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By: Koadri Abir

Lamine Loubna

And

Bouzidi Sara

TOPIC

**Immunopathogenesis and evaluation of Biologic
Therapies for Psoriasis**

Jury:

Dr.Bouhedda Amina

Mohamed Boudiaf M'sila University

Chairman

Dr.Ben Cheikh Dalila

Mohamed Boudiaf M'sila University

Supervisor

Dr.Fatmi Ahlam

Mohamed Boudiaf M'sila University

Examiner

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Dedication

To the one who was my paradise on earth, the inexhaustible wellspring of tenderness,

To the one who carried me through hardship upon hardship, and raised me on love, patience, and generosity...

To my dear mother, whose prayers were the secret to my success, and whose smile fueled my journey through life.

And to the one who taught me the meaning of strength and perseverance, and who stayed up nights for me so I could reach this day,

To my beloved father, who was my first support and my role model in struggle and sacrifice.

To my brothers and sisters, my childhood companions and fellow travelers, who shared my joys and supported me in times of hardship, and who were always a source of support and reassurance.

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To all my friends and colleagues, who shared with me moments of study, hard work, and success, and who were the best companions on this journey.

And to everyone who taught me a single letter, offered me advice, or supported me with a kind word without expecting anything in return.

ABIR

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Abstract

Increased cardiovascular risk is one of the many inflammatory comorbidities linked to psoriasis, an immune-mediated inflammatory skin condition. By promoting keratinocyte hyperproliferation and feed-forwarding circuits of persistent T cell-mediated inflammation, the interleukin (IL)-23/IL-17 axis plays a crucial role in the immunopathogenesis of psoriasis and associated comorbidities. The downstream part of the psoriatic inflammatory cascade is significantly influenced by IL-17. The unique mechanisms of action of IL-17 and IL-23 in the immunopathogenesis of psoriasis and associated comorbidities are covered in this review, along with the important therapeutic advantages of specifically blocking these cytokines in patients with moderate to severe plaque psoriasis.

Résumé

Le psoriasis est une condition cutanée inflammatoire d'origine immunitaire liée à plusieurs comorbidités inflammatoires, y compris un risque augmenté de problèmes cardiovasculaires. Le rôle central de l'axe interleukine (IL)-23/IL-17 dans l'immunopathogenèse du psoriasis et des comorbidités associées est de stimuler une hyperprolifération des kératinocytes tout en entretenant un cycle d'inflammation chronique à médiation lymphocytaire T. L'IL-17 occupe une place significative dans l'aval de la chaîne inflammatoire liée au psoriasis. Cette revue explore les modes d'action spécifiques de l'IL-17 et de l'IL-23 dans le développement immunopathologique du psoriasis et des comorbidités liées, ainsi que les avantages thérapeutiques notables de la suppression ciblée de ces cytokines chez les patients souffrant de psoriasis en plaques modéré à sévère.

ملخص

الصدفية مرض جلدي التهابي ذو منشأ مناعي، يرتبط بالعديد من الأمراض الالتهابية المصاحبة، بما في ذلك زيادة خطر الإصابة بأمراض القلب والأوعية الدموية. يلعب محور الإنترلوكين-23/الإنترلوكين-17 دورًا محوريًا في الآلية المناعية المرضية للصدفية والأمراض المصاحبة لها، وذلك من خلال تحفيز تكاثر الخلايا الكيراتينية بشكل مفرط، وتفعيل حلقات التغذية الراجعة للالتهاب المزمن بواسطة الخلايا التائية. يلعب الإنترلوكين-17 دورًا هامًا في المرحلة اللاحقة من سلسلة التفاعلات الالتهابية في الصدفية. تتناول هذه المراجعة الآليات المتميزة لعمل الإنترلوكين-17 والإنترلوكين-23 في الآلية المناعية المرضية للصدفية والأمراض المصاحبة لها، بالإضافة إلى الفوائد العلاجية الهامة لتنشيط هذه السيتوكينات بشكل انتقائي لدى المرضى الذين يعانون من الصدفية اللويحية المتوسطة إلى الشديدة.

List of abbreviations

ACT1 = NF-kappa-B activator 1

AD: Atopic Dermatitis

AEs = Adverse Events

BSA: Body Surface Area

cAMP: Cyclic Adenosine Monophosphate

DC: Dendritic Cell

DDC: Dermal Dendritic Cell

LC: Langerhans Cell

pDC: Plasmacytoid Dendritic Cell

mDC: Myeloid Dermal Dendritic Cell

Th17: T helper 17 cell

Th22: T helper 22 cell

Treg: Regulatory T cell

Trm: Tissue-resident memory T cell

Th1: T helper 1 cell

Th9: T helper 9 cell

Th2: T helper 2 cell

KC: Keratinocyte

TNF- α : Tumor Necrosis Factor-alpha

IFN: Interferon

TGF- β : Transforming Growth

TLR: Toll-like Receptor

TCR: T-cell Receptor

AMP: Antimicrobial Peptide

LL-37: Cathelicidin

ADAMTSL5: ADAMTS-like protein 5

CARD14: Caspase Recruitment Domain Family Member 14

FOXP3: Forkhead box P3

ROR γ t: Retinoic acid-receptor-related orphan receptor-gamma-t

MPO: Myeloperoxidase

NOX2 / NADPH oxidase: Nicotinamide Adenine Dinucleotide Phosphate oxidase

ROS: Reactive Oxygen Species

NETs: Neutrophil Extracellular Traps

MCET: Mast Cell Extracellular Traps

PAMPs: Pathogen-Associated Molecular Patterns

DAMPs: Damage-Associated Molecular Patterns

JAK / STAT: Janus Kinase / Signal Transducer and Activator of Transcription

NF- κ B: Nuclear Factor kappa-light-chain-enhancer of activated B cells

TRAF2: TNF Receptor-Associated Factor 2

RIP: Receptor-Interacting Protein

MAP3K: Mitogen-Activated Protein Kinase Kinase Kinase

IKK: I κ B Kinase

Act1 / TRAF3IP2: NF- κ B activator 1 / TRAF3-interacting protein 2

CCL / CCR: Chemokine Ligand / Chemokine Receptor

CXCL / CXCR: C-X-C Motif Chemokine Ligand / Receptor

E-selectin / ICAM-1 / VCAM-1: Adhesion molecules

PsO: Psoriasis

PsA: Psoriatic Arthritis

HLA: Human Leukocyte Antigen

DLQI: Dermatology Life Quality Index

Fc receptor = Fragment crystallizable receptor

FDA = Food and Drug Administration

GPP = Generalized Pustular Psoriasis

HLA-Cw6: Human Leukocyte Antigen Cw6

HRQoL = Health-Related Quality of Life

IgG = Immunoglobulin G

IL-12R β 1 = Interleukin-12 Receptor beta 1

IL-17R = Interleukin-17 Receptor

IL-23R = Interleukin-23 Receptor

IMIDs = Immune-Mediated Inflammatory Diseases

KOH: Potassium Hydroxide

MCS: Mental Component Summary

NK cells = Natural Killer cells

PASI: Psoriasis Area and Severity Index

PCS: Physical Component Summary

PEGylated = Polyethylene glycol–modified

PGA: Physician’s Global Assessment

PsA = Psoriatic Arthritis

PSORS1: Psoriasis Susceptibility 1

SF-36: Short Form (36) Health Survey

Th1 = T helper 1 cells

Th17 = T helper 17 cells

TNFi = Tumor Necrosis Factor inhibitors

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Introduction

Introduction

The innate and adaptive immune systems, as well as genetic and environmental variables, interact to cause psoriasis, a common chronic immune-mediated inflammatory skin condition (Nestle *et al.*, 2009). It is characterised by scaly, erythematous plaques and is linked to a significant decline in patients' quality of life (Villaseñor-Park *et al.*, 2012). Furthermore, it is now identified as a systemic inflammatory condition and is associated with other comorbidities, such as metabolic syndrome and cardiovascular disorders. The most prevalent clinical manifestation is plaque psoriasis, which can range in severity from mild to severe based on the degree of the disease (Nestle *et al.*, 2009).

Psoriasis involves dysregulation of immune responses caused by interactions between T cells, dendritic cells, environmental variables, and cytokines, albeit the precise aetiology of the condition is still unclear (Mahil *et al.*, 2015). Th1 and Th17 pathways are activated when activated keratinocytes stimulate dendritic cells, which then release IL-12 and IL-23 (Sharma *et al.*, 2015). TNF- α , IL-22, and IL-17 are among the pro-inflammatory cytokines produced by these immune cells that encourage keratinocyte activation and maintain chronic inflammation (Lowe *et al.*, 2013). The pathophysiology of psoriasis revolves around the IL-23/Th17 axis, in which Th17 differentiation is induced by IL-23 and IL-17 functions as a crucial effector cytokine (Grine *et al.*, 2015). Furthermore, $\gamma\delta$ T cells, neutrophils, and mast cells also generate IL-17, which contributes to its increased levels in psoriatic lesions (Lin *et al.*, 2011). In general, persistent inflammatory activity in psoriasis is maintained by deregulation of this system (Isailovic *et al.*, 2015).

Advances in our knowledge of the immunopathogenesis of psoriasis over the last thirty years have resulted in the creation of extremely successful biologic treatments. Regulatory bodies including the FDA and EMA have approved TNF- α inhibitors, IL-12/23p40 inhibitors, and IL-17 inhibitors for the treatment of moderate-to-severe plaque psoriasis. Targeted suppression of the IL-23 and IL-17 pathways has been the focus of more recent research, and a number of new biologic medicines are presently undergoing clinical development (Ratner, 2015). These advancements show a move in psoriasis care toward mechanism-based therapeutic approaches (Campa *et al.*, 2015).

Chapter I : General Information on Psoriasis

chaptreI. General Information on Psoriasis

I.1. Definition of Psoriasis

Psoriasis is a chronic, immune-mediated inflammatory skin disease characterized by the rapid proliferation of keratinocytes(Abdulridha *et al.*, 2025). Cytokines secreted by activated local immune cells are responsible for this excessive proliferation (Baliwag *et al.*, 2015). leading to the formation of well-demarcated, erythematous (red), scaly plaques on the skin(Abdulridha *et al.*, 2025).

I.2. Clinical Manifestations and Classification

I.2.1. Clinical Manifestations

The scalp and extensor surfaces, especially the elbows, knees, and lumbosacral area, are frequently affected by psoriasis, which manifests as distinct erythematous plaques coated in silvery scales. genital area, nails, and palmoplantar region may also be affected. The Koebner phenomenon, which indicates active disease, can result from mechanical, chemical, or radiation trauma to the skin, which might cause new psoriatic lesions at the afflicted spot. Pitting, oil patches, subungual hyperkeratosis, nail dystrophy, and onycholysis are examples of nail presentations(Sharma *et al.*,2025).

I.2.2. Classification of Psoriasis

I.2.2.1. Psoriasis and plaques

Plaque psoriasis, the most prevalent type, is characterized by distinct salmon pink plaques with silvery-white scale that are usually distributed symmetrically and affect the scalp, trunk, and extensor surfaces, particularly the elbows and knees (Fig.I). Where scales have been removed, bleeding spots may be visible (Auspitz sign) (Raharja *et al.*, 2021).



Figure I.I. Chronic plaque psoriasis. Widespread, symmetrically distributed and well-demarcated erythematous, scaling plaques. Extensor surfaces such as elbows and knees are typically affected(Raharja *et al.*, 2021).

I.2.2.2. Psoriasis Flexural

Flexural or inverted psoriasis is the term used to describe psoriasis that is localised in skinfolds. Friction and moisture in skin creases do not cause squamous lesions. Bright crimson, symmetrical, infiltrative, fissured plaques with unique outlines are how lesions appear (Tüzün *et al.*, 1994).

This type of psoriasis is diagnosed by fissured plaques with crisp outlines. It is more common in obese people, and seborrhoeic lesions are more likely to occur. In general, this type is more resistant to traditional therapies (Tüzün *et al.*, 1994).



Figure I.II.Inverse psoriasis of the right axilla in an infant: minimal erythematous patch.

