljnja istraživanja kako bi se još više unaprijedila terapija i poboljšala kvaliteta života pacijenata oboljelih od psorijaze.

**Ključne riječi:** psorijaza, kvaliteta života, terapija psorijaze, istraživanja.



# 1. Introduction

In this Graduation paper, I choose to cover the topic of one of the most prevalent, important and interesting topics in my eyes – Psoriasis. Especially focusing on the current treatment options and looking on broad perspective on the way that treatment process has changed during the years.

Psoriasis is a chronic condition that requires therapy for the rest of one's life. The quality of life of patients is frequently impacted, and comorbidities are prevalent. The general purpose of this thesis was to investigate treatment regimens, evaluations, and comorbidity in psoriasis patients in order to develop treatment methods that function in everyday practice and enhance patients' quality of life.

The last generations brought a huge change in the way that we look at the disease and most importantly- they provided us a better understanding of the disease process, with far better understanding of the long-term prognosis and changes in the clinical course. The economic burden, comorbidities and the changes of treatments of psoriasis during the years- all can influence the way that the medical society refers to the disease and improve the care of the patients. All of these, may inform decisions also on the process of resource allocation, benefitting not only patients but also the society in general.

Psoriasis is a chronic skin condition, beside the cutaneous manifestations, it is associated with an increased risk of psoriatic arthritis, depression and cardiovascular disease and far many comorbidities which are still under investigation. Over the past 100 years, our understanding of the disease has improved and as a result of that, more effective therapies have been developed during the years. My goal in this paper is to cover mainly the treatment modalities, and to investigate the way the treatment interferes with patient's life and to cover the way we approached the disease through the entire history.

Psoriasis is an inflammatory immune-mediated illness that creates obvious symptoms of inflammation such as elevated plaques and scales on the skin. Although there is indication of genetic susceptibility, the origin of psoriasis has remained a mystery over time. The role of the immune system in the development of psoriasis is also a popular topic in research.

The broad consensus nowadays is that hyperproliferation is induced by cytokines generated by activated resident immune cells, an invasion of T cells, dendritic cells, and innate immune system cells, as well as the keratinocytes themselves. Polymorphisms within or near a variety of genes encoding: cytokines, cytokine receptors, or parts of their signal transduction pathways have been discovered in genome-wide association studies attempting to study the link between cytokines and hyperproliferation. A significant variety of inflammatory cytokines have been discovered to be higher in psoriatic skin, and the serum concentrations of a subset of them have also been linked to the severity of psoriasis illness. Most of the clinical aspects of psoriasis, such as keratinocyte hyperproliferation, enhanced neovascularization, and skin inflammation, are largely explained by the combined impact of the cytokines identified in psoriasis lesions. Understanding which cytokines play a key role in the illness process can lead to the identification of possible treatment targets. These days, several cytokines have been successfully addressed as therapeutic targets, transforming the treatment of this illness(1).

Psoriasis can be caused by both external and internal causes, such as mild trauma, sunshine, infections, systemic drugs, and stress(2). A hyperactive immune system causes skin cell growth to speed up, resulting in this symptom. It takes about a month for normal skin cells to develop and shed. This takes only three to four days for psoriasis skin cells to accomplish. Skin cells gather on the skin's surface instead of shedding. Psoriasis causes itch, burn, and sting some people. Scales and plaque psoriasis may appear on any part of the body, commonly found on the elbows, knees, and scalp. Psoriasis related inflammation can also affect various organs and tissues in the body. Persons with psoriasis are more likely to acquire additional health problems. For example, one in every three people with psoriasis will develop psoriatic arthritis. Swelling, stiffness, and discomfort in the joints and surrounding regions are all symptoms of psoriatic arthritis. Psoriatic arthritis is frequently misdiagnosed, especially in its milder variants. However, it's critical to start treating psoriatic arthritis as soon as possible to avoid irreversible joint injury(3).

## 1.1 History of psoriasis

The ancient scholars believed that psoriasis was included among the various skin conditions called Tzaraath (translated as leprosy in Hebrew) in the Torah (the Hebrew Bible), a condition known as a punishment for slander.

The person was considered as -"impure" ("Tumah" in the Hebrew bible) during their diseased phase and were treated by the "Kohen" (kohen is used in the Torah to refer to priests, whether Jewish or pagan). Although today, it's more likely confusion arose from the miss-use of the same Greek term for different condition. It's known today that the Greeks used the term lepra (λεπρά in greek) for scaly skin conditions. Also, they were using the term "Psora" to describe itchy skin conditions (4). Willan's lepra characterized it in the late 18th century, when English doctors Robert Willan and Thomas Bateman were able to separate it from other skin illnesses. "Leprosy" may be identified by the regular or circular form of patches, whereas psoriasis is usually irregular, as they noted. Willan distinguished two groups: Psora leprosa and leprosa graecorum (5).

Furthermore, in Historical books it it's been described in Ancient Rome- by Cornelius Celsus. Another ancient description of the disease was found by the British dermatologist Thomas Bateman- who fined the possible link between psoriasis and arthritic symptoms in 1813(6).

Because this thesis is dealing mainly about the different treatments, it was important to me to explore also about the treatment of the disease in ancient times, during the history of psoriasis we can observe changes with treatments of dubious effectiveness and high toxicity. In the 18th and 19th centuries, the most common treatment was the Fowler's solutions, which contains a poisonous and carcinogenic arsenic compound, which was the standard treatment used by dermatologists as a treatment for psoriasis(4). Mercury was also used for psoriasis treatment during this period. Later on, Sulfur, iodine, and phenol were used also as a common treatment for psoriasis. During these times, psoriasis was incorrectly considered as an infectious disease. In the 19th century -coal tars were widely used with ultraviolet light irradiation as a topical treatment approach in the early 1900s(2). During those time periods, psoriatic arthritis cases were ineffectively treated with IV (intra-venous) administered gold preparations which were the same treatment used to treat rheumatoid arthritis.

## 1.2 The economic burden on the society

According to reports, the yearly cost of treating psoriasis in the United States is projected to be over \$32.5 billion in indirect expenditures, with \$12.2 billion in direct costs. The most significant direct expense is the cost of pharmaceuticals, with biologic therapy being the most common these days. These expenditures can skyrocket, particularly if the patient has a co-morbid condition like heart disease, hypertension, diabetes, lung illness, or psychological problems. The additional costs associated with co-morbidities are projected to be \$23,000 per person per year (7).

## 1.3 Epidemiology

Psoriasis is estimated to affect 2–4% of the population of the western world (7). The rate in which it affects the patients can varies according to the patient- age, region where he lives and ethnicity, it's a combination of environmental and genetic factors which thought to be responsible for these differences. Unlike thought beforehand, it can occur at any age, although it most commonly appears for the first time between the ages of 15 and 25 years. Approximately one third of people with psoriasis report being diagnosed before age 20 (8). Psoriasis affects both sexes equally (9).

Psoriasis affects in the United States alone around 8 million Americans and occurs more frequently in adults. Psoriasis is about five times more common in people of European descent than in people of Asian descent (10).

In patients with inflammatory bowel disease- such as Crohn disease or ulcerative colitis we can observe an increased risk of developing psoriasis, and for some unknown reason it seems that psoriasis is more common in countries farther from the equator. Persons who are white skin, particularly those with origins from European ancestry are more likely to have psoriasis and on the other hand the condition is relatively uncommon in African Americans and extremely uncommon in Native Americans (11).

Other studies suggested that the onset of psoriasis was bimodal with two peaks of the disease – the first between 16 and 22 and the second between 57 and 60 years of age (12). Psoriasis occurs

in children also, however, there are only minimal number of studies on the incidence or prevalence of psoriasis in children, and those that do exist reveal variations between almost absence of juvenile psoriasis in Taiwan, China (13) and 1.37% lifetime prevalence in 0–17-year-old children in Germany while in 2008–2009, a study of 2194 children in Egypt found that the prevalence of psoriasis among people 18 years of age and younger was 0.05% (14).

## 1.4 Pathogenesis

The conception of the pathogenesis of the disease was changed during the last decades. During the early 80's it was thought that both keratinocytes and T cells are suggested to have key functions in its pathogenesis. It was thought that keratinocytes seem to contribute the cutaneous immune responses through the expression of cytokines and have shown an augmented expression of interleukin-23 (IL-23). IL-23 is important to activate memory T cells to produce Interferon-gamma (IFN- $\gamma$ ) which contributes to the perpetuation of the inflammatory process (15). Immunophenotyping had also confirmed the presence of T-cell in an early phase of the disease and together with the response of psoriasis to the T cell inhibiting therapy cyclosporine or a lymphocyte-selective toxin, T cells are suggested as the driving force in the pathogenesis of psoriasis. At the site of inflammation, activated T-lymphocytes predominantly release type 1 cytokines like IFN- $\gamma$ , tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and IL-2 (16).

Those discoveries were important landmarks in the way that we understand and approach the disease till these days. But today with the modern technology and the new data that is provided to the new generation we have changed the way we understand the disease pathogenesis.

In the past 15 years, we had a breakthrough in the understanding of the pathogenesis of psoriasis which have been translated into targeted and highly effective therapies providing fundamental insights into the pathogenesis of chronic inflammatory diseases with a dominant IL-23/Th17 axis.

Disturbances in the innate and adaptive cutaneous immune responses are now recognized to play a role in the development and maintenance of psoriatic inflammation (17). The endogenous danger signals and cytokines that co-exist with autoinflammatory perpetuations in some individuals induce the activation of the innate immune system. On this basis, we may conclude that psoriasis exhibits autoimmune disease characteristics on an auto-inflammatory background, with both processes operating at the same time and even potentiating one another.