I.2.2.3. Psoriasis Guttate

Children and young adults are often affected by this kind of psoriasis. Lesions typically arise following streptococcal infections and appear abruptly as tiny droplets or, less frequently, as squamous psoriatic papules(FigIII)The HLA-Cw6 gene is most commonly linked to this type of psoriasis. Antistreptolysin titers are frequently high. Lesions usually go away on their own when the infection regresses. The face, head, proximal extremities, and trunk are typically affected. Usually, they regress in three to four months. Lesions can occasionally get larger and resemble psoriatic plaque(Van De Kerkhof & Nestlé, 2003).



Figure I.IV Guttate psoriasis: a close-up image showing the characteristic fine scale (Kimmel & Lebwohl, 2018)

I.2.2.4. Psoriasis erythrodermique

Psoriatic lesions cover about 80% of the body's surface in this generalised form of psoriasis. The lesions are predominantly erythematous, and the classic papules and plaques have lost their distinctive characteristics(FigV) .Patients with erythrodermic psoriasis may experience hypothermia due to extensive vasodilation. Desquamation can also cause protein loss and other systemic issues such as lower extremity oedema, as well as cardiac, hepatic, and renal failure. There is a significant danger of cardiovascular or septic shock, so these findings should be continuously monitored. It presents a severe, potentially deadly, and treatment-resistant clinical picture (Wolff et al., 2008).

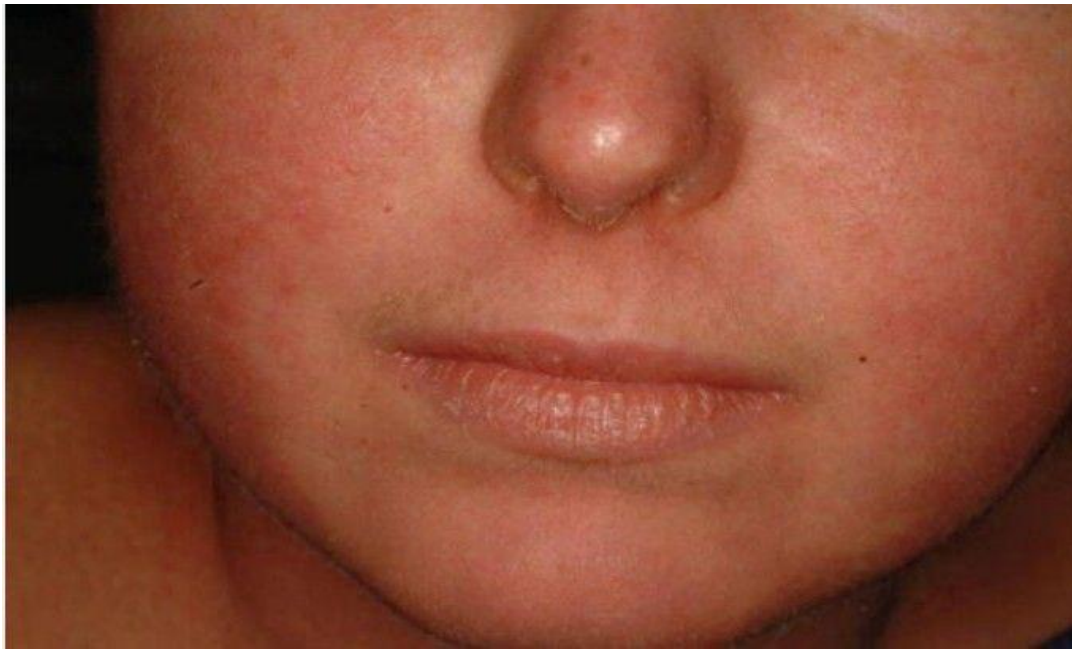


Figure I.VI.Erythrodermic psoriasis: a close-up of the face shows erythema with areas of desquamation(Kimmel & Lebwohl, 2018).

I.2.2.4. Pustular psoriasis

Yellowish pustules on an erythematous background are the hallmark of pustular psoriasis, an uncommon immune-mediated systemic skin condition with a range of clinical manifestations and distribution patterns(Tsuchida *et al.*, 2019). The pustules are characterised by a sterile, mostly neutrophilic infiltration and can be localised or widespread(Negrotto & Correale, 2019).

I.2.2.4.1 palmoplantar pustulosis

Palmoplantar pustulosis is a type of pustular psoriasis that only affects the palms and soles. Recurrent eruptions of sterile pustules on the palmar and plantar surfaces are a characteristic of this condition (Raposo & Torres, 2016)(Fig. V).



Figure I.VII. Palmoplantar pustulosis: a mild case on the palmar surface(Kimmel & Lebwohl, 2018).

I.2.2.4.2 Generalized pustular psoriasis

This is an uncommon type of psoriasis that develops into pustules. It is most commonly observed in young people. It may appear on its own or as a consequence of psoriasis vulgaris, such as when systemic steroid treatment is abruptly stopped, when triggering factors change, when hypocalcaemia occurs, or when irritating therapy is administered (Fig .VIII) . It begins abruptly on an erythematous backdrop and is accompanied by nonspecific symptoms including polyarthralgia, lassitude, and a high fever. Leukocytosis, lymphopenia, an increase in sedimentation rate, and a negative nitrogen balance are all evident. New pustules form once the pustules dry out in a few days. Due to its propensity to spread, peripustular erythema can cause erythrodermia. It needs to be handled right away. The acute phase may result in a deadly course if the disseminated form is not treated (Gülekon, 2008).



Figure I.IX. Pustular psoriasis: pustules on a background of erythema. Desquamation is also prominent here (Kimmel & Lebwohl, 2018)

I.3. Epidemiology of Psoriasis

The prevalence of psoriasis varied by country due to changes in regional and country-specific age patterns. Australia had the highest physician-diagnosed lifetime prevalence of psoriasis in adults (2.38%), followed by Norway (2.36%), Israel (2.28%), Denmark (2.26%), Romania (2.24%), Germany (2.20%), Sweden (2.10%), Poland (2.06%), and Italy (2.00%) (fig.X). (Parisi *et al.*, 2020).

Plaque psoriasis is at least as common in African and Middle Eastern nations as it is in Western nations, where the prevalence in the overall white population is said to be between 1% and 3%(Egeberg *et al.*, 2017).

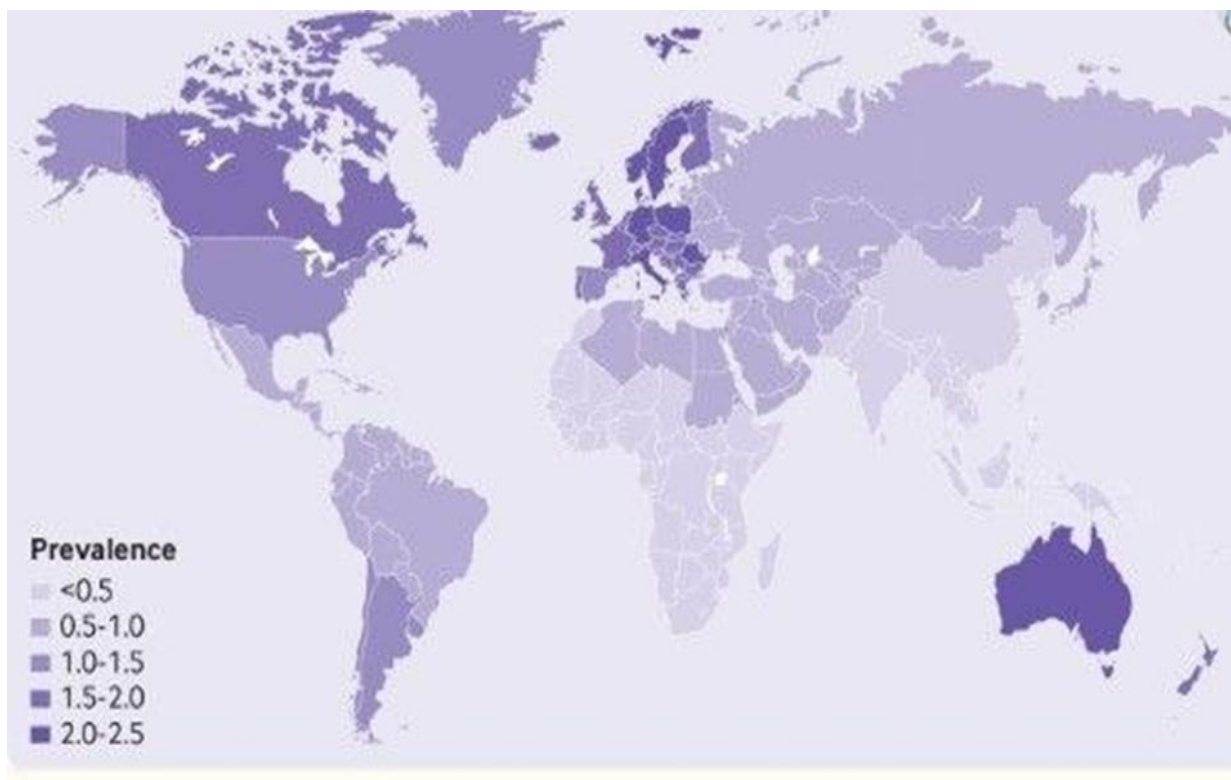


Figure I.XI. Lifetime (physician or dermatologist diagnosed) prevalence of psoriasis in adults by country(Parisi *et al.*, 2020)

I.4. Risk Factors of Psoriasis

I.4.1. Genetic factors

The pathophysiology of psoriasis is significantly influenced by genetics. A positive family history is reported by up to 40% of patients. There are several susceptibility loci (Majewski *et al.*, 2025) (chromosomal regions associated with susceptibility to psoriasis (Elder, 2018)), the most important of which. Psoriasis Susceptibility 1 (PSORS1) on chromosome 6p21. The Human Leukocyte Antigen Cw6 (HLA-Cw6) allele, which is found in this area, is highly linked to early-onset and more severe disease characteristics (Majewski *et al.*, 2025)

I.4.2. Environmental factors

✓ Infections, particularly streptococcal pharyngitis, in which the tonsils' oligoclonal T-cell proliferation is triggered by streptococcal colonisation, and the skin and peripheral blood may also have the same T-cell repertoire

✓ Aspects of stress and psychology

✓ Drugs such immune checkpoint inhibitors (like pembrolizumab), beta-blockers, lithium, and antimalarials (To *et al.*, 2025)

(Beta-blockers alter intracellular calcium levels, which impact granulocyte function and keratinocyte proliferation via lowering cyclic adenosine monophosphate (cAMP) level (Awad *et al.*, 2020).

✓ Abruptly stopping corticosteroids

✓ Alcohol consumption and smoking

✓ Metabolic syndrome and obesity (Mehta & Sathe, 2025)

I.4.3. Age, Gender, and Severity of Psoriasis

psoriasis can strike at any age, it is more prevalent in young and middle-aged people, and it affects men more frequently and women earlier (Pan & Zhang, 2014). While the dramatic drop in hormone levels during perimenopause frequently corresponds with increased disease activity, higher oestrogen levels are linked to improved symptoms, indicating that sex hormones may be important regulatory elements in psoriasis (Raychaudhuri *et al.*, 2003).