The outermost layer of the skin, made composed of keratinocytes, is one of the key clinical findings in psoriasis. The interaction of keratinocytes with many various cell types (including innate and adaptive immune cells or even vasculature) spanning the dermal layer of the skin shapes the formation of psoriatic plaques, which is not limited to inflammation in the epidermal layer. The etiology may be divided into two phases: an initiation phase initiated by trauma (also known as the "Koebner phenomenon"), an infection phase, and a maintenance phase defined by a chronic clinical development (18).

Dendritic cells are now known to have an important function in the early stages of psoriasis. Dendritic cells are antigen-presenting cells with a high level of expertise. However, the exact mechanism by which they activate in psoriasis is unknown. The identification of  $\alpha$ -antimicrobial peptides (AMPs), which are released by keratinocytes in response to damage and are always overexpressed in psoriatic skin, is one of the hypotheses about the disease's mechanism. The LL37,  $\alpha$ -defensins, and S100 proteins are among the most investigated psoriasis-associated AMPs(18). Cathelicidin, also known as LL37, has been linked to psoriasis pathogenesis. Injured keratinocytes release them, which then form complexes with self-genetic material from other damaged cells. In plasmacytoid dendritic cells, LL37 coupled to DNA triggers toll-like receptor 9 (TLR-9) (pDCs)(19).

Activation of those pDC's seems to be a key in starting the development of the psoriatic plaque and is characterized by production of type I-IFN (IFN- $\alpha$  and IFN- $\beta$ ). Type-I IFN (Interferon) signaling the promotion of myeloid dendritic cells (mDC) as well as phenotypic maturation, also has been implicated in Th1 and Th17 differentiation and function, including IFN- $\gamma$  and interleukin IL-17 production (20).

IFN- $\gamma$  has important rule and contribute to hyperproliferation of keratinocytes in the skin by inhibiting their apoptosis. Later, IL-2 stimulates the T-lymphocyte proliferation and TNF- $\alpha$

activates and increases keratinocyte proliferation. Among the effects of TNF- $\alpha$  are stimulation of production of cytokines from T-lymphocytes and macrophages, chemokine release from macrophages, and the expression of adhesion molecules to vascular endothelial cells. The inflammation leads to oxidative stress that may have systemic consequences since high levels of oxidants stimulate the formation of atherosclerotic lesions in the vessel walls which may lead to a higher cardiovascular disease risk.

Beside that there are both external and systemic triggering factors that can cause psoriasis. The elicitation of psoriasis by injury to the skin, which is also called the Koebner phenomenon is observed in approximately 25% of patients with psoriasis(21). Infections may also induce or exacerbate psoriasis. Strongest evidence of these phenomena exists for the induction of guttate psoriasis that follows tonsillar *Streptococcus pyogenes* infection, which appears to involve initial Super-Antigenic T-cell activation by streptococcal toxins, followed by an antigen-specific T cell response which could then also respond against auto-antigens of the skin(22). However, so far researchers have failed to identify this superantigen.

Current hypotheses imply that a hereditary element may play a role in the illness's pathogenicity. A child's chance of developing psoriasis is roughly 40% if both parents have the disease, 15% if one parent has the disease, and 5% if a sibling has the disease. Psoriasis was shown to be concordant in roughly 60% of monozygotic twins and 20% of dizygotic twins in twin studies (23).

The PSORS1 (Psoriasis Susceptibility 1) locus on chromosome 6p is the most important genetic factor of psoriasis, accounting for 35 to 50 percent of the disease's heritability(24).

Three genes have been the focus of research. HLA-C (associated variant, HLA-Cw 06 allele) encodes a class I MHD protein. CCHCR1 (associated variant, WWCC) encodes the x-helical rod protein 1 and Corneodesmosin (associated variant, allele 5) encodes the protein Corneodesmosin. Other interesting associations outside of the PSORS1 locus are the deletion of the late cornified envelope 3Ben 3C, which encode proteins that have a role in the skin barrier function and the higher genomic copy number of beta-defensins that have both antimicrobial and proinflammatory properties.

These days two major immune system genes are under constant investigation, refers to as interleukin-12 subunit beta (IL-12B) on chromosome 5q, and IL-23R on chromosome 1p, who expresses the interleukin-23 receptor which further involved in the process of T cell differentiation. IL-23 receptor and IL-12B have both been strongly associated with psoriasis (25).

T-cells involved always in the inflammatory process that leads to psoriasis. Those genes found on the pathway which causes upregulation of the tumor necrosis factor- $\alpha$  and nuclear factor  $\kappa$ B, two genes involved in inflammation. The first gene directly associated with psoriasis was identified as the CARD14 gene located in the PSORS2 locus. A unique and rare mutation found on the gene encoding for the CARD14-regulated protein plus an environmental trigger was enough to cause plaque psoriasis (26).

## 1.5 Histological features

Histologically the thickening of the epidermis, also known as acanthosis, is seen in psoriatic plaques, along with parakeratosis, hyperkeratosis, and elongated rete ridges, or papillomatosis (27).

Acanthosis and papillomatosis - caused by accelerated proliferation of basal and precipitous differentiation of supra-basal keratinocytes which contains abnormal replacement of annular squamous with nucleated cells in the stratum corneum also called parakeratosis and by a loss of normal granular layer with thickening of the stratum corneum AKA hyperkeratosis (28).

Besides that, the supra-basal psoriatic keratinocytes are senescent also, which contributes furthermore to the resistance of plaques to apoptosis and transformation. Instead of that, erythema can also be explained as greater number of dilated dermal blood vessels within the dermal papillae (29).

During the stage of plaque development, neutrophils infiltrate to the inflamed tissue, they later build spongiform pustule, so-called Munro's micro-abscesses by invading to epidermis or migrate into the stratum corneum. These micro-abscesses have been observed only on epidermal



compartments with parakeratotic phenotype. The number of infiltrating neutrophils correlates with the severity of psoriatic plaques and is only restricted to pustule and guttate psoriasis(30).

We can observe CD4+ and CD8+ T cells, which are abundant in the psoriatic epidermis, in addition to neutrophils infiltrate, not only it affects the epidermis, but it also affects the dermal compartment, causing alterations in immune cell composition. -T lymphocytes, dendritic cells, and macrophages make up the most of the dermal inflammatory infiltrate, with a modest fraction of neutrophils visible. Infiltrating CD11c+ dendritic cells during inflammatory psoriatic reactions are most typically detected in the upper portion of the dermis, whereas T cells consisting of roughly 75 percent CD4+ and only 25 percent CD8+ T lymphocytes are found mostly in the tips of dermal papillae (31).

## 1.6 Environmental factors as triggers

Triggers for psoriasis are being study for years already, current theories suggest that psoriasis can be provoked or exacerbated by a variety of different environmental factors, particularly infections and drugs. Streptococcal infection is highly associated with guttate psoriasis. In a study of Mallbris et al. (32), at the time of illness initiation, 63% of patients with guttate psoriasis phenotype had acute streptococcal pharyngitis. The use of medications including lithium, beta-blockers, angiotensin converting enzyme inhibitors, antimalarial treatments, and IFN- has also been linked to the onset or worsening of the condition (33).

Severe acute chronic or mental stress can potentially cause the debut of psoriasis. Smoking has been discussed as a risk factor for psoriasis. While several studies have managed to show a clear linkage between psoriasis and cigarette smoking patients, with psoriasis are at least twice as likely to smoke cigarettes than the general population, and some reports have shown that smoking has a negative effect on psoriasis(34). Heavy tobacco consumption also confers an increased risk of more clinically severe disease (35). Physical trauma like- surgical incisions or tattoos can give rise to the Koebner phenomenon (36). The Koebner phenomenon constitutes psoriasis plaques that form at the site of a skin injury, and usually occurs within one to two weeks of injury to the dermis.

Various microorganisms in our world associated with the provocation or exacerbation of psoriasis. Certain strains of *Staphylococcus Aureus* can produce enterotoxin, one of the theories is that exacerbation of psoriatic lesions is most likely mediated via toxin secretion (37).

Due to the potential of Staphylococcal enterotoxins to activate a high frequency of T cells, known as superantigens, these enterotoxins are very effective T-cell activators. Superantigens bind to the MHC class II on APCs and the TCR on T cells at the same time. APCs and T cells cross-link, resulting in polyclonal activation of CD4+ and CD8+ T cells. This results in a large number of T cells proliferating and producing an excessive amount of cytokines(38). Another well-known fact is that  $\beta$ -hemolytic streptococci (Group A, C and G) isolated from the tonsils, are associated with both acute and chronic forms of psoriasis (39). The role of the *Malassezia* species in psoriasis not have been determined yet, they might play an important role, especially in psoriasis involving the scalp, eyebrows, ears and seborrheic areas of the trunk. Normally, healthy skin is colonized by *Staph. aureus* in 5 - 30% compared with approximately 60% of patients with psoriasis (40). Gram negative bacteria can make up only small proportion of the skin flora, mostly in moist intertriginous areas and not on dry skin. *Candida albicans* colonizes the skin, genital mucosa and/or intestinal mucosa of 30–70% of healthy individuals at any given time and, under normal circumstances, the fungus does not cause significant disease (41).

## 1.7 Assessment options

Variety of assessment tools have been used through the years to evaluate the severity of psoriasis, but there is always some lack of standardization between them.

Recently, quality-of-life measures have been adopted across the world, which have improved psoriasis evaluation, but there is a need for consensus in order to make accurate comparisons between researches. The Psoriasis Area and Severity Index (PASI) was the most widely used metric to describe the amount of psoriasis in randomized controlled trials, while the Dermatology Life Quality Index (DLQI) was the most commonly used instrument to quantify quality of life (42).

The Psoriasis Area and Severity Index (PASI) -is the most widely used tool for the measurement and assessment of the severity of psoriasis. It combines assessment of the severity of lesions and the area affected of psoriasis -combined into a single score within the range of 0 to 72. The body is divided into four sections: head (10% of the body area), arms (20%), trunk (30%) and legs (40%). Each of these areas is scored separately, and the four scores are then combined. For each section, we use the percentage of the area of skin involved to estimated and then transformed into a grade from 0 to 6.

PASI is the most validated objective method to measure the severity of psoriasis especially because it has a high intra-rater reliability and a good inter-observer correlation when used by trained assessors like specialized dermatologist(43). The system is very sensitive to changes and reflects disease improvement or deterioration throughout the disease process, although the sensitivity to change for small areas of involvement is poor(43).The PASI 75 concept was frequently used, referring to the percentage of patients who improved their PASI by 75% from baseline to the primary endpoint, which was generally 12 to 16 weeks of therapy. The aim of therapy is blanching, and the European Medicines Agency considers treatment effective if the patient improves by 90% or more (PASI90 response) compared to their baseline Psoriasis Area and Severity Index (PASI). The Body Surface Area (BSA) is another regularly used scale. It's a tool for estimating the level of psoriasis involvement by measuring one palm of the hand, which represents 1% of the total body surface area.

The advantages of BSA over other scales that have been in used, it is his quickness and convenient to use, with a low test-retest variability for the same observer. However, there is moderately high inter-rater variability and the method is likely to overestimate the extent of psoriatic lesions.

The Dermatology Life Quality Index is another extensively used technique (DLQI). It is a ten-item questionnaire that assesses the quality of life of dermatological illness patients. Symptoms and sentiments, daily activities, leisure, job and school, personal connections, and treatment satisfaction are the six subscales in total.

The DLQI has a maximum value of 30, with a higher score indicating a lower quality of life. A 5-point improvement in the DLQI total score is estimated to be the lowest clinically relevant change. Patients with a DLQI total score of 0 are included in the definition of a clinically significant response if their baseline score is less than 5 points (44).

We often use a set of intervals of DLQI scores:

0-1=no effect at all on patient's quality of life, 2-5=small effect, 6-10=moderate effect, 11-20=very considerable effect and 21-30=extremely substantial effect. The reliability and validity of the DLQI is well-established (45).

## 1.8 Disease impact on patient's life

Psoriasis is a complicated illness, and as a result, clinical manifestations lower health-related quality of life (HRQoL), including impairment in everyday activities, which has a negative impact on the patient's productivity. Aside from that, the therapy can be painful, time-consuming, and come with the potential of serious adverse effects (46).

Some of the lesions in psoriasis sufferers may ache, itch, bleed, or burn. Skin scaling, erythema, and edema are examples of other symptoms that might influence physical HRQoL both directly and indirectly by decreasing mobility, vitality, sleep, and rest(47).

Psoriasis can cause visible disfiguration in the patient's appearance, which can lead to negative reactions from the patient and others, resulting in decreased emotional functioning, negative body and self-image, psychological discomfort, and strained social interactions. Only patients with depression or chronic lung illness had poorer psychological HRQoL than patients with psoriasis, despite the physical and psychological burden of eleven diseases such as cancer, ischemic heart disease, and congestive heart failure (48).

Psoriasis often affects activities of daily living like clothing, personal hygiene, sporting, and sexual activities which were reported by the patient to be adversely affected in 27% to 56% of patients with moderate to severe disease. Besides that, the effects of the disease extend to the professional lives of patients with close to 70 percent of patients reporting adverse impact in this domain(49). Psoriasis can also affect work productivity. It has been estimated that approximately 35% of absenteeism and 45% of presenteeism in patients with the psoriasis result directly from the disease

(50). It should be highlighted that cultural and socioeconomic variables might influence symptom experience, perception, and even presentation, possibly making illness impact generalization across cultures difficult.

## 2. Treatment options

Psoriasis treatment choices are many these days, with the goal of assisting patients in maintaining control of their illness. Most persons with lesser problems, on the other hand, can receive effective therapy from their medical practitioner. The general practitioner should send those individuals to a dermatologist if the symptoms are severe or if they are not responding well to therapy.

### 2.1 Topical treatments for psoriasis

Today we know that the topical therapy when used as a singular therapy (also known as monotherapy) is considered to be useful only in those patients which considered to have milder forms of the disease. These days, topical therapy is the treatment of choice in patients with psoriasis affecting < 10% body surface area (BSA) which is regarded as modest. (51) Sometimes psoriasis affecting sensitive regions such as the face, flexures, and genitals may also be treated with it. (51) Topical medicines are also utilized in combination treatment for psoriasis that affects more than 10% of the BSA (moderate/severe psoriasis) and is treated with ultraviolet (UV) light or systemic drugs.

In today's environment, medicines such as topical corticosteroids, vitamin D analogs, salicylic acid, coal tar, and anthralin are available in a variety of formulations such as solutions, foams, and shampoos. Nail psoriasis can be treated with topical corticosteroids, vitamin D analogs, and tazarotene. Those drugs are also employed as an adjuvant therapy in situations with moderate to severe illness that is being treated with UV light or systemic medicines at the same time. Emollients could be also beneficial in the treatment of moderate to severe psoriasis. Older topical agents such as anthralin and coal-tar are no longer in use these days, and their use has decreased

over time. When considering treatments options for thick limiting plaques- salicylic acid is often used in conjunction with other topical medications such as topical corticosteroids and calcineurin inhibitors to promote the absorption of the latter into the psoriatic plaques. Low to mid potency topical corticosteroids are now mostly utilized for face or flexural psoriasis and are considered high powerful when applied to palmoplantar or thick psoriasis lesions. Meanwhile, combining non-corticosteroid therapy with topical corticosteroids may make it easier to avoid using long-term topical corticosteroids (51).

### 2.1.1 Salicylic acid

Salicylic acid is a chemical that can be extracted from the bark of the white willow and the leaves of the wintergreen plant, but it may also be synthesized. It possessed a variety of properties, including bacteriostatic, fungicidal, and keratolytic effects, and its salts, known as salicylates, are used as analgesics.

When it comes to the mode of action of salicylic acid, research have demonstrated that it causes corneocyte desquamation via two mechanisms. To begin, dissolving the intercellular cement material reduces the intercellular cohesion of the horny cells. Second, it lowers the pH of the stratum corneum, resulting in increased skin hydration and softness (52).

Salicylic acid is a keratolytic agent, or skin peeling agent, that works by causing the skin's outer layer to shed. It is a frequent and successful therapy for psoriasis, calluses, corns, keratosis pilaris, and warts, among other skin disorders. It primarily functions as a "scale lifter" in psoriasis therapy, softening and removing psoriasis scales. Salicylic acid operates by inhibiting COX-1 and COX-2 in a direct and irreversible manner, reducing the conversion of arachidonic acid into the precursors of prostaglandins and thromboxane. Salicylates are commonly used to treat a variety of rheumatic disorders due to their analgesic and anti-inflammatory properties, as well as their ability to facilitate the shedding of epidermal cells. Salicylic acid inhibits uridine-5-diphosphoglucose (UDPG) oxidation competitively with nicotinamide adenosine dinucleotide (NAD) and noncompetitively with UDPG. It also prevents the Glucuronic group of uridine-5-phosphoglucuronic acid (UDPGA) from being transferred to a phenolic acceptor. The delay of wound healing caused by salicylates is most likely due to the inhibition of Mucopolysaccharide production (53).

Salicylic acid is about 90% plasma protein bound, is extensively digested, and about 10% is eliminated unaltered in the urine, with a volume of distribution of around 170 mL/kg of body weight.

One of the major concerns about salicylic acid as a topical treatment for psoriasis is the risk of chronic or acute systemic intoxication, which can cause severe symptoms such as oral mucosa burning, frontal headache, central nervous system symptoms, metabolic acidosis, tinnitus, nausea, and vomiting(54). They are more likely to occur with topical treatments due to vast body surfaces, with larger odds in youngsters, especially when death instances have been documented. Scientists can make decisions based on that knowledge. A concentration greater than 10% and application on bigger surfaces should be avoided, especially in youngsters, according to the findings. More than 20% of the BSA should not be treated with salicylic acid. A sequential therapy is performed when bigger areas require a salicylic acid treatment for early keratolysis. Salicylic acid poisoning can be avoided with careful clinical management (55).

### 2.1.2 Topical steroid agents

The adrenal cortex produces the glucocorticoid hydrocortisone, sometimes known as cortisol. Hydrocortisone is used for a variety of diseases, including immunological, inflammatory, and malignant conditions. When Edward Kendall discovered it in the 1930s, he named it Compound F, or 17-hydroxycorticosterone. The FDA finally authorized hydrocortisone on August 5, 1952. When hydrocortisone binds to the glucocorticoid receptor, it inhibits phospholipase A2, NF-kappa B, and other inflammatory transcription factors, leading to the activation of anti-inflammatory genes. The therapeutic index of hydrocortisone is broad, and its half-life is brief (56).