Additionally, the severity of psoriasis is influenced by alcohol and smoking, and the correlation between these two factors is greater in males than in women. (Napolitano *et al.*, 2020) The greater rates of

smoking and alcohol usage seen in men compared to women may help to explain these findings(Kindratt *et al.*, 2018)

Between 82.6% and 97.1% of psoriasis patients had psoriasis vulgaris. Over 90% of psoriasis patients were categorised as having mild or moderately severe psoriasis(Pan & Zhang, 2014)

I.5. Impact of psoriasis on quality of life

I.5.1. Physical and social Impact

found that psoriasis had a major impact on many elements of patient life, including the need to miss work or school due to painful and disfiguring skin lesions that can induce physical impairment and poor task performance(Nowowiejska *et al.*, 2021)Furthermore, some patients mentioned concerns with their financial status in terms of the expense of medical care, time lost from work, and transportation fees (Bulat *et al.*, 2020)

I.5.2. Psychological Impact

Psoriasis is commonly related with psychological issues such as stress, anxiety, and depression, as well as substance misuse(Ferreira *et al.*, 2016)

Although there have not been enough research to prove a precise mechanism explaining an obvious cause-and-effect relationship, particularly in the molecular mechanisms of depression and psoriasis, numerous studies have suggested a bidirectional relationship between them (Tohid et al., 2016). discovered that depression and psoriasis are linked not only via inflammatory cytokines, but also by neurotransmitters such as melatonin. Furthermore, dissatisfaction with treatments and stigmatization, particularly if the condition affects the face or genital area, can contribute to depressed symptoms(Ferreira *et al.*, 2016)

I.6. Diagnosis, Severity Assessment

I.6.1. Diagnosis of Psoriasis

I.6.1.1. Clinical Diagnosis

Since psoriasis is a clinical diagnosis, a skin biopsy is typically not required for the disease's classic manifestations(Fredriksson & Pettersson, 1978)

I.6.1.2. Lesion Characteristics

The distinctive lesions are erythematous, scaly, and well-defined plaques. The plaques could hurt and/or itch. Their form might be uneven, circular, or oval, and they are frequently placed symmetrically(Fredriksson & Pettersson, 1978)

I.6.1.3. Clinical Signs

Points of little bleeding (the "Auspitz sign") may appear when the xerotic scale is scraped off. The Koebner phenomenon is the development of lesions at trauma or injury sites(Fredriksson & Pettersson, 1978)

I.6.1.4. Common Sites

The intergluteal cleft, scalp, and extensor surfaces (knees and elbows) are where the plaques are most commonly encountered(Fredriksson & Pettersson, 1978)

I.6.1.5. Variants

Variants of palmoplantar psoriasis and palmoplantar pustulosis can affect the palms and soles. Inverse, guttate, erythrodermic, and generalised pustular psoriasis are further types of psoriasis(Fredriksson & Pettersson, 1978)

I.6.2. Severity Assessment of Psoriasis

Numerous scoring methods have been put out to evaluate the severity of psoriasis(Puzenat *et al.*, 2010).

I.6.2.1. Dermatology Life Quality Index

A popular tool for measuring health-related quality of life (HRQoL) in dermatology is the DLQI. It is a 10-item survey that assesses how having a skin condition affects six dimensions of quality of life: treatment, daily activities, leisure, work and school performance, symptoms and feelings, and personal relationships(Shikiar *et al.*, 2006)

Based on the following answers, each of the ten questions receives a score of 0, 1, 2, or 3: "not at all," "a little," "a lot," or "very much." The scores for each aspect can be expressed as a percentage of either 3 or 6, and the maximum score for each aspect is either 3 (for one question) or 6 (for two questions). Each question's score is added up to determine the overall DLQI, which yields a numerical score between 0 and 30 (or a percentage of 30)(Shikiar *et al.*, 2006). The degree of quality-of-life impairment increases with a higher score.

Regarding the impact on a patient's life, the DLQI scores have the following meanings(Basra *et al.*, 2008):

0 to 1 = no impact

2 to 5 = minor impact

6 to 10 = moderate impact

11 to 20 = very large influence; 21 to 30 = very large effect(Finlay & Khan, 1994)

I.6.2.2. Short Form 36 health survey

The SF-36 is a 36-item general health status questionnaire (Ware, 1993). It is divided into eight domains: physical function, role limitations-physical, vitality, general health perceptions, bodily pain, social function, role limitations-emotional, and mental health. Two overall summary scores can be obtained: a Physical Component Summary (PCS) and a Mental Component Summary (MCS) score (Wyrwich, Nienaber, *et al.*, 1999). The PCS and MCS ratings range between 0 and 100, with higher values suggesting greater health (Wyrwich, Tierney, & Wolinsky, 1999).

I.6.2.3. Psoriasis Area and Severity Index

In order to determine the PASI (Psoriasis Area Severity Index) score, which ranges from 0 to 72, the evaluator must take note of the erythema, thickness, scaling, and percentage of the affected area in four sections (head/neck, trunk, lower and upper limbs) (Walsh *et al.*, 2013).

The PASI instrument showed sufficient content validity, internal consistency, and moderate intraobserver variation in the assessment of severity in individuals with plaque psoriasis. PASI can be suggested for the scientific assessment of plaque psoriasis severity despite several drawbacks (Puzenat *et al.*, 2010).

I.6.2.4. Physician's Global Assessment

This tool [Physician's Global Assessment (PGA)] only assesses the characteristics of the lesion, measuring the thickness, scaling, and degree of erythema of psoriasis lesions throughout the body. It grades on a six-point scale, from 0 (no lesion) to 6 (severe); it does not, however, offer information on the disease's extent (Walsh *et al.*, 2013). It showed minimal intraobserver variation, moderate interobserver variation, and sufficient content validity (Puzenat *et al.*, 2010).

Table I.1. Validity and Minimal Clinically Important Difference of Outcome Measures (Syed, 2017)

Instrument	Type	Evidence of Validity	MCID	References

DLQI	10-item, dermatology-specific quality-of-life questionnaire	yes	3.2	(Mattei et al., 2014) (Ruderman et al. 2003) (Shikiar et al. 2006)
PGA	Single estimate of a patient's disease severity at a given time based on induration, erythema, and scaling	yes	Unknown	(Feldman et al., 2004) (Weisman et al., 2003)
PASI	Numeric score ranging from 0 to 72, based on assessments of four body areas and severity of induration, erythema, and scaling	yes	Unknown	(Ashcroft et al., 1999) (Carlin et al., 2004) (Feldman et al., 2004) (Gourraud et al., 2012)
SF-36	Consists of eight health domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) for which a subscale score can be calculated. It also provides 2 component summary scores: physical and mental. Scores range from 0 to 100, with higher scores indicating better health.	Only responsiveness in psoriasis	2.5to5.0	(Mease & Menter, 2006) (Frendl & Ware, 2014)

LQI = Dermatology Life Quality Index; MCID = minimal clinically important difference PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment; SF-36 = Short-Form (36) Health Survey(Syed, 2017)

I.6.3. Differential Diagnosis

Depending on how the patient presents, there are several different ways to diagnose psoriasis. The diagnosis is simple when the skin findings are typical, with symmetrically located

erythematous, strongly defined scaling plaques on the extensor surfaces. Psoriasis can be diagnosed based on nail findings, gluteal cleft, and skin involvement in the periumbilical area. Atypical instances and psoriasis variations, however, may make diagnosis more challenging (Lisi, 2007).

I.6.3.1. Atopic Dermatitis

Clinically, AD is characterised by extremely itchy, erythematous patches and plaques, frequently accompanied by excoriations, lichenification, and xerosis as a result of recurrent cycles of itching and scratching (Bieber *et al.*, 2017). In adults, AD lesions often affect the face, neck, and dorsal portions of the hands in addition to flexural areas including the antecubital and popliteal fossae (Weidinger *et al.*, 2018). On the other hand, PSO is distinguished by distinct, erythematous plaques that are covered in silvery-white scales, and the pruritus is usually milder than in AD (Griffiths *et al.*, 2021). Although they can develop on any anatomical region, these psoriatic lesions frequently show up on extensor surfaces, such as the scalp, knees, and elbows (Armstrong & Read, 2020).

I.6.3.2. Seborrheic Dermatitis

Histopathological analysis revealed that psoriasis was considerably more likely to have clubbed and uniformly elongated rete ridges, spongiform micropustules of Kogoj, and mounds of parakeratosis with neutrophils. Seborrheic dermatitis was substantially more frequently associated with follicular plugging, shoulder parakeratosis, and conspicuous lymphocytic exocytosis (Park *et al.*, 2016).

I.6.3.3. Tinea / Fungal Infections

Tinea capitis or seborrheic dermatitis may be taken into consideration when making a differential diagnosis for scalp psoriasis. The appearance of well-defined, xerotic plaques with silvery scale that may go above the hairline's edge can be used to identify psoriasis lesions. By using fungal culture, potassium hydroxide (KOH) to prepare skin scrapings, or histology if a biopsy is done, tinea can be differentiated from psoriasis (Murphy *et al.*, 2007).

I.6.3.4. Pityriasis Rosea

Though they frequently show differently, lymphomatoid papulosis, pityriasis rosea, pityriasis lichenoides chronica, tinea versicolor, and secondary syphilis are all included in the differential diagnosis for guttate psoriasis. (Lisi, 2007).

I.6.4. Histopathology

Early lesions include vasodilation, papillary dermal oedema, and leukocyte infiltration before epidermal alterations. These alterations are followed by compact hyperkeratosis, granular layer loss, epidermal hyperplasia, and focal parakeratosis. Dilated, convoluted papillary capillaries with mixed inflammatory infiltrates are seen.

Fully formed plaques show parakeratosis with focal orthokeratosis, a near absence of the granular layer, elongated and clubbed rete ridges, and suprapapillary epidermal thinning. Munro microabscesses and mixed dermal infiltrates of lymphocytes and neutrophils are prevalent, as are dilated papillary veins and the odd necrotic keratinocyte (FigVII). (Mehta & Sathe, 2025).

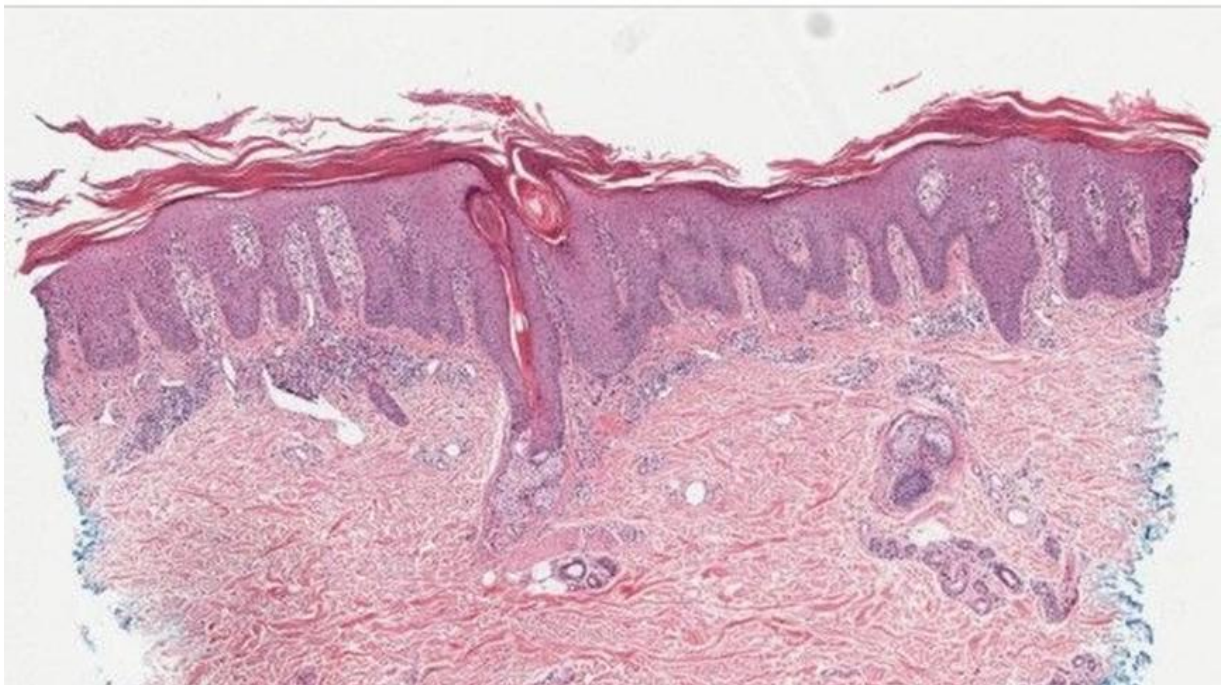


Figure I.XII. Psoriasis Dermopath. The image shows fully developed plaques with parakeratosis, loss of the granular layer, elongated and clubbed rete ridges, suprapapillary epidermal thinning, dilated papillary dermal vessels, and mixed inflammatory infiltrates with Munro microabscesses. Contributed by N Sathe, MD(Mehta & Sathe, 2025).

ChapterII:
Immunopathogenesis of
psoriasis.

chaptreII. Immunopathogenesis of psoriasis.

II.1. Immune cells involved

keratinocytes contribute to disease progression by secreting chemokines and antimicrobial peptides . which promote the recruitment and activation of immune cells(Kamata & Tada, 2023)., This interaction between immune cells and keratinocytes leads to abnormal keratinocyte proliferation and differentiation(Kamata & Tada, 2023). Moreover, local psoriasis relapses are caused by a population of Tm cells(Owczarczyk Saczonek *et al.*, 2020). Overall, psoriasis is caused by a complicated cascade of events involving the interaction of numerous cytokines and diverse cells, (FigureII.I) such as :

II.1.1. The dendritic cell (DC) :

a crucial component of the resident skin immune system, is found in two different microanatomical compartments in normal skin: dermal DCs (DDCs), which are found in the dermis, and Langerhans cells (LCs), which are mostly found in the epidermis(Ochoa *et al.*, 2008).

II.1.2. Neutrophils:

The most prevalent type of innate immune cells are neutrophils. Neutrophils play harmful functions in autoimmune disorders and chronic inflammation(Chiang *et al.*, 2019). It is currently believed that neutrophils act as mediators between the innate and adaptive immune systems(Jaillon *et al.*, 2013) .

II.1.3. Macrophages.

Skin-resident macrophages play a role in tissue homeostasis, adaptive immunity coordination, and innate immunity(Nazimek & Bryniarski, 2024).

II.1.4. Keratinocytes:

The "first-line responding" skin cells to the pathogenic environment of psoriasis are keratinocytes(Büchau & Gallo, 2007).

II.1.5. Th17 cells:

A number of autoimmune and inflammatory diseases are mediated by dysregulated Th17 responses, and T helper (Th) 17 cells play vital roles in host defense. Interleukin (IL)-22 is coexpressed by Th17 cells, and epidermal keratinocytes express its receptor(Tokura *et al.*, 2010).

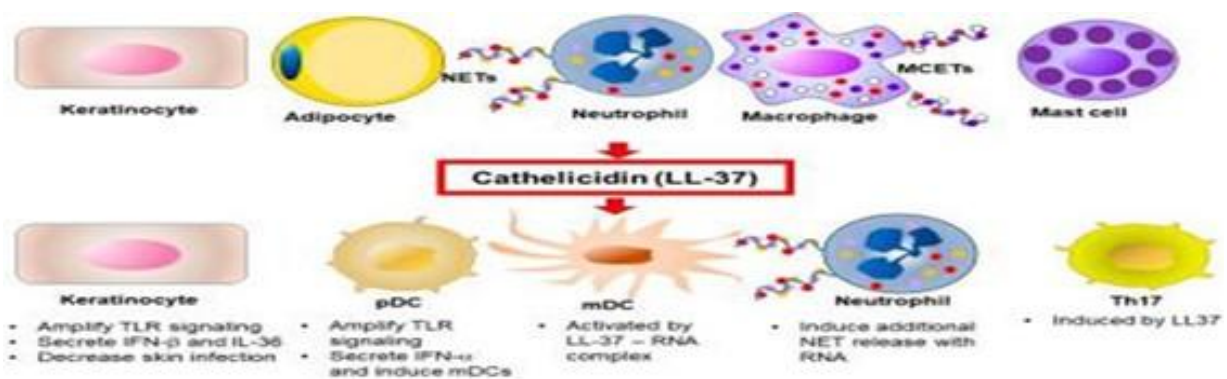


Figure II.II.Source and function of cathelicidin in psoriasis.(Takahashi, 2020)

Cathelicidins are produced by keratinocytes, adipocytes, and recruited neutrophils in inflammatory skin. In psoriasis, its active form, LL-37, stimulates immune cells through TLR, NET, MCET, pDC, mDC, Th, IL, and IFN.

II.1.9. Adaptive immunity.

pDCs produce type I interferons (IFN- α , IFN- β), while mDCs release TNF and IL-6(Ganguly *et al.*, 2009). This environment promotes mDC stimulation and T17 cell differentiation in the skin and lymph nodes(Ghoreschi *et al.*, 2010).Simultaneously, autoreactive CD4⁺ or CD8⁺ T-cells emerge against LL-37, which is generated during infections(Zanetti, 2005). or skin trauma(Lande *et al.*, 2007). The primary signal for T17 activation in psoriasis plaques is the increased IL-23 production by mDCs(Lowes *et al.*, 2014). Furthermore, IL-17 acts synergistically with TNF to enhance the transcription of pro-inflammatory genes, resulting in high IFN- γ and IL-17 levels(Lowes *et al.*, 2014) .(FigureII.III).

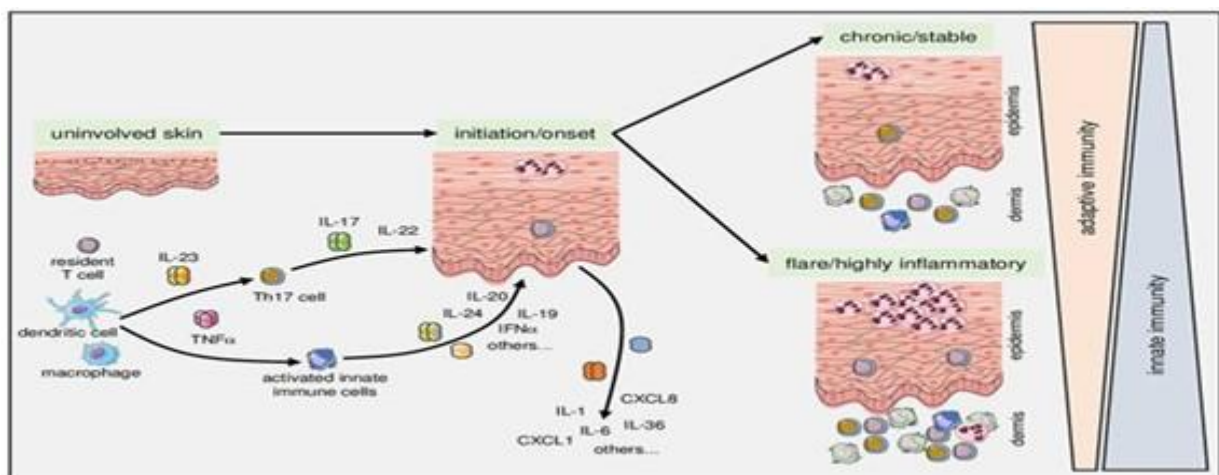


Figure II.III. The complex interplay of innate and adaptive immune mechanisms in the onset, course, and activity of psoriasis. (Schön, 2019)

The pathophysiology of psoriasis is centered on interactions between the innate (dendritic cells, macrophages) and adaptive (T cells) immune systems, where different mediators dictate the clinical expression toward chronic stable vs. severely inflammatory and/or pustular psoriasis.

II.2. Development and pathophysiology of psoriasis.

The development of psoriasis is influenced by both genetic and environmental factors, with HLA-C*06:02 identified as the major susceptibility allele (4). Psoriatic lesions arise following the infiltration and activation of CD8⁺ T cells within the epidermis. These cells display marked clonality and conserved T-cell receptor (TCR) patterns, suggesting that shared autoantigens may drive disease-specific immune responses (5–9). Despite this genetic predisposition, psoriasis is not a congenital disorder.

Dendritic cells (DCs) play a central role in the initiation of psoriasis since they are the main cellular source of interferon- α (IFN- α), tumor necrosis factor- α (TNF- α), interleukin-12 (IL-12), and interleukin-23 (IL-23) (Wang & Bai, 2020). Plasmacytoid dendritic cells (pDCs) infiltrate psoriatic skin and become activated to produce IFN- α early in the course of the disease (Nestle *et al.*, 2005). LL37 acts as a primary mediator of pDC activation by binding self-DNA and self-RNA complexes, which stimulate Toll-like receptor 7 (TLR7) and Toll-like receptor 9 (TLR9), leading to interferon production (Lande *et al.*, 2007). (Figure II.IV)

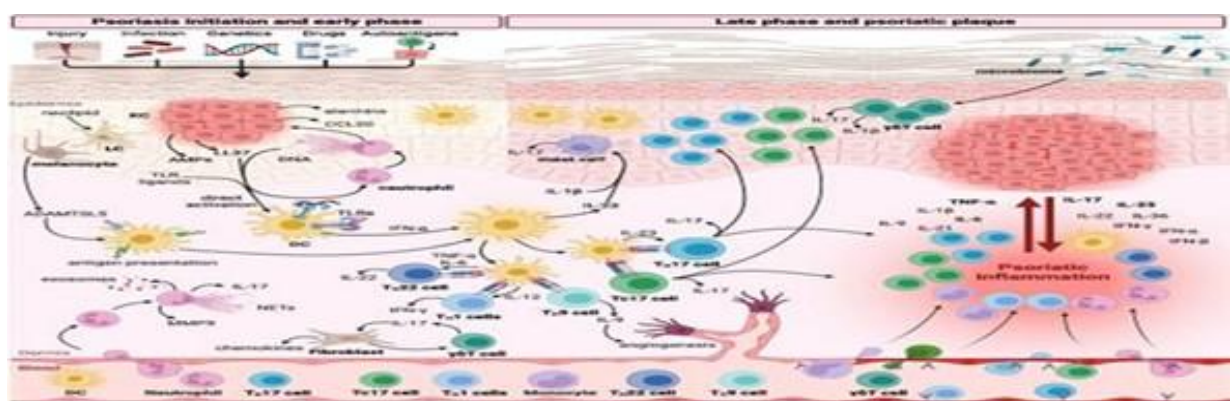


Figure II.IV. Dysregulation of immune response in psoriasis. (Sieminska, 2024)

Early phase neutrophils, activated keratinocytes, and dendritic cells stimulate T cells (T_H17, T_C17, T_H9, T_H1, T_H22, $\gamma\delta$ T cells) in psoriasis caused by skin injury, infection,

medications, and autoantigens. This propels the late stage, which is marked by significant immune cell infiltration, elevated cytokines, enhanced angiogenesis, and hyperproliferation of KCs.

Naive T cells develop into Th1 cells in response to IL-12 stimulation, leading to increased IFN- γ release (Schlaak *et al.*, 1994). IFN- γ then activates antigen-presenting cells, which subsequently produce and release the chemokine CCL20. This in turn recruits IL-17A⁺ T cells to lesional skin, resulting in the accumulation of local inflammation. At the same time, IFN- γ together with IL-17A stimulates keratinocytes, leading to the production of antimicrobial peptides and activation of the innate immune response (Hawkes *et al.*, 2017). These activated keratinocytes then release IL-18 and IL-1 β , which further enhance Th1 activity and initiate the early development of Th17 cells. (Chung *et al.*, 2009)

Naive T cells then differentiate into Th17 cells under the stimulation of IL-1 β , TGF- β , IL-6, and IL-23 through activation of the transcription factor ROR γ t (Yang *et al.*, 2008). Th17 cells stimulated by IL-6, IL-1 β , and IL-23 are mainly involved in autoimmune and chronic inflammatory disorders. Th17 cells subsequently secrete IL-17A, IL-12, IL-22, and IL-9, which act directly or indirectly on keratinocytes, leading to abnormal proliferation and the release of cytokines and chemokines such as IL-6, IL-8, TNF- α , CCL20, and CXCL1/2/3/5/8 (Hawkes *et al.*, 2017). (Figure II.V)

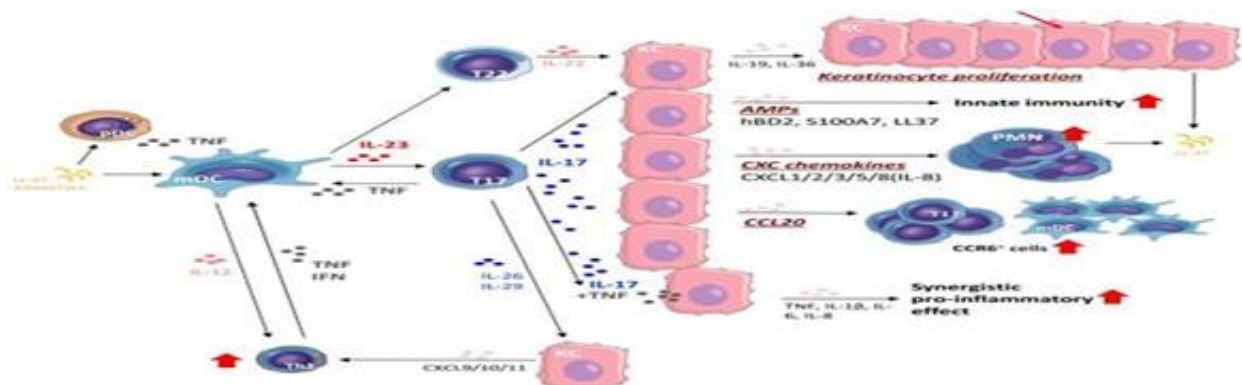


Figure II.V. IL-23/T17-mediated effects on epidermal keratinocytes in psoriatic skin. (Hawkes, 2017)

The effects of IL-17 on keratinocytes, which are controlled by IL-23, include the induction of epidermal hyperplasia (via IL-19, IL-36), the upregulation of antimicrobial peptides (hBD2, S100A7, LL-37), the recruitment of leukocyte subsets (neutrophils, mDCs) through

chemokines, and the transcription of pro-inflammatory genes (TNF, IL-1 β , IL-6, and IL-8) that maintain inflammation in psoriatic skin.