The development of the first topical corticosteroid revolutionized dermatologic therapy. Pharmacologic effects of corticosteroids are primarily anti-inflammatory by many mechanisms: they produce vasoconstriction, interfere with leukotriene pathways, decrease DNA synthesis and mitotic rate in epidermis, suppress mast cells, interfere with epidermal Langerhans' cell antigen presentation and keratinocyte interleukin-1 expression, suppress fibroblast activity, and alter dermal ground substance. These effects are the basis for both the therapeutic benefits and the adverse reactions associated with topical corticosteroid administration (57,58). Topical

corticosteroids are grouped according to their potency. Potency is determined by chemical structure, concentration, vehicle, with ointment being most potent and application techniques (e.g., occlusion may greatly enhance the effect) (58).

Side effects of topical corticosteroids use include cutaneous atrophy, striae, redness and dryness, acne, folliculitis, itching, teleangiectasia and burning sensation. Atrophy is of particular concern on the face and intertriginous skin, sites where percutaneous penetration is facilitated. Infants and children have an increased risk of developing adverse effects and are best served using topical corticosteroids with relatively low potency (58).

### 2.1.3 Calcipotriol

Calcipotriol is a synthetic vitamin D2 derivative that is administered topically. The most common application of these synthetic vitamins is to treat mild plaque psoriasis. When it comes to pharmacodynamic characteristics, sun exposure influences the conversion of 7-dehydrocholesterol to vitamin D3 (cholecalciferol) in the skin. Meanwhile, the mechanism by which calcipotriol aids psoriasis remission is unknown.

On the other hand, it has affinity with calcitriol for the vitamin-D receptors, while on the same time it being less than 1% the activity in regulating calcium metabolism. The vitamin D receptor belongs to either thyroid or steroid receptor family, and it can be found on the cells of a lot of different tissues including thyroid, bone, kidney, and T cells of the immune system. T-cells are known to have a major role in psoriasis has been explained before, therefore it's believed to undergo some modulation in the process of gene expression with binding of calcipotriol to vitamin D receptors. That modulation among others is thought to cause the affect gene products related to the differentiation of the cell and as well to proliferation (59).

The fact that these drugs are scarcely absorbed systemically is the primary explanation for their lack of systemic side effects. Calcipotriene metabolism is fast after systemic absorption, and it follows the same path as natural hormone metabolism. The primary metabolites of the original substance are significantly weaker. The most common complaint about the expected adverse effects is local pain. Vitamin D3 analogues can be used with other topical or systemic drugs to



assist manage these side effects, such as topical corticosteroids or narrow-band UVB phototherapy (60) .

The use of a vitamin D supplement may help increase the efficiency of topical corticosteroid treatment for psoriasis while also lowering the risk of numerous adverse effects frequently associated with corticosteroid therapy.

Because of the risk of inactivation with either medication, using other topical medicines in combination required extra caution. Topical vitamin D3 analogues can be a cost-effective addition to a psoriasis treatment program, especially when their tolerability increases compliance and avoids the need of more expensive systemic medications (61).

#### 2.1.4 Topical calcineurin inhibitors

Calcineurin inhibitors, such as Tacrolimus and Pimecrolimus, are immunosuppressive medicines used to diminish the activity of the patient's immune system and hence the risk of organ rejection after an organ transplant. Treatment of severe atopic dermatitis, severe refractory uveitis following bone marrow transplants, and the skin disorder vitiligo are all possible uses. It was identified in the fermentation broth of a Japanese soil sample containing *Streptomyces Tsukubaensis* in 1984. Tacrolimus is a macrolide in chemical terms. It inhibits peptidyl-prolyl isomerase activity by forming a novel complex with the immunophilin FKBP-12. This FKBP12-FK506 complex inhibits calcineurin, which prevents T-lymphocyte signaling and production of IL-2 (62).

Tacrolimus is an anti-psoriasis medication that can be either orally or used topically. Topical tacrolimus has been shown to help in inverse psoriasis. This appears to be due to the fact that these psoriatic lesions have less induration than hyperkeratotic psoriasis plaques on the body, allowing for more skin penetrance. Researchers also observed that treating inverse psoriasis with topical tacrolimus renders the skin more sensitive to the negative effects of topical corticosteroid

treatment. As a result, a topical preparation that does not produce skin shrinkage, telangiectasia, or striae may be a useful supplement to current topical therapy choices. Aside from that, oral tacrolimus has been found in multiple studies to be effective in the treatment of severe, resistant psoriasis. Systemic tacrolimus may be more appropriate for certain persons with a higher cardiovascular risk than cyclosporin (62).

Albumin and alpha-1-acid glycoprotein were shown to be responsible for 99 percent of the protein in human plasma. This is true regardless of the concentration, which might be anywhere between 5 and 50 ng/mL. In humans, fewer than 1% of the dose is excreted in its entirety in the urine. Fecal elimination accounted for 92.630.7 percent and urine elimination accounted for 2.31.1 percent when administered intravenously (63).

Adult healthy volunteers, kidney transplant patients, liver transplant patients, and heart transplant patients had elimination of around 35, 19, 12, and 24 hours, respectively. In juvenile liver transplant recipients, the elimination was  $11.5 \pm 3.8$  hours, in pediatric kidney transplant patients was  $10.2 \pm 5.0$  (range 3.4-25) hours (64).

Some of the worst adverse effects include blurred vision, liver and kidney problems, seizures, tremors, hypertension, hypomagnesemia, diabetes mellitus, hyperkalemia, itching, insomnia, and disorientation. The LD50 is between 134 and 194 mg/kg (rat).

Tacrolimus has been shown to be beneficial in the treatment of psoriasis when used orally and topically. The efficacy of topical tacrolimus treatment has been proven in cases with inverse psoriasis and psoriasis affecting the face, genitalia, and nails. Apart from that, topical tacrolimus appears to have a role as a corticosteroid-sparing medicine with less side effects than other topical therapies(65).

Researchers observed that oral tacrolimus was beneficial, especially in people with severe resistant plaque psoriasis. Because the side effects of systemic tacrolimus are less severe than those of cyclosporin, it may be a better option for those who have a lot of cardiovascular and metabolic problems(66).

However, on a wider scale, such randomized control studies must be carried out before oral tacrolimus administration may become a routine component of psoriasis treatment (67).

## 2.2 Systemic therapy

When discussing about patients with moderate to severe psoriasis, for some of them the topical treatment is just not enough. In this cases-topical therapy needs to be indicated in combination with systemic treatments.

To indicate a systemic approach, the following criteria have to be met: a PASI greater than 10 or a PASI less than 10 but with the involvement of scalp, face, hands, nails, palmoplantar, or genital area. Another option is psoriasis which appears with severe symptoms which cannot be controlled by topical treatment only. One of the other options is severe impact of the disease on the patient quality of life, for instance patients with DLQI  $\geq 10$ . The last option is when there's a presence of an active psoriatic arthritis, in this case it's required to start with systemic treatment independently with the PASI score.

When choosing the right treatment to your patient, some parameters should be as well considered in the choice of treatment which includes: disease characteristics (severity or the location of lesions), other parameter may be- patient's related features (sex, age, previous treatment failures), lastly, the treatments characteristics (efficacy or safety issues).

### 2.2.1 Methotrexate

Methotrexate is an antineoplastic drug that is used to treat a wide range of disorders, including moderately severe and severe plaque psoriasis, palmoplantar pustulosis, generalized pustular psoriasis, nail psoriasis, and psoriatic arthritis. The medicine is most usually administered for patients who have not responded to topical therapy, phototherapy, or acitretin treatment. Another alternative for these people who are contraindicated or difficult to administer is to use a combination of these treatments (68). This medicine is also used in conjunction with other immunosuppressive drugs, particularly in biological treatments. Methotrexate is responsible for inhibiting the production of antibodies against biologic medicines in this type of combination,

hence increasing their effectiveness. For example, in the treatment of psoriasis in children, a combined therapy of methotrexate and etanercept is employed (69). When the first biological treatment using TNF alpha antagonists was introduced, this was the combination that was employed.

Methotrexate is a derivative of aminopterin, which is a folic acid analogue and antimetabolite. It works by blocking dihydrofolate reductase, an enzyme that converts dihydrofolic acid to tetrahydrofolic acid. In 1951, aminopterin was initially used to treat psoriasis and rheumatoid arthritis. Methotrexate is now used to treat almost all kinds of moderate to severe psoriasis, including psoriatic arthritis (70).

Methotrexate is now prescribed at a weekly dosage of 7.5–25 mg. Once a week, in three separate dosages at 12-hour intervals, commonly known as "Weinstein's method." Methotrexate can be given once a week in a single dosage of 2.5–25(71). When comparing studies, physicians, and patients, it appears that subcutaneous methotrexate administration is now the preferred method. Because it may impact the result of your patient's treatment, the convenience factor is particularly significant, especially when arranging therapy for patients with severe psoriasis (72).

When it comes to action mechanisms, methotrexate works in a variety of ways, including anti-inflammatory, antiproliferative, and immunosuppressive effects. Methotrexate inhibits dihydrofolate reductase (DHFR), which leads to the activation of folic acid, which has an inhibitory impact on the activity of thymidylate synthase, which is a critical component in purine and pyrimidine synthesis, and ultimately leads to DNA synthesis. During the S-phase of the cell cycle, such an obstruction in the route is most common. Later on, this interference results in growth and apoptotic suppression. As a result of this suppression of DNA synthesis, methotrexate restricts the option for epithelial hyperplasia and reinforces death of activated T cells while also decreasing neutrophil chemotaxis. Apart from that, methotrexate causes a reduction in the production of a number of pro-inflammatory cytokines (TNF- and interleukin-1)(73).

There are various options for addressing methotrexate pharmacokinetics: methotrexate is virtually entirely absorbed after parenteral injection. Peak concentrations are found after 30 to 60 minutes with intramuscular administration. Methotrexate concentrations in the serum can surpass 100 micrograms per milliliter because it diffuses passively within cells. The medication was

shown to be 50 percent protein bound in serum. When looking at medication absorption after oral delivery, the drug becomes largely inactivated in the GI tract as well as the liver, resulting in limited bioavailability. Because penetration into the pleura and CSF is sluggish, it takes 30 times longer to reach peak concentration than in the serum. While the half-life of Methotrexate during the terminal elimination phase in patients receiving psoriasis therapy ranges between 3 and 10 hours, about 90% of the medication is removed unaltered(70).

Methotrexate has a teratogenic impact thus it should be used with caution. It is also contraindicated in pregnant and breastfeeding women. The medication is known for causing serious prenatal abnormalities, including neural tube anomalies (74). Between weeks 6 and 8, congenital abnormalities are most common. Aside from that, methotrexate affects spermatogenesis, affecting male fertility, and as a result, partners of methotrexate patients must be advised that they should not become pregnant for at least 3 months after treatment ends. Before pregnancy, female patients must go through at least one full ovulation cycle after stopping the medicine (75).

### 2.2.2 Acitretin

Acitretin is considered as an oral retinoid -used in the treatment of severe psoriasis. What makes that drug special and differentiates it from other drugs is when comparing to other systemic therapies for psoriasis (for exp. methotrexate or cyclosporine) is that it has no immunosuppressive effect. The lack of immunosuppression is an important fact, since it makes acitretin safe to use in the treatment of psoriasis patients with a history of chronic diseases for example like: HIV, hepatitis B/C or malignancies which have a contraindication for systemic immunosuppressive therapy. Acitretin is considered to be one of the first treatments for pustular psoriasis. Acitretin, on the other hand, is believed to be less successful as a single treatment for psoriasis with persistent plaques. Additional agents, such as UVB or psoralen + UVA phototherapy, can help to boost the drug's efficacy (76).

When looking into the drug's history, evidence suggests that the significance of vitamin A-rich foods was recognized as a medicinal treatment as far back as ancient Egypt, most notably for night blindness in nutrient-deficient individuals. McCollum found vitamin A many thousand years later, in 1913. During the 1920s, the significance of vitamin A in sustaining proper epithelial differentiation was extensively explored (77).

Both topical and systemic vitamin A derivatives, referred to as "retinoids," are presently employed in the treatment of psoriasis in modern times.

There are now two retinoids that are suggested for the treatment of psoriasis. Topical tazarotene and systemic acitretin. Both found to be the most effective in combination with other treatment options.

When considering the structure, retinoid molecules are comprised of three structural domains: 1. a cyclic ring 2. a polyene side chain 3. polar end group.

This classification of retinoid into molecules is based on specific substitutions at each of the three domains.

First-generation retinoids- considered as non-aromatic and occur naturally. Second generation retinoids are considered as monoaromatic retinoid derivatives with alterations in the cyclic ring. Lastly, third-generation retinoid derivatives are considered as polyaromatic due to modifications at the polyene side chain (78).

Acitretin is a second-generation retinoid that is highly lipophilic, which means it has a higher serum bioavailability. Interactions between retinoic acid receptors (RAR) and retinoid-X-receptors in the cell nucleus promote the physiological effects of retinoids. Different receptor isomers exist and are distributed differently throughout tissue, with RAR being the most prevalent in the epidermis and RAR being restricted to dermal fibroblasts. The nuclear hormone receptor superfamily includes these receptors. Ligand binding causes retinoid receptor dimerization, which allows for selective binding and changes in gene expression (79). Induction of gene expression occurs through binding of retinoid receptor complexes at gene promoter regions. Alternatively, when discussing suppression of genes- the expression occurs with the binding and sequestration of other associated transcription factors and cofactors. Many of the cytokines implicated in all types of psoriasis, including interleukin-17, are mediated by the JAK-STAT signaling pathway. It

has been observed that acitretin decreases the expression of STAT1 and STAT3, which as a result interferes with the JAK-STAT pathway (80). This kind of process inhibits keratinocyte proliferation and furthermore the expression of multiple cytokines. Among his other effects, acitretin also reduces Th1 and Th17 cell activity and the expression of IFN- $\gamma$ (81). When considering the drugs pharmacokinetics-following first-order kinetics, a single 40 mg dosage generated a maximum plasma concentration of 241 ng/mL in 1.9 hours and an elimination half-life of 5.52 hours in psoriasis patients (82). When discussing the volume of distribution, it was 0.78 L/kg with likely distribution to one or two compartments. Acitretin is also found in skin tissue and on subcutaneous fat within 5h of an oral dose of 25 mg after a month of daily treatment, although it doesn't accumulate in adipose tissue. When considering longer studies, it can be observed that psoriasis patients were treated with daily 40 mg acitretin for 4 weeks with the dose adjusted for clinical efficacy for weeks 5–12 with a maximum dose of 70 mg daily(82).

Acitretin monotherapy is effective in clinical trials, but on the other hand, results are difficult to interpret because of high rates of drop out, adverse side effect profile, use of different measures than the standard measures are now in use to assess psoriasis severity in clinical trials. With given alternate types of mechanisms of action, retinoids proved to be effective in combination treatment with other agents – when randomized open-label trial of 60 patients with psoriasis, three treatment groups were tracked for 24 weeks. It been observed that: 30% fewer patients who received the treatment of acitretin monotherapy, achieved a 75% improvement in PASI score PASI 75 (83) . Although those clinical trials have been focused on chronic plaque psoriasis, it seems that acitretin is also safe and efficacious in two other subsets of psoriasis patients. When comparing to methotrexate, cyclosporine and photochemotherapy (PUVA) therapy, acitretin was found to be more effective in treating generalized pustular psoriasis and is widely used for palmoplantar psoriasis, particularly the pustular variety. On the study they noticed that acitretin reduced the mean number of pustules in palmoplantar pustulosis patients by 93% (84). Moving forward, despite the absence of high-quality randomized research on the subject, a meta-analysis of 12 acitretin patients on clinical trials found that 83.3 percent of erythrodermic patients improved or went into remission(85).

Acitretin is subcategorized under a category X drug – the meaning of that is it is safe during pregnancy and the teratogenicity of acitretin is the largest safety risk (among the risk are-craniofacial and spinal tube abnormalities can occur if taken during early fetal development)(76).

When discussing the systemic absorption of the drug and mechanism of action of acitretin it can cause undesirable side effects. When mucocutaneous complaints seems to be the greatest limiting factor for the patients in continuation of acitretin treatment. Other than that, other side effects that limit use of the drug (include alopecia, blurred vision, cheilitis, dermatitis, depression, dry eyes, epistaxis, headaches, fatigue, gastrointestinal upset, irritability, myalgias and joint pain, photosensitivity, nail changes and tremors). Discussing the toxicity of acitretin- the drug in general has dose dependent toxicity which can result in: transaminitis, pseudotumor cerebri, hyperostosis, and hyperlipidemia. Overdose symptoms are: vertigo, nausea, drowsiness, vomiting, and headache, which mimics closely hypervitaminosis A(86).

## 2.3 Phototherapy and photochemotherapy

Sun exposure and skin illness have been linked for five millennia, dating back to the ancient Egyptians. When Downs and Blunt discovered that exposure to light suppressed fungus development in test tubes in 1877, the present scientific age of medical light treatment for skin illnesses began. An increasing medical interest in the potential of light to heal and cure parasitic skin disorders has resulted from ongoing study. This resulted in Niels Finsen receiving the Nobel Prize in Medicine in 1903 for his groundbreaking work demonstrating that light could effectively cure cutaneous mycobacterium TB (lupus vulgaris), a debilitating disease prevalent at the time (87).

When we go back in time, we can see that phototherapy has been used to treat skin disorders as far as we can tell. The earliest were the Egyptians, who were famed for their ability to use sunlight to treat a variety of skin ailments in ancient times. Other early civilizations, such as the Romans and the Greeks, accomplished the same thing. Particularly for the treatment of psoriasis, have just recently emerged, with important advancements beginning in the early twentieth century. Dr. William Goeckerman revealed the benefits of employing UV radiation in conjunction with unrefined coal tar to treat psoriasis in 1925. Researchers first noticed that UV light has an interesting effect of delaying the rapid growth of skin cells in people with psoriasis. They then demonstrated the effectiveness of topical psoralens followed by UVA light in clearing psoriatic plaques in 1974, though research was done as early as 1970 for the treatment of vitiligo.



Researchers realized in the 1980s that a more defined wavelength of UVB was particularly efficient in treating psoriasis, and narrowband UVB was born (nb UVB) (88). Since 1980s, phototherapy and photochemotherapy have been widely used to treat stable psoriatic lesions, including trunk, scalp, arms and legs, and partial nail psoriasis. A variety of light/lasers with different mechanisms of action have been developed for psoriasis including ultraviolet B (UVB), psoralen ultraviolet A (PUVA), pulsed dye laser (PDL), photodynamic therapy (PDT), intense pulsed light (IPL), light-emitting diodes (LED), and so on. Because light/laser each has specific therapeutic and adverse effects, it is important to adequately choose the sources and parameters in management of psoriasis with different pathogenic sites, severities, and duration of the disorder.