Th22 cells then produce IL-22, which is a potent inducer of keratinocyte hyperproliferation (Ekman *et al.*, 2019). At the same time, IL-22 inhibits normal keratinocyte differentiation. Through activation of the STAT3-mediated IL-23 signaling pathway, IL-22 leads to psoriatic dermatitis and epidermal acanthosis (Zheng *et al.*, 2007).

Treg cells become dysfunctional in psoriasis. Although increased levels of FOXP3⁺ Treg cells are observed in both peripheral blood and skin lesions, these cells lose their immunosuppressive capacity and fail to control inflammation due to alterations in their number, function, and chemotaxis (Soler *et al.*, 2013). In response to the inflammatory environment, Treg cells exhibit a high degree of plasticity and may convert into IL-17A⁺FOXP3⁺CD4⁺ Th17-like cells, which display strong pro-inflammatory activity and further exacerbate psoriatic inflammation (Kleinewietfeld & Hafler, 2013). (Figure II.VI)

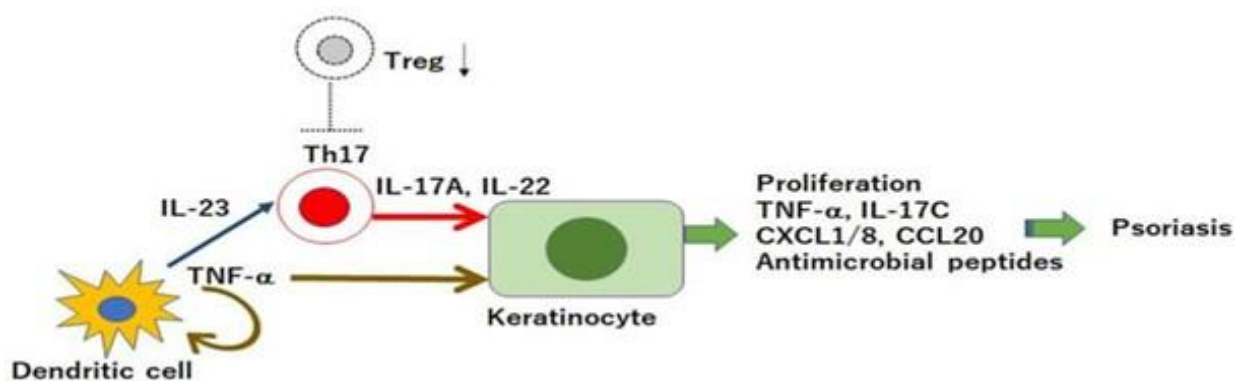


Figure II.VI. Tumor necrosis factor (TNF)- α /interleukin (IL)-23/IL-17 axis, and the defect in regulatory T cells (Tregs) in the pathogenesis of psoriasis. (Kanda, 2021)

While malfunctioning Tregs are unable to restrict Th17 cells in psoriasis, dendritic cells leak TNF- α , which induces IL-23. Th17 cells then create IL-17A and IL-22, which act on keratinocytes to promote proliferation and produce cytokines, antimicrobial peptides, or chemokines, causing inflammation.

Rapid cell growth causes keratinocytes to undergo incomplete keratinization, leaving the nucleus in epidermal keratinocytes (Griffiths & Barker, 2007), a condition known pathologically as parakeratosis. Beyond LL37, another significant autoantigen in psoriasis has been identified as ADAMTS-like protein 5 (ADAMTSL5), which is specifically expressed by melanocytes in the

epidermis and stimulates CD8⁺ T cells. The progression of the disease is further driven by specific molecular alterations. Mutations in the CARD14 gene in keratinocytes increase IL-17A signaling and accelerate the onset of psoriatic dermatitis (Moos et al., 2019; Wang *et al.*, 2018). Conversely, dermatitis development and neutrophil recruitment are significantly decreased when keratinocytes delete the IL-17 receptor. Psoriatic skin inflammation is also encouraged by the increased production of polyamines by keratinocytes (Lou *et al.*, 2020). Furthermore, the downregulation of Galectin-7 (Chen *et al.*, 2021), along with exosomes and miRNA generated from keratinocytes, controls the etiology of psoriasis and amplifies the inflammation of psoriatic skin (Huang *et al.*, 2021). (Figure II.VII)

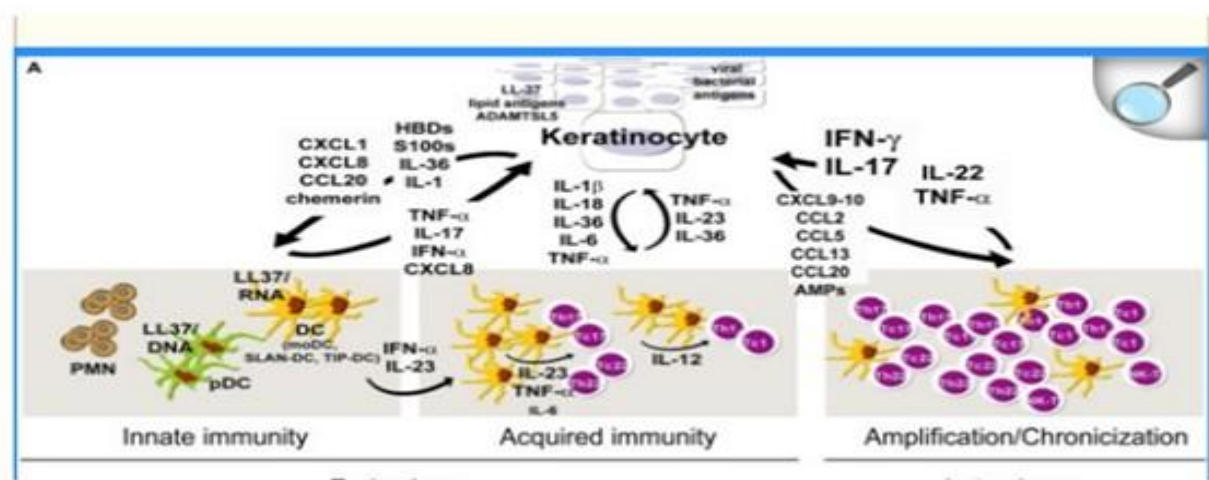


Figure II.VII. Aberrant interplay of keratinocytes and immune cells in psoriasis. (Albanesi, 2018)

Keratinocytes generate trigger factors (LL37/nucleic acid complexes, lipid antigens, ADAMTSL5), AMP, chemokines, and IL-1 cytokines during the first stage; LL37 activates DC, promoting T cell proliferation. During the chronic phase, keratinocytes exhibit altered differentiative processes, hyperproliferate, and overexpress inflammatory mediators due to a T-cell cytokine milieu (IFN- γ , TNF- α , IL-17, and IL-22).

Tissue-resident memory T lymphocytes in epidermal skin compartments show the capacity to sustain and even promote disease recurrence in psoriasis (PsO) patients in remission (Cheuk *et al.*, 2014). CD8⁺ tissue-resident memory T cells continue to produce high amounts of IL-17A years after effective PsO treatment is stopped, which may promote inflammation and recruit circulating leukocytes into tissue upon disease triggers (Cheuk *et al.*, 2014).

Tumor necrosis factor-alpha (TNF- α) In psoriasis, TNF- α promotes adhesion molecules like E-selectin, ICAM-1, and VCAM-1 in papillary dermal vessels, facilitating leukocyte migration into inflamed skin (Zhang *et al.*, 2024).(FegureII.VIII)

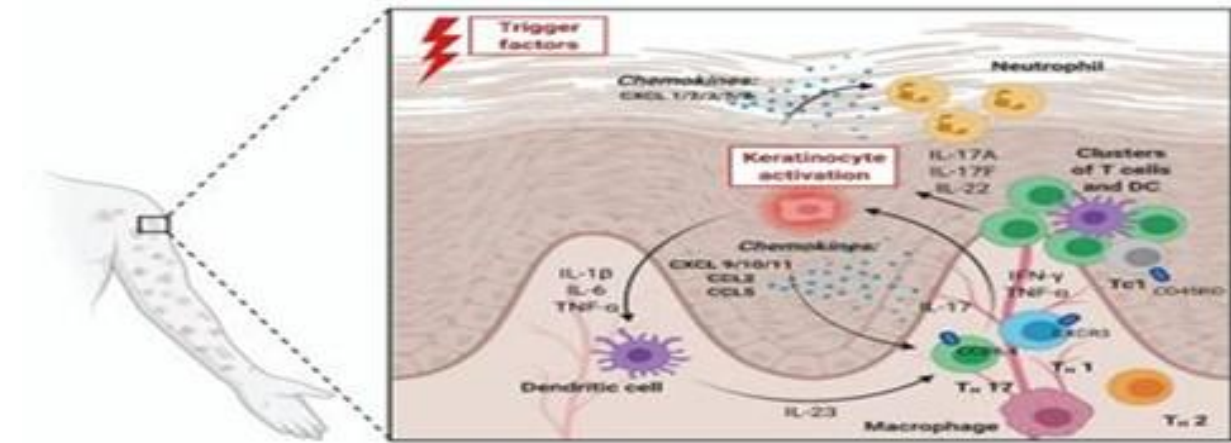


Figure II.VIII.Chemokine-mediated inflammatory pathways in psoriasis.(Zdanowska, 2021)

The pathophysiology of psoriasis involves chemokines (CCL/CCR, CXCL/CXCR), dendritic cells, T lymphocytes (Th1, Th17, Th2), and cytokines (IL, IFN- γ , TNF- α).

the interaction between autoreactive T cells and resident keratinocytes creates the inflammatory and immunological circuits responsible for the onset, development, and persistence of psoriasis ... Specifically, through the NF- κ B-hsa-miR-27a-3p-galectin-3 axis, TNF- α promotes psoriatic inflammation by increasing CXCL-1/8 expression in keratinocytes ...

II.3. Signaling pathways involved.

such as TNF- α , IL-17, and IL-23, signal transduction pathways downstream to the cytokine receptors, and different activated transcription factors regulate Th1 and Th17 immune responses(Tseng *et al.*, 2021), In many respects, constitutive or inducible immune circuits found in normal human skin are amplified in the immunological pathways that become active in psoriasis(Lowes *et al.*, 2014).

II.3.1. TNF- α signaling pathway

An important cytokine in innate immune responses, TNF-alpha is elevated in the circulation and lesional skin of psoriatic patients (Schottelius *et al.*, 2004). making it essential for maintaining clinical symptoms (Ovcina-Kurtovic & Kasumagic-Halilovic, 2022). It binds to TNFR1 and TNFR2 to mediate the activation of the NF- κ B family (Wu & Bruggeman, 2014). specifically

through signaling molecules such as TRAF2, RIP, MAP3K, and the IKK complex (Li & Lin, 2008). This transcription factor controls the activation of proinflammatory genes (*Moorchung et al., 2014*).