Phototherapies occur in cabins equipped with fluorescent lights that generate UV light of a certain wavelength. In a dermatology office or hospital, the therapy is commonly administered three times each week (89).

PUVA is used to treat a range of skin diseases in addition to psoriasis, including eczema, vitiligo, mycosis fungoides, prurigo nodularis, and graft-versus-host disease (89). PUVA is exceptionally effective. It has been shown to reduce the Psoriasis Area and Severity Index by 75% or more (PASI-75) in 80% of patients, which is comparable to many of the biologic medications available today (89). This makes PUVA particularly useful as a second-line agent when topical medications or UVB phototherapy have failed.

In psoriasis, antigen-presenting cells (dendritic and macrophage cells) stimulate and drive the development of naive helper T (Th) cells into Th1 and Th17 cells, resulting in the production of Th1 and Th17 cytokines that promote inflammation and epidermal hyperplasia. Phototherapy has been demonstrated to reduce the pro-inflammatory Th1/Th17 axis while increasing the counter-regulatory Th2 pathway, resulting in clinical improvement (90).

Apoptosis is a type of planned cell death that can be triggered by a few factors such as hypoxia, infection, heat, and radiation. Organized cell death can also be triggered by disruption to cellular membranes, damage to intracellular organelles, and activation of tumor suppressor genes. Cell shrinkage, membrane blebbing, and chromosomal DNA fragmentation are all common morphological alterations in apoptosis. Apoptosis has been linked to the effectiveness of phototherapy in the treatment of psoriasis in several studies. Apoptosis appears to be induced in a variety of skin cell types, which is interesting. UVB radiation caused selective apoptosis and

substantial T lymphocyte depletion in epidermal psoriatic tissue, but very modestly in the dermis, according to one research. Keratinocytes were found to undergo apoptosis in this study, but only in response to high levels of UVB. The scientists came to the conclusion that the elimination of activated lymphocyte clones was responsible for the long-term therapeutic benefits reported with phototherapy (91). DNA damage, notably the creation of pyrimidine dimers, and disruption to the cellular membrane are considered to cause UVB-mediated apoptosis in human epithelial cells, culminating in death receptor activation and the initiation of the apoptosis cascade. UV radiation is expected to cause TNF, IL-1, and EGF receptors on cell surfaces to cluster and internalize, as well as activate CD95 surface molecules, all of which start pathways that lead to programmed cell death. UV radiation is also thought to cause apoptosis by causing reactive oxygen species to form, which damage cellular, mitochondrial, and nuclear membranes, as well as harming DNA directly (92).

Photochemotherapy, PUVA, has a long track record of success. PUVA inhibits cell proliferation and suppresses the immune system. The number of epidermal and dermal CD3+ T-lymphocytes, as well as CD4, CD8, and IL-2 receptor+ subsets, is significantly decreased in PUVA-treated psoriatic skin. Interleukin-1b (IL-1b), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumor necrosis factor-  $\alpha$  production and release were inhibited in psoriatic patients' peripheral blood mononuclear cells before and after PUVA treatment (TNF-a). Although the number of Langerhans cells is decreased following PUVA, psoriasis remission appears to be unaffected by the degree of this impact. In psoriatic individuals, PUVA had no discernible effect on complement components or immunoglobulin levels. Despite all of these facts and its lengthy history of usage, the mechanism of action of PUVA treatment on psoriatic skin is still unknown. When researchers evaluated the antiproliferative, antiangiogenic, and apoptotic effect of PUVA and compared it to local corticosteroid treatment and the clinical picture of the illness, they used the above-mentioned novel perspectives on the etiology of psoriasis. PUVA can lower the amount of proliferating epidermal cells and correct the pathologically altered pattern of keratinocyte differentiation markers (91).

In the literature, different ideas have been proposed to explain the therapeutic advantages of phototherapy in the treatment of psoriasis. Phototherapy's therapeutic benefits have been linked to cell-cycle arrest. Lower levels of p53, a cell-cycle suppressor protein and greater levels of cyclin D1 -a cell-cycle promoter protein was discovered in skin biopsies of psoriatic lesions in a case-

control study comparing 25 psoriasis patients to 10 healthy controls. After psoriatic skin was subjected to either nb UVB or PUVA treatment, both p53 and cyclin D1 were normalized (93).

There are some risks and possible side effects of PUVA treatment. Some of the potential short-term side effects include burning, itching, and pigmentation of the skin. Burns, which often appear as redness, tenderness, and blistering, may start 24–72 h after treatment in up to 10% of patients during the clearance phase (89).

Long-term risks of PUVA treatment include cataracts, skin aging changes, and skin cancer. Cataracts are considered a theoretical risk, as studies on humans with proper eye protection have not confirmed an increase in the risk of cataracts with UVA exposure (89). Skin aging changes may include dryness, wrinkling, and freckling, which may disappear after treatment is stopped, though freckling may persist indefinitely. PUVA can lead to an increased risk of non-melanoma and melanoma skin cancers, particularly among light-skinned individuals (89). The risk of genital skin cancer may also be increased, but may be prevented with proper shielding.

Phototherapy is a very effective and safe treatment option for patients whose psoriasis is not well controlled on topical therapies alone. To date, UVB light is primarily for stable plaque psoriasis and PDL for topical psoriatic lesions with small area, both of which are safe and effective. PUVA has better curative effects than UVB for managing refractory psoriasis plaques if its side effects can be better controlled. PUVA requires patient compliance with consistent treatments to achieve maximal results. When administered and monitored properly, PUVA can help patients safely achieve clearance and in many cases provide long-lasting remission.

In brief, various phototherapies have been used either in different combinations or as monotherapy. The modality has become a mainstay in the treatment of mild-to-moderate psoriasis without systemic adverse events in today's clinical practice.

## 2.4 Biological therapy

Thanks to the introduction of biologic medications, psoriasis treatment has improved dramatically in the previous two decades. Oral options like methotrexate were the sole way to treat psoriasis systemically before biologic drugs were available. Methotrexate, despite its success in treating psoriasis, has a poor safety profile, whereas oral retinoids and cyclosporine are two more instances of oral therapies having significant black box risks. There are now biologic drugs that are far more effective than pharmaceuticals like methotrexate while also avoiding any black box warnings. Another benefit is that during the maintenance phase of treatment, some of the more contemporary biologic medicines only require four injections per year (94). Biological treatment is the application of drugs that target a pathologic process' immunological or genetic mediator. Psoriasis therapy has vastly improved with the development of biological-based medicines. In the last decade, several biological treatments for psoriasis have been available. Alefacept and efalizumab were two previous medicines that blocked T-cell activation and migration. Infliximab, etanercept, and adalimumab are some of the more recent medications that target TNF- $\alpha$ . Infliximab, etanercept and adalimumab are drugs that specifically suppress the cytokine tumor necrosis factor (TNF)-alpha's function in psoriasis skin and joint symptoms in clinical studies (95). TNF alpha is known to be raised in psoriatic patients' skin and synovium, and the success of these drugs in treating psoriasis and PsA underlines its significance in their etiology. Those drugs are being used on a regular basis, even though they are no longer considered first-line therapy for psoriasis. The earliest biologics, which were used as an alternative to small molecules, targeted T-cell activation and migration. The introduction of tumor necrosis factor  $\alpha$  inhibitors, which were already licensed for various inflammatory conditions, including rheumatic diseases, resulted in a considerable improvement in prognosis. With advancements in our understanding of psoriasis pathophysiology, highly focused and effective medicines have emerged, with the goal of not just improving but even clearing psoriasis. These achievements pave the way for more advanced aims in the future, such as tailoring treatment to each patient's specific needs. Mechanistic investigations with patients treated with new highly focused biologics might point us in the right direction (96).

It is undeniable that biologic treatment for psoriasis has made significant progress in terms of both safety and effectiveness. This new therapeutic paradigm was made feasible by advances in our

understanding of psoriasis pathogenesis. Psoriasis was still largely thought to be a disease with epidermal hyperproliferation thirty years ago. The role of the immune system in the pathogenesis of psoriasis has been underlined in recent studies, which cytokines are implicated in the pathophysiology of psoriatic illness now has a defined mechanism, down to the molecular level. Keratinocytes, natural killer T cells, plasmacytoid dendritic cells, and macrophages are among the cell types implicated in the first cascade of psoriasis pathogenesis. These cells produce cytokines that activate myeloid dendritic cells, which then produce IL-12 and IL-23. Both of these cytokines have an important role in the pathophysiology of psoriasis. IL-12 stimulates native T cells to differentiate into Th1 cells (which generate Interferon and Tumor necrosis factor  $\alpha$ ), whereas IL-23 promotes the proliferation of Th17 and Th22 cells. TNF- $\alpha$ , IL-17, and IL-22 are produced by Th17 cells. When all of these multiple molecular signaling pathways are considered, it is thought that IL-23-mediated activation of the Th17 pathway is the predominant contributor to the inflammation seen in psoriasis (97).

The fact that biologic treatments for IL-17 and IL-23 are more efficacious may indicate that these pathways are more significant in the pathophysiology of psoriasis and that psoriasis patients, on average, have more pathology in this route.

In comparison to the era of more broad immunosuppression reflected by traditional oral drugs, biologic therapies interact with a particular cytokine like IL-17 or IL-23 in a targeted manner, revolutionizing the ability to treat psoriasis. This is an enhanced therapy regimen in which targeted immunomodulation has significantly improved the safety and efficacy of biologic medicines.

### 2.4.1 IL-17 inhibitors

Interleukin-17 has six components (IL-17A–IL-17F), and all of their receptors have just been lately discovered. By producing cytokines and chemokines, attracting neutrophils, activating anti-microbial proteins, and changing T-helper cell development, this family is primarily engaged in the host defensive mechanisms against bacteria, fungus, and helminth infection. By producing inflammatory cytokines and chemokines, IL-17A and other family cytokines are also implicated in the development of psoriasis, psoriatic arthritis, and ankylosing spondylitis, and antibodies against IL-17A as well as the receptor IL-17RA are being effectively employed to treat these

disorders. By activating anti-microbial proteins in infected regions and attracting neutrophils through the production of chemokines, IL-17A and IL-17F play significant roles in host defense against bacterial and fungal infection. In antifungal immunity, Th17 cells are a major source of IL-17A. Th17 cell differentiation is promoted by cytokines generated by dendritic cells and macrophages, which recognize fungal cell-wall components via C-type lectins like Dectin-1 and Dectin-2, as well as the mannose receptor (98).

Anti-IL-17 inhibitors secukinumab, ixekizumab, and brodalumab have been authorized to treat moderate-to-severe plaque psoriasis. According to study findings published in *Pharmacoeconomics – Clinical Practice*, ixekizumab delivers higher quality-adjusted life-years (QALYs) to patients with psoriatic arthritis (PsA) with concurrent moderate to severe plaque psoriasis at a slightly lower cost than secukinumab. Researchers in the United Kingdom compared the cost-effectiveness of two interleukin-17A antagonist biologic disease-modifying antirheumatic medicines (bDMARDs) with similar PsA treatment efficacy: ixekizumab and secukinumab. The goal of the study was to find the treatment that resulted in the greatest clinical improvement while costing the least to patients and the healthcare system (99). In bDMARD-naïve and -experienced patients, ixekizumab was less expensive and delivered more quality-adjusted life-years (QALYs) based on list pricing, however the cost reductions and QALY increases were limited to modest. The total cost of bDMARD-naïve patients was £155,455, whereas secukinumab was £155,530. (Year 2017 values). 7.989 QALYs vs. 8.127 QALYs. Total expenditures were £140,051 vs £140,264 in bDMARD-experienced patients, and total QALYs were 3.996 vs 3.875. Ixekizumab delivered higher QALYs at a little lower cost than secukinumab, and the findings were the most susceptible to medication price fluctuations. Other aspects in clinical decision-making might include patient preferences for the quantity of injections and secret pricing discounts (99).

Ixekizumab is an anti-IL-17A humanized immunoglobulin G subclass-4 (IgG4) antibody used to treat plaque-type psoriasis. To reduce the danger of immunogenicity from repeated injections, this molecule was created as a humanized IgG4 isotype. In cell-based experiments, ixekizumab binds to human IL-17A at a conformational epitope, neutralizing the proinflammatory action of IL-17A/F heterodimers. It's given subcutaneously, with a starting dose of 160 mg and then 80 mg in weeks 2, 4, 6, 8, 10, and 12. A maintenance dosage of 80 mg is given every four weeks after that. 10.5 days is the average elimination half-life (100).

After 12 weeks of induction therapy, ixekizumab outperformed placebo and etanercept in terms of the number of patients who achieved a 75 percent decrease from baseline in the Psoriasis Area and Severity Index and those who achieved a static Physician Global Assessment score of 0 or 1. Ixekizumab produced clinical responses as early as week 1. Patients who received ixekizumab saw improvements in their overall health, itching, and job productivity. Ixekizumab clinical responses were maintained for an additional 48 weeks of maintenance therapy. In trials, ixekizumab was well tolerated and had minimal immunogenicity for up to 60 weeks of treatment. Ixekizumab is an effective and generally well tolerated therapeutic option for people with moderate to severe plaque psoriasis, according to published evidence. It has the advantage of just requiring one maintenance dosage every four weeks (101).

When discussing another drug in this group, secukinumab is a completely human G1k monoclonal antibody that binds to IL-17A and suppresses it. Treating a range of diseases like plaque psoriasis, ankylosing spondylitis, psoriatic arthritis, and active non-radiographic axial spondyloarthritis, it is now FDA authorized.

The loading dosage of 300 mg subcutaneously administered at weeks 0, 1, 2, 3, and 4 is followed by a maintenance dose of 300 mg subcutaneously every 4 weeks for the treatment of psoriasis. 150 mg may be sufficient for maintenance dose in patients with low body weight and mild illness severity. Patients who may require greater dosages, such as those with resistant illness and/or a higher BMI, may benefit from increasing secukinumab dosing to 300mg subcutaneously every 2 weeks during maintenance(102). In terms of injection site responses and discomfort, it is one of the most well-tolerated biologic injectables. While several biologics have been linked to an increased risk of TB reactivation and onset, notably TNF-alpha inhibitors, no studies have revealed evidence of an elevated tuberculosis risk with secukinumab.

Secukinumab is a first-in-class recombinant high-affinity, completely human monoclonal antibody of the IgG1/kappa isotype that exclusively targets IL-17A in the treatment of psoriasis. Secukinumab disrupts the psoriasis pathologic process by binding to IL-17A and prevents it from interacting with the IL-17 receptor expressed on keratinocytes, for example. Secukinumab works by preventing and reversing essential pathologic processes in psoriasis, resulting in normalization of skin histology (103).

After secukinumab therapy, serum levels of total IL-17A (free and secukinumab-bound IL-17A) climb to plateau serum values in psoriasis patients. Serum levels gradually drop after therapy ends, indicating the kinetics of clearance of secukinumab-bound IL-17A. After secukinumab therapy, there are no significant changes in IL-17F, showing that secukinumab binds to and neutralizes free IL-17A (103).

The pharmacokinetics of secukinumab were first investigated in healthy volunteers using intravenous and subcutaneous doses. Peak medication concentrations were obtained between 5 and 6 days after a single subcutaneous dosage (150 mg or 300 mg)(104).

The authors of a clinical trial looked at the impact of numerous parameters on the tolerance of a 0.9 percent saline injection, such as injection volume (0.4–1.6 mL), injection site (abdomen or thigh), and injection rate (0.15 or 0.45 mL/s). Pain at the injection site was a primary factor determining patient tolerance, as measured by a 100mm visual analogue scale (VAS) (both statistically and clinically significantly favoring abdomen over thigh). With bigger quantities, pain intensity scores were statistically higher. Surprisingly, injection rate had little effect on subject tolerance (105).

Even though no human interaction studies have been conducted, there is no indication that IL-17A influences the expression of CYP450 enzymes. Increased amounts of cytokines restrict the production of several CYP450 enzymes during chronic inflammation. Thus, medicines that target the IL-17 pathway might potentially result in a 'normalization' of CYP450 levels, as well as reduced exposure to CYP450-metabolized concomitant drugs (106).

Secukinumab is highly effective in the treatment of a variety of diseases. Dedicated trials for difficult to treat regions including scalp, nail, and palmoplantar psoriasis have been performed, with evidence demonstrating sustained effectiveness for more than two years for the latter two(107). Secukinumab is more effective than numerous other subcutaneous biologic medicines, outperforming both etanercept and ustekinumab in head-to-head studies (108).

In addition to its extraordinary therapeutic efficiency, it has a very high recapture rate. After a sudden discontinuation and subsequent flare, 95% of patients reached PASI 75 by week 12(94).

Secukinumab showed considerable effectiveness over placebo in all aspects of PsA, including joint symptoms, skin symptoms, dactylitis, enthesitis, and patient-reported outcomes, in over 1000



patients throughout FUTURE 1 and FUTURE 2, with responses lasting up to 52 weeks. Furthermore, more than 80% of patients who received secukinumab showed no signs of disease development on radiographs. Efficacy was found in both anti-TNF-IR and anti-TNF-naïve individuals, independent of the presence of concurrent Methotrexate medication. Secukinumab's safety profile was similar with prior psoriasis trials, with no new or unexpected adverse findings. These findings underline the critical role of IL-17A in the pathogenesis of PsA, and when combined with encouraging results from previous trials in ankylosing spondylitis, secukinumab appears to be a promising addition to the therapeutic options for PsA and other chronic and severe rheumatic disorders (106).

### 2.4.2 IL-23 inhibitors

In recent years, a new age has dawned, with more information and understanding of the mechanisms that produce psoriasis, particularly when considering the function of T-helpers 17. Ustekinumab, guselkumab, tildrakizumab, and risankizumab are interleukin-23 inhibitors that have emerged as safe and effective therapies for moderate-to-severe plaque psoriasis. Ustekinumab and guselkumab have also been authorized for psoriatic arthritis therapy. Selective interleukin-23 inhibitors require less frequent dosing than interleukin-17 inhibitors and may offer a superior risk profile, with lower candidiasis and inflammatory bowel disease risk. Overall, these very successful drugs are helping to raise the bar for psoriasis outcomes by improving patient quality of life and resolving skin lesions and joint symptoms(109).

IL-23 is a heterodimeric cytokine made up of the IL-12p40 subunit and a new p19 component. It belongs to the IL-12 cytokine family. Interleukin-23 is largely produced as a disulphide-linked complex with the polypeptide p19 binding protein p40 by activated macrophages and dendritic cells (DCs) in peripheral tissues (skin, intestinal mucosa, and lung). IL-23 has an effect on inflammatory cells and relies on cytokines' capacity to bypass regulatory systems. Anti-IL-23 medicines have a high level of safety and clinical efficacy. Although inhibiting the IL-23 immune axis is enough to cure many autoimmune illnesses, there is a risk of severe infections and other adverse effects (110).