Furthermore, the interaction between autoreactive T cells and resident keratinocytes creates the inflammatory and immunological circuits responsible for the onset, development, and persistence of psoriasis (Kamata & Tada, 2023). Specifically, through the NF- κ B-hsa-miR-27a-3p-galectin-3 axis, TNF- α promotes psoriatic inflammation by increasing CXCL-1/8 expression in keratinocytes (Qiu *et al.*, 2023).

II.3.2. IL-23/IL-17 pathway:

By promoting keratinocyte hyperproliferation and feed-forwarding circuits of persistent T cell-mediated inflammation, the interleukin (IL)-23/IL-17 axis plays a crucial role in the immunopathogenesis of psoriasis and associated comorbidities (Menter *et al.*, 2021). Although it is evident that IL-23 promotes and sustains Th17 lymphocyte development (Schön & Erpenbeck, 2018), The IL-23/IL-17 axis has been connected to disease pathology through PsA correlations with single nucleotide polymorphisms in IL23R and TRAF3IP2 (Act1), a protein downstream of the IL-17 receptor (IL-17R) (Suzuki *et al.*, 2014).

II.3.3. JAK-STAT signaling pathway:

the Janus kinase family of upstream activators (JAK1, 2, 3, and TYK2) a number of cytokines, including IL-12, 23, 22, 6, 17, and interferon (IFN)- γ , are regulated intracellularly in the IL-23/IL-17 axis by Janus kinase (JAK) signal transducer and activator of transcription (STAT) (Loo *et al.*, 2023). In the development and pathophysiology of psoriasis and inflammatory disorders that resemble psoriasis, Signal Transducer and Activator of Transcription (STAT)3 has recently come to light (Calautti *et al.*, 2018). (Figure II.IX)

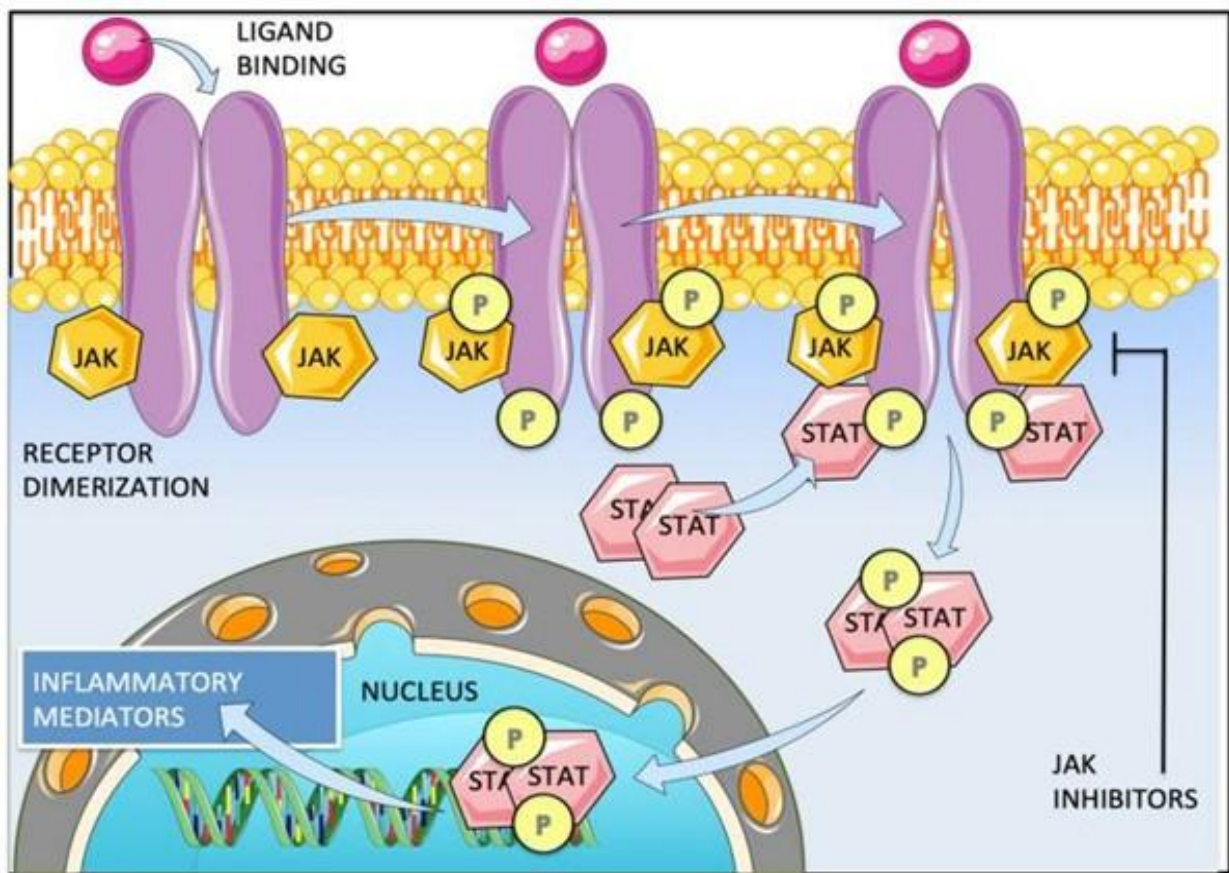


Figure II.IX.JAK/STAT signaling pathway in psoriasis.(Furtunescu, 2024)

JAKs are activated by cytokine-induced receptor dimerization, which phosphorylates the receptor and attracts STATs. These STATs then dimerize, go to the nucleus, and control the expression of inflammatory genes.

Chapter III:

**Biologic therapies and their
evaluation in psoriasis**

chaptreIII. Biologic therapies and their evaluation in psoriasis

III.1. General Overview of Biological Therapies

The treatment of psoriasis and psoriatic arthritis has significantly improved throughout the last 20 years due to the development of biologic treatments(Hawkes *et al.*, 2018). Oral drugs like methotrexate were the only alternatives available for the systemic treatment of moderate to severe psoriasis prior to the development of these medicines. Drugs that are more effective than methotrexate can now be used without any significant risks thanks to biologic treatments(Brownstone *et al.*, 2021).

III.1.1. Definition

Tumor necrosis factor inhibitors (TNFi: infliximab, etanercept, adalimumab, certolizumab pegol), interleukin (IL)-17 inhibitors (secukinumab, ixekizumab, brodalumab), an IL-12/23 inhibitor (ustekinumab), and IL-23p19 inhibitors (guselkumab, tildrakizumab, and risankizumab) are approved biologics for the treatment of moderate-to-severe psoriasis (Strober *et al.*, 2018).

III.1.2. Mecanisms of action

Biologics that target T cells and cytokine modulators (anti-cytokines) are the two primary groups of biological products used to treat psoriasis based on their mechanisms of action(Martin *et al.*, 2013). We give a summary of the mechanisms of action and associated pharmacodynamic properties of these licensed biological agents with clinically established therapeutic targets. (Prieto-Pérez *et al.*, 2013)

III.1.3. Indications

types of plaque psoriasis that range from moderate to severe. (Rao et al., 2023) In pediatric GPP, a few biologics have shown effective.Additionally, biologic medications (infliximab, secukinumab, and certolizumab) have been used to treat GPP in pregnant individuals.The IL-36 receptor antagonist spesolimab was recently authorized for the treatment of GPP. (Blair, 2022)

III.2. Main classes of Biotherapies

Biologic therapies used in psoriasis include tumor necrosis factor-alpha (TNF- α) inhibitors (etanercept, infliximab, and adalimumab), interleukin-12/23 (IL-12/23) inhibitor (ustekinumab), and interleukin-17 (IL-17) inhibitor (secukinumab), which are among the main approved biologic agents for the treatment of moderate-to-severe psoriasis in the EU and USA(Zweegers *et al.*, 2014).

III.2.1. Anti-TNF- α

A family of biologics called TNF- α inhibitors is used to treat moderate to severe plaque psoriasis. In particular, the NF- κ B signaling pathway is activated by TNF- α , a proinflammatory cytokine linked to the pathophysiology of psoriasis (Honma & Hayashi, 2021). Currently, etanercept, certolizumab, infliximab, and adalimumab are the four FDA-approved TNF alpha inhibitors.

Currently, the FDA has approved etanercept, certolizumab, infliximab, and adalimumab for the treatment of PsA (Kamata & Tada, 2020).

III.2.1.1. Mechanisms of action :

IMIDs are initiated and maintained by several TNF- α -mediated (auto)immune mechanisms. In summary, anti-TNF- α therapy affects the immune system by: (a) decreasing the expression of pro-inflammatory cytokines, chemokines, acute phase proteins, and adhesion molecules; (b) raising the number of circulating regulatory T cells; and (c) decreasing the migration of inflammatory cells from the blood to the inflammatory tissue. While anti-TNFs have the ability to destroy cells by directly binding to transmembrane TNF- α produced in different cells, etanercept also neutralizes lymphotoxin. Wu et al. recently demonstrated that binding of anti-TNF- α to transmembrane TNF- α impacts intracellular signaling and can lead to either cell growth arrest or inhibition of cytokine production in addition to programmed cell death (Wu *et al.*, 2021).

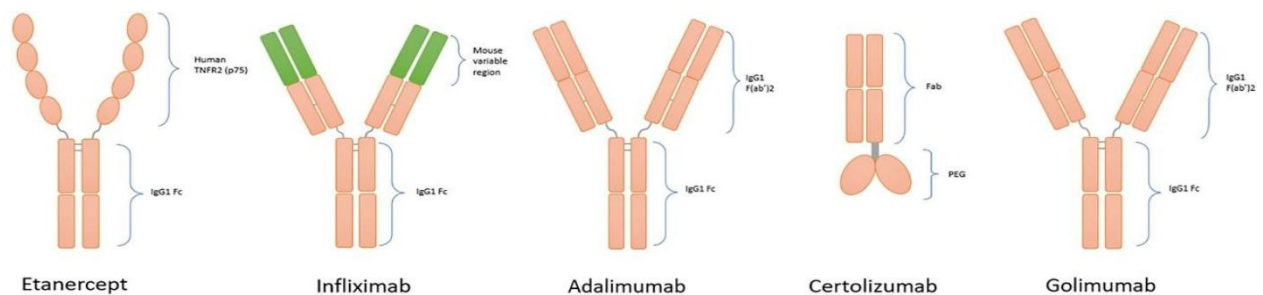


Figure III.I. Molecular structure of approved anti-TNFs. The five approved anti-TNFs, presented in chronological order of first approval (Evangelatos *et al.*, 2022)

a) Etanercept: A recombinant fusion protein called etanercept prevents TNF- α from attaching to TNF receptors 1 and 2. Etanercept does not exhibit antibody-dependent cellular cytotoxicity in spite of its Fc region complement binding domain. (Honma & Hayashi, 2021).

b) Certolizumab: A PEGylated TNF- α antibody fragment is called certolizumab. In particular, certolizumab lacks the Fc component of immunoglobulin, which reduces the production of anti-

drug antibodies and, consequently, immunogenicity and efficacy loss. Additionally, certolizumab minimizes placental transfer in pregnant women by not binding the IgG neonatal Fc receptor (Honma & Hayashi, 2021).

c) Infliximab: The human IgG1 κ constant region and a high-affinity anti-human TNF- α antibody's murine variable antigen-binding region make up the chimeric monoclonal IgG1 antibody infliximab. In particular, infliximab can bind to soluble and membrane-bound TNF- α (Honma & Hayashi, 2021).

d) Adalimumab: The completely human monoclonal IgG1 antibody adalimumab has the ability to bind to both soluble and membrane-bound TNF- α .(Honma & Hayashi, 2021)

III.2.1.2. Safety profile:

TNF- α inhibitors have well-documented safety characteristics. Nasopharyngitis, upper respiratory tract infections, and infection site responses are common side effects of all TNF- α inhibitors (Singh *et al.*, 2021). In line with its current safety profile, a five-year surveillance registry of psoriatic patients treated with etanercept did not find any new safety signals (Kimball *et al.*, 2015).

III.2.2. Anti-IL-12/23

The only IL-12/IL-23 inhibitor currently licensed by the FDA for the treatment of moderate to severe plaque psoriasis is ustekinumab. A monoclonal human IgG1 antibody called ustekinumab targets the p40 subunit of both IL-12 and IL-23. Th1 and Th17 cell development is aided by the cytokines IL-12 and IL-23, which are released by mDCs. In particular, ustekinumab prevents the development of psoriasis by blocking the IL-12/Th1 and IL-23/Th17 pathways (Honma & Hayashi, 2021).

III.2.2.1. Mechanisms of Action:

In the receptor complexes IL-12 (IL-12R β 1/ β 2) and IL-23 (IL-12R β 1/23R) on NK and T cells, ustekinumab exclusively binds to the p40 subunit of IL-12 and IL-23, preventing these cytokines from connecting with the IL-12R β 1 receptor chain . Ustekinumab efficiently neutralizes IL-12 and IL-23-mediated cell signaling, activation, and cytokine production by blocking their coupling to the IL-12R β 1 receptor (Benson *et al.*, 2011).

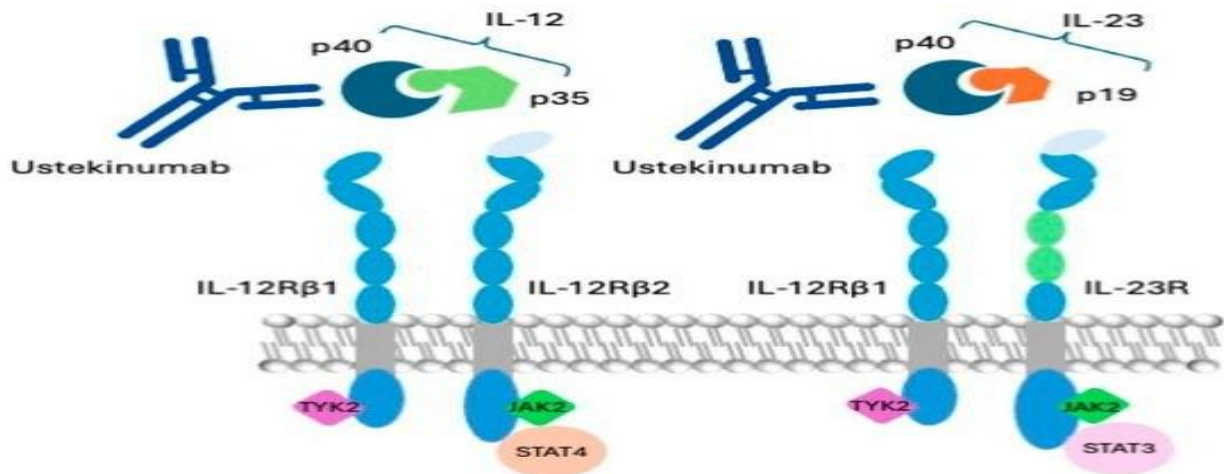


Figure III.II. Ustekinumab mechanism of action.(Carmona-Rocha & Puig, 2024)

III.2.2.2. Clinical efficacy:

Ustekinumab has a clear adverse effect profile and is a well-tolerated biologic. Headache, nasopharyngitis, upper respiratory tract infections, exhaustion, and pruritus are the most frequent side effects (Honma & Hayashi, 2021)

III.2.3. Anti-IL-17

Another type of biologics used to treat moderate to severe plaque psoriasis is IL-17 inhibitors. In particular, ACT1 adaptor protein-dependent and independent pathways link the proinflammatory cytokine IL-17 to the pathophysiology of psoriasis (Schadler *et al.*, 2019). As of right now, the FDA has approved three IL-17 inhibitors: brodaluma, ixekizumab, and secukinumab. Phase III trials for bimekizumab are presently underway (Schadler *et al.*, 2019).

III.2.3.1. Mechanism of action of anti-IL-17:

The role of anti-IL-17 monoclonal antibodies in psoriatic arthritis and psoriasis. The IL-23/IL-17 axis plays a major role in the pathophysiology of psoriasis and psoriatic arthritis. An inflammatory cascade is started when dendritic cells release IL-23, which activates Th17 cells. The stimulated Th17 cells subsequently release a lot of IL-17. The IL-17 family then causes keratinocytes to proliferate excessively, which leaves the skin with silvery-white plaques, erythema, and localized papules. Three different kinds of monoclonal antibodies were used in this trial to treat psoriasis and psoriatic arthritis by blocking IL-17A, IL-17R, and IL-17A/F, which stops the inflammatory cascade.(Wang, Wang, Liu, Hong, Ru, Sun, Chen, Zhang, Lin, *et al.*, 2023).

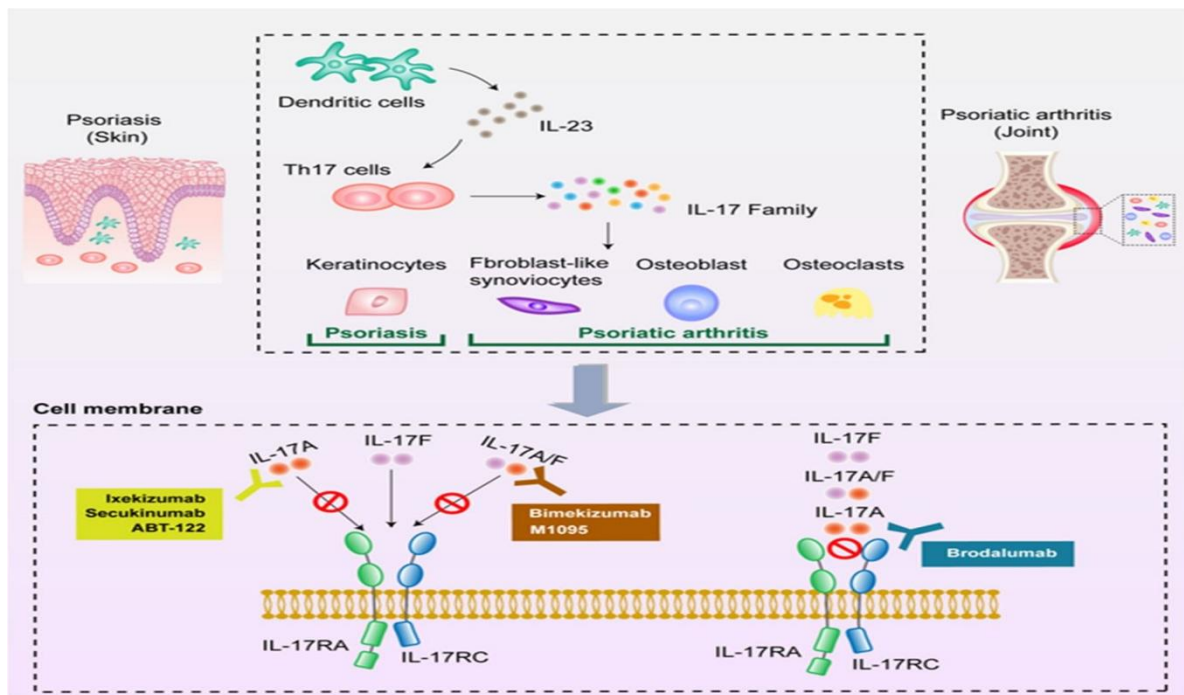


Figure III.III.: Schematic diagram of the mechanism of action of anti-interleukin-(IL)-17 drugs.(Wang, Wang, Liu, Hong, Ru, Sun, Chen, Zhang, Lin, & Li, 2023)

a) Ixekizumab:

The FDA has approved ixekizumab, a humanized IgG4 monoclonal antibody against IL-17A, to treat moderate to severe plaque in patients six years of age and older. Ixekizumab is given to adults in doses of 160 mg at week 0, 80 mg at weeks 2, 4, 6, 8, 10, and 12, and then 80 mg every four weeks after that.(Mosca *et al.*, 2021).

b) Secukinumab: The FDA approved Secukinumab, a recombinant completely human IgG1 κ monoclonal antibody against IL-17A, to treat patients with moderate to severe plaque psoriasis who are six years of age or older.(Food & Administration, 2016).

c) Brodalumab :The FDA authorized the use of brodalumab, a human monoclonal IL-17 receptor antibody (RA), to treat people with moderate to severe plaque psoriasis.(Mosca *et al.*, 2021).

d) Bimekizumab: is a humanized IgG1 monoclonal antibody under investigation that inhibits IL-17A and IL-17F at the same time.(Reich *et al.*, 2021)

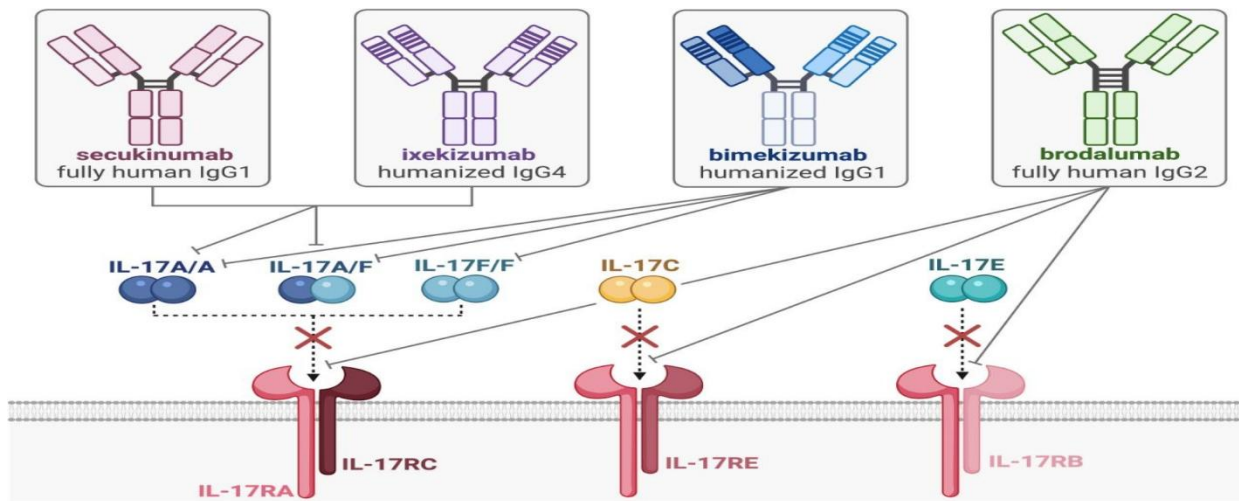


Figure III.IV. Anti-IL-17 inhibitors' mode of action. Interleukin (IL) and immunoglobulin G (IgG). BioRender.com was used to create it. (Yeung *et al.*, 2022)

III.2.3.2. Safety profile:

IL-17 inhibitors have mild to moderate safety profiles, which are extensively documented. Injection site reactions and upper respiratory tract infections are common side effects of all IL-17 inhibitors. IL-17 inhibitor medication has also been linked to mucocutaneous candidiasis (Singh *et al.*, 2021).

III.2.4. Anti-IL-23

In recent years, there has been a lot of interest in the development of IL-23 selective medications. (Parigi *et al.*, 2022). Some IL-23p19 inhibitors have been developed and approved to treat psoriasis (risankizumab, guselkumab, and tildrakizumab) and psoriatic arthritis (risankizumab and guselkumab) (Vuyyuru *et al.*, 2023).