Guselkumab is a monoclonal antibody to human immunoglobulin G1 lambda that inhibits IL-23. IL-23 is an inflammatory cytokine that stimulates CD4+ T-helper cells and, through them, the Th17 cell pathway, which starts the inflammatory cascade that leads to psoriatic plaque development. Guselkumab increased skin clearance and symptomatic relief in psoriasis dermatological symptoms in clinical trials. A subcutaneous injectable form of guselkumab that was approved in July 2017 for the treatment of adult patients with moderate-to-severe plaque psoriasis. This medicine should be used by adults with moderate-to-severe plaque psoriasis who are not candidates for systemic conventional treatment or phototherapy (111).

Guselkumab is an IL-23 antibody that targets the p19 alpha subunit. The p19 and p40 subunits of IL-23 are discovered to be over-expressed in the state of psoriasis and other autoimmune inflammatory skin disorders. Guselkumab binds to the p19 component of IL-23 in dendritic cells and keratinocytes, blocking its interaction with the IL-23 receptor, preventing the production of additional pro-inflammatory cytokines and chemokines via activation of immune cells such Th17 cells. As a result, guselkumab inhibits excessively elevated signaling of inflammatory cascades that promote epidermal abnormalities such as keratinocyte hyperproliferation and the development of psoriatic plaques. The maximal plasma concentration (C<sub>max</sub>) of guselkumab following a 100mg subcutaneous injection is  $8.09 \pm 3.68$  mcg/mL, which is attained after around 5.5 days. Guselkumab, like other human IgG monoclonal antibodies, is likely to be eliminated as smaller peptide units in the kidneys and feces. In patients with plaque psoriasis, the half-life of guselkumab is 15 to 18 days. There have been no animal studies to investigate the effect of guselkumab on carcinogenesis, mutagenesis, or reproductive impairment. Guselkumab dosages of up to 100mg/kg twice-weekly subcutaneously administered into guinea pigs had no influence on reproductive measures (112).

In two recent real-life studies, the effectiveness of guselkumab therapy was also assessed. While 55 patients with moderate-to-severe plaque-type psoriasis were treated with guselkumab for 36 weeks in the first trial, which was conducted in Spain. At 36 weeks, 100% of patients had a PASI 75 response (compared to 87.1 percent in our research), roughly 75% had a PASI 90 response (compared to 80.6 percent in our study), and nearly 55 percent had full remission (67.7 percent in the Spanish study). The efficacy and tolerability of guselkumab for psoriasis in a multi-center research up to 16 weeks was also investigated in the second study, which was conducted in France.

At week 16, 38.3 percent of patients had a PASI of 100, and 50.6 percent had a PASI of 90 (113, 114). The effectiveness findings in this research were positive, they were able to identify top responder patients who potentially benefit even more. These were individuals who had no concomitant conditions, were new to previous biological therapy, or had only had a few prior biologic therapies. Complete remission was reported in both patient categories at 52 weeks, compared to around 50% of individuals obtaining complete remission with comorbidities or those who had previously received biologic therapies. Both univariate and multivariate analyses revealed that these two factors were very significant (115).

Clinical trials are continually looking for novel medications, including biologics, to help people with psoriasis control their illness and improve their quality of life. The understanding of the etiology and pathophysiology of psoriasis has progressed dramatically in recent years. The revelation of the important involvement of the interleukin (IL) 23/IL-17 immunological axis in the pathogenesis of psoriasis has opened up new avenues for drug development, one of which being risankizumab.

Risankizumab is an IL-23-specific IgG1 monoclonal antibody that has been entirely humanized. It was authorized by the FDA and is now available for the treatment of moderate-to-severe plaque psoriasis in people who are clinically eligible for systemic therapy or phototherapy(116). Risankizumab is for the treatment of moderate-to-severe plaque psoriasis in patients who are not suitable for systemic therapy or phototherapy. One of his other indications is the treatment of adult patients with active psoriatic arthritis(117).

Risankizumab works by preventing the release of pro-inflammatory cytokines and chemokines, which can cause redness, discomfort, and plaques on the skin. Risankizumab binds to the p19 component of the human IL-23 cytokine with a high affinity, blocking its activity on the IL-23 receptor. IL-23 is a human cytokine that has a role in inflammatory and immunological processes, particularly in peripheral tissues(116). The polarized type-1 T cell-mediated inflammatory response is mediated by IL-23. In addition to psoriasis patients' blood, type-1 T lymphocytes are detected in significant numbers in psoriasis-affected skin. Type-1 T cells boost the expression of several inflammatory genes that trigger inflammatory cascades by enhancing the activity of interferon (IFN)-gamma(118). The etiology of plaque psoriasis has been linked to

variants of the gene producing the IL-23 p19 subunit and the IL-23 receptor, making IL-23 an attractive target for risankizumab treatment(116).

After a subcutaneous injection, the absolute bioavailability of risankizumab is predicted to be around 89 percent. Peak concentration (C<sub>max</sub>) was obtained between 3-14 days after starting risankizumab medication in a clinical investigation (118). Using a predictive pharmacokinetic model, projected risankizumab trough plasma concentrations in individuals with psoriasis were 1.72 1.11 g/mL at week 16 of therapy and 1.36 0.923 g/mL at week 52 of treatment (119). In people with plaque psoriasis, the estimated volume of distribution at steady state is 11.2 L (34%), however this may fluctuate with increased body weight(120). Risankizumab's metabolic route has yet to be identified. Risankizumab, being a humanized IgG1 monoclonal antibody, is anticipated to be catabolized into tiny peptides and amino acids in the same way as endogenous IgG is catabolized(121). Risankizumab has a half-life of roughly 28 days in plaque psoriasis patients. The daily systemic clearance is predicted to be 0.31 L. (24 percent). Label according to one research, risankizumab clearance differed by 37% between individuals. Risankizumab clearance is reported to decrease when body weight rises. Label despite this propensity, in overweight patients, no dosage change is recommended(121).

When addressing the use of drugs during pregnancy, there is minimal information on the use of risankizumab in pregnant women. There is no evidence of an increased risk of serious birth abnormalities, miscarriage, or ill consequences on the mother or fetus. It's worth noting, though, that human IgG has been known to cross the placenta, and this medicine might do the same to the developing embryo. Risankizumab is an IgG antibody with characteristics that are presumably comparable to those of risankizumab. Women of reproductive potential should use appropriate contraception during treatment and for at least 20 weeks following the final dosage, according to the Canadian monograph for risankizumab(122).

When comparing phase I clinical trials, 39 people were given risankizumab, 18 of them got it intravenously, 13 got it subcutaneously, and 8 got the placebo. There were a few cases of side effects, but they happened at the same rate in both the placebo and experimental groups. Risankizumab-treated patients experienced four major adverse events, all of which were determined to be unrelated to the drug. Risankizumab was linked to clinical improvement in patients starting on week 2 and lasting up to 66 weeks following therapy. 87 percent, 58 percent,

and 16 percent of risankizumab-treated patients, regardless of dosage, achieved 75 percent, 90 percent, and 100 percent reductions in the Psoriasis Area and Severity Index (PASI) at week 12 of treatment, compared to placebo-treated patients. In risankizumab-treated individuals, there was a significant link between treatment-related molecular alterations and PASI improvement(123). In a phase III program involving four clinical trials, the effectiveness, safety, and tolerability of risankizumab were compared against ustekinumab, adalimumab, and placebo in the treatment of plaque psoriasis. The effectiveness and tolerability of risankizumab were validated in these studies (124).

### 3. Conclusion

Fortunately, the range of treatment alternatives has expanded in recent years. It should be noted that there are several treatment procedures that are not covered in full in this document. The length of remission and recurrence ratios in the context of different therapeutic choices for moderate and severe psoriasis will be a future research subject. Furthermore, a future necessity of health evaluation will be the examination of mixed outcomes such as the improvement of psoriatic symptoms and the reduction of symptoms in psoriatic arthritis.

From a clinical standpoint, it is encouraging that the number of treatment operations for chronic severe skin disease has steadily grown in recent years. Alternative procedures can now be tried in situations of specific contraindications or ineffectiveness. Furthermore, by modifying the therapeutic technique after a period, the danger of long-term negative effects can be lowered. Phototherapy in conjunction with topical compounds, oral fumaric acid esters, retinoids (in combination with phototherapy or topical substances), methotrexate, and the novel biologics are now part of the therapeutical algorithm for moderate to severe psoriasis. Future research should focus on therapeutical techniques that are difficult to study in this work, such as physical, balneological, climatic, educational, and complicated rehabilitation treatment, all of which may have beneficial impacts on people with moderate to severe psoriasis. The economic evaluation, like the medical therapy management of moderate and severe psoriasis, refers to a strategic therapeutic idea that, to a significant degree, corresponds to the algorithm in medical practice.

I would like to finish my paper with a quote: "Sometimes you will be in control of your illness, and other times you'll sink into despair, and that's okay! Freak out, forgive yourself, and try again tomorrow." (Kelly Hemingway)

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## 5. Biography

Chen Siboni, born in August 1992 in Israel. Served as a medic in the Inelegance unit, (Israel Defense Forces) 2011-2014. Started medical school 2016 at the School of Medicine, University of Zagreb. Graduate on the summer of 2022.

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