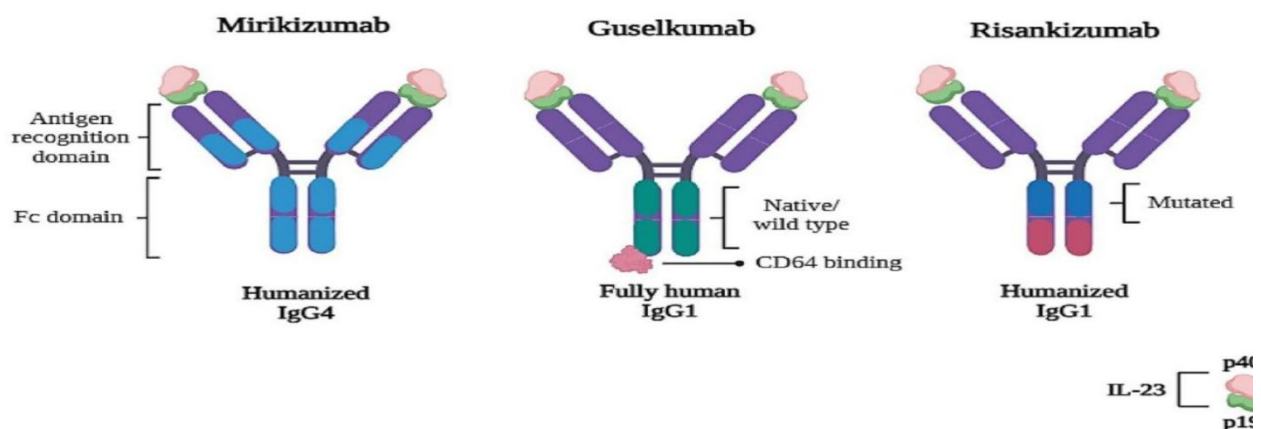


Figure III.V.: IL-23 inhibitors molecular structure and differences (Schulze *et al.*, 2023)

a) Risankizumab: The only IL-23p19 inhibitor available at the moment is risankizumab, a humanized IgG1 monoclonal antibody that specifically suppresses IL-23 by focusing on its p19 subunit. It was first authorized to treat psoriatic arthritis and moderate-to-severe plaque psoriasis.(McFeely *et al.*, 2022)

b) Mirikizumab: A humanized IgG4 variant monoclonal antibody that specifically targets IL-23 p19 subunit (Sandborn *et al.*, 2020)

c) Guselkumab: Plaque psoriasis and psoriatic arthritis can currently be treated with guselkumab, a completely human IgG1-lambda that suppresses p19 IL-23. (Peyrin-Biroulet *et al.*, 2023).

III.2.4.1. Safety profile

The safety features of IL-23 inhibitors are moderate and well-established. The most commonly reported side effects are upper respiratory tract infections and injection site reactions (Armstrong & Read, 2020).

III.3. Treatment response and follow-up:

Avoiding impairment in everyday life is a significant result of psoriasis treatment (Strober *et al.*, 2016). For patients with moderate-to-severe psoriasis, total skin clearance as determined by the Psoriasis Area and Severity Index (PASI) is a desirable and attainable result thanks to contemporary biologic treatments like interleukin-17 and IL-23 inhibitors (Manalo *et al.*, 2015).Clinical trials have shown that there are clinically significant differences in health-related quality of life (HRQoL) and the burden of skin symptoms between achieving complete skin clearance (PASI 100) and nearly complete skin clearance (PASI 90 to < 100, indicating 90 to < 100% improvement) (Strober *et al.*, 2016).

III.4. Tolerance and adverse effects:

General disorders and administration site conditions (mild to moderate) are the most often reported adverse events (AEs) in our study, with investigation anomalies coming in second. Patients on TNF- α inhibitors have been found to have higher rates of infection, with sinusitis, pharyngitis, and upper respiratory tract infections being the most often reported (Sehgal *et al.*, 2015). as well as a higher chance of contracting opportunistic infections (Lockwood *et al.*, 2018).

III.5. Limitations and perspectives of biologic therapies:

The high cost of biologic medicines is another major issue. Patients and healthcare systems are financially burdened by the high cost of these drugs. Most psoriasis patients who responded to a survey indicated that they wanted a more affordable treatment choice (Porter *et al.*, 2022). However, the creation of biosimilars presents the possibility of lower medication costs as the

patents for some biologic drugs are about to expire. Their availability can increase accessibility, boost cost-effectiveness, and provide patients more treatment options. The effects of TNF- α inhibitor biosimilars were comparable to those of the original (García-Beloso *et al.*, 2022), Therefore, it is anticipated that biosimilars of the IL-17 and IL-23 inhibitors will have comparable effects. While moderate-to-severe psoriasis has been the primary focus of biologic therapy, mild psoriasis is still mostly treated with localized therapies such calcineurin inhibitors, topical corticosteroids, and vitamin D analogues. For individuals with mild psoriasis who do not respond well to topical treatments, more focused and efficient systemic therapies are required, even if these treatments can effectively control symptoms in many situations. Furthermore, several psoriasis subtypes, include scalp.(Ghafoor *et al.*, 2022), nail,(Thomas *et al.*, 2021) genital.(Kelly & Ryan, 2019)., palmoplantar.(Misiak-Galazka *et al.*, 2020)., and generalized pustular psoriasis(Hoegler *et al.*, 2018), present particular difficulties with regard to management and treatment satisfaction. The available treatments for these particular subtypes frequently don't produce satisfying outcomes. To find more efficient and specialized methods to meet the unique requirements of various patient groups, additional study and development are required.(Lee & Kim, 2023)

ChapterIV:

**Comparative Analysis and
Research Gaps**

chaptreIV. Comparative Analysis and Research Gaps

IV.1. Comparative efficacy of biologics

More recent biologic treatments have shown greater effectiveness in treating moderate-to-severe plaque psoriasis when compared to conventional biologics. Adalimumab and ustekinumab were less successful than bimekizumab, which had the greatest PASI90 response rates (Gordon *et al.*, 2021), followed by risankizumab, guselkumab, and secukinumab¹⁸. The combined inhibition of IL-17A and IL-17F, which improves reduction of psoriatic inflammation, is probably the reason for bimekizumab's higher efficacy(Adams *et al.*, 2020). Secukinumab outperformed adalimumab and ustekinumab,¹⁸ which performed similarly but had no discernible benefit⁶,(Sbidian *et al.*, 2022)t, while risankizumab and guselkumab had equivalent efficacy with less frequent treatment (Warren *et al.*, 2021).

The choice of psoriasis treatment requires consideration of several important factors (Kaushik & Lebwohl, 2019). In patients with moderate-to-severe plaque psoriasis, IL-23 p19 inhibitors have demonstrated a favorable long-term safety profile, with no significant increase in major infections, cardiovascular events, or malignancies over a five-year period. Guselkumab (Blauvelt *et al.*, 2023), tildrakizumab ,(Thaçi *et al.*, 2021) and risankizumab (Papp *et al.*, 2021) have shown consistent safety in clinical trials and long-term extension studies, with non-serious infections being the most frequently reported adverse event (Blauvelt *et al.*, 2022). Their safety in patients with comorbidities and previous biologic treatment failures is further supported by real-world evidence (Gargiulo *et al.*, 2022). IL-23 inhibitors are also associated with fewer immune-related adverse effects compared to IL-17 inhibitors (Crowley *et al.*, 2019) and anti-TNF agents (Mastorino *et al.*, 2022). However, psoriasis remains a chronic disease, and current evidence is still insufficient to support fully individualized treatment strategies, highlighting the need for further research (Camela *et al.*, 2022).

When compared to less targeted biologic treatments such TNF- α inhibitors (adalimumab, etanercept, certolizumab pegol, infliximab) and the IL-12/23 inhibitor ustekinumab, IL-17A and IL-23 inhibitors showed greater efficacy(D'Angelo *et al.*, 2017). According to clinical data, psoriatic skin symptoms significantly improve in about 90% of patients treated with IL-17A or IL-23 inhibitors (Kim & Krueger, 2017). The central significance of the IL-23/IL-17A axis in the immunopathogenesis of psoriasis, where IL-17 is crucial in the inflammatory cascade affecting skin and joints, explains this greater efficacy. Because standard biologic medicines are less specific

in their targeting of the illness pathway, targeted inhibition of IL-23 and IL-17A is thought to be more successful(Menter *et al.*, 2021).

IL-23 inhibitors don't seem to raise the risk of inflammatory bowel disease or candidiasis, but real-world registry data are still needed to verify their long-term tolerability(Bilal *et al.*, 2018).

Relapse rates were comparable in patients who did not receive maintenance medication following initial clearance of plaque psoriasis; within six months, around half of patients saw a recurrence of disease severity to roughly half of their pretreatment level. When compared to intermittent clearance-based treatment approaches, maintenance photochemotherapy given once a week or every three weeks has been demonstrated to lower recurrence rates and improve overall disease management. A subgroup of about one-fifth of patients, however, were able to sustain a good remission for over 16 months without the need for ongoing maintenance medication. To find early indicators of long-term remission and recurrence risk, however, more thorough data on therapy response across patient subgroups is required (Vella Briffa *et al.*, 1981).

conclusion

Conclusion:

In conclusion, psoriasis is a complicated skin condition that affects people both physically and psychologically. Achieving the best results is still difficult, despite advancements in our knowledge of its underlying mechanisms and the creation of several therapeutic approaches. With the development of new biologic drugs that target particular pathways, the therapy of psoriasis appears to have a bright future. Developments in topical therapies, especially with microneedles and nanoparticle-based carriers, have the potential to enhance psoriatic plaque therapy efficacy and drug delivery. Personalised therapy techniques depend on the identification and validation of biomarkers using multi-omics technology. Even if these developments have a lot of promise, cooperation between scientists, medical professionals, and business stakeholders is essential to putting these findings into practical practice. Optimising the management of psoriasis also requires tackling the issues of drug resistance, side effects, and excessive costs. In the end, this will result in better outcomes and a higher standard of living for those who have this long-term skin problem. (Lee & Kim, 2023)

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الصدفية مرض جلدي التهابي ذو منشأ مناعي، يرتبط بالعديد من الأمراض الالتهابية المصاحبة، بما في ذلك زيادة خطر الإصابة بأمراض القلب والأوعية الدموية. يلعب محور الإنترلوكين-23/الإنترلوكين-17 دورًا محوريًا في الآلية المناعية المرضية للصدفية والأمراض المصاحبة لها، وذلك من خلال تحفيز تكاثر الخلايا الكيراتينية بشكل مفرط، وتفعيل حلقات التغذية الراجعة للالتهاب المزمن بوساطة الخلايا التائية. يلعب الإنترلوكين-17 دورًا هامًا في المرحلة اللاحقة من سلسلة التفاعلات الالتهابية في الصدفية. تتناول هذه المراجعة الآليات المتميزة لعمل الإنترلوكين-17 والإنترلوكين-23 في الآلية المناعية المرضية للصدفية والأمراض المصاحبة لها، بالإضافة إلى الفوائد العلاجية الهامة لتثبيط هذه السيتوكينات بشكل انتقائي لدى المرضى الذين يعانون من الصدفية اللويحية المتوسطة إلى الشديدة

Abstract

Psoriasis is an immune-mediated inflammatory skin disease associated with numerous inflammatory comorbidities, including increased cardiovascular risk. The interleukin (IL)-23/IL-17 axis plays a central role in the immunopathogenesis of psoriasis and related comorbidities by acting to stimulate keratinocyte hyperproliferation and feed-forwarding circuits of perpetual T cell-mediated inflammation. IL-17 plays an important role in the downstream portion of the psoriatic inflammatory cascade. This review discusses the distinct mechanisms of action of IL-17 and IL-23 in the immunopathogenesis of psoriasis and related comorbidities plus the significant therapeutic benefits of selectively inhibiting these cytokines in patients with moderate to severe plaque psoriasis.

Résumé

Le psoriasis est une maladie inflammatoire cutanée à médiation immunitaire associée à de nombreuses comorbidités inflammatoires, notamment un risque cardiovasculaire accru. L'axe interleukine (IL)-23/IL-17 joue un rôle central dans l'immunopathogenèse du psoriasis et des comorbidités associées en stimulant l'hyperprolifération des kératinocytes et en alimentant un cercle vicieux d'inflammation chronique à médiation lymphocytaire T. L'IL-17 joue un rôle important dans la partie aval de la cascade inflammatoire psoriasique. Cette revue examine les mécanismes d'action distincts de l'IL-17 et de l'IL-23 dans l'immunopathogenèse du psoriasis et des comorbidités associées, ainsi que les bénéfices thérapeutiques significatifs de l'inhibition sélective de ces cytokines chez les patients atteints de psoriasis en plaques modéré à sévère.