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Molecular and Cellular Profiling of Psoriatic Scar:

Exploring Early vs Late Intervention

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SUMMARY

List of Abbreviations

ACE	Angiotensin converting enzyme
ADA	Adalimumab
AMPs	antimicrobial peptides
APCs	Antigen presenting cells
AQP9	Aquaporin-9
ASN	Autonomic nervous system
BMI	Body mass index
BSA	Body Surface Area
CCL20	Chemokine ligand 20
CCL4	Chemokine ligand 4
CCR6	Chemokine receptor 6
CFR	Coronary Flow Reserve
CHF	Chronic heart failure
CRP	C reactive protein
CVD	Cardiovascular disease
CXCR8	Chemokine Ligand 8
DCs	Dendritic Cells
DIP	Distal interphalangeal
DLQI	Dermatology Life Quality Index
DMF	Dimethyl fumarate
DMSO	Dimethyl sulfoxide
EDC	Epidermal Differentiation Complex
eDCs	Epidermal DC
EDTA	Ethylenediaminetetraacetic acid
EGF	Epidermal Growth Factor
EP	Early psoriasis
ESR	Erythrocyte sedimentation rate
ETA	Etanercept
FAE	Fumaric acid esters
FDA	Food and Drug Administration
FDG-PET/CT	F-fluorodeoxyglucose positron emission tomography/computed tomography
FGF-2	Fibroblast growth factor-2

Foxp3+	transcription factor Foxp3
FSC-H	Forward scatter area
G-CSF	Granulocyte colony-stimulating factor
GLUT-4	Glucose transporter type 4
GM-CSF	Granulocyte-macrophages colony-stimulatin factor
GPP	Von Zumbush generalized pustular psoriasis
GWAS	Genome-wide association studies
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HPA	Hypothalamic-pituitary-adrenal
HSV	Herpes simplex virus
IBD	Inflammatory Bowel Disease
ICAM-1	Intercellular adhesion molecule-1
IFN-α	interferon-α
IFN-β	interferon-b
IFN-γ	Interferon γ
IFNs	Interferons
IFX	Infliximab
IGF	Insulin-like growth factor
IL-1	Interleukin 1
IL-12	Interleukin 12
IL-17	Interleukin-17
IL-17R	Ineterleukin-17 receptor
IL-22	Interleukin-22
IL-23	Interleukin 23
IL-23R	IL-23 receptor
IL-35	Interleukin-35
IL-6	Interleukin 6
IMIDs	Immune mediated inflammatory disease
IRS-1	Insulin receptor substrate-1
JAKs	Janus kinases
LCE	Late Cornified Envelope
LCs	Langerhans cells

LDL	Low-density lipoprotein
LP	Late psoriasis
LYVE-1	Lymphatic vessel endothelial hyaluronan receptor 1
M-CSF	Macrophages colony-stimulating factor
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant proteine-1
MDC	Macrophage-derived chemokine
mDCs	Myeloid dendritic cells
MHC	Major histocompatibility complex
MI	Myocardial infarction
mIHC	Multiplex immunohistochemistry
miRNAs	microRNAs
MRI	Magnetic resonance imaging
MX1	MX Dynamin Like GTPase 1
nAChRs	Nicotinic acetylcholine receptors
NAFLD	Non -alcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NF-AT	Nuclear transcription factor of activated T cells
NF-κB	Nuclear factor kappa B
NSAIDs	Non steroidal anti inflammatory drugs
oxLDL	Oxidized LDL
PASI	Psoriasis Area and Severity Index
PB	Peripheral blood
PBMC	Peripheral blood mononucelat cells
PD-1	programmed cell death 1
pDC	Plasmacytoid dendritic cells
PDE4	Phosphodiesterase 4
PDGF-AA	Platelet-derived growth factor-AA
PGA	Physician's Global Assessment
PLA2G4D	Phospholipase A2 group IV
PPP	Palmoplantar Pustolar Psoriasis
PsA	Psoriatic Arthritis
PsGA	Psoriasis Global Assessment
PSORS	Psoriasis susceptibility loci

RARs	Retinoic acid receptors
RORγt	transcription factors of the RAR-related orphan nuclear receptor
ROS	Reactive oxygen species
RT	Room temperature
sCD40L	Soluble CD40 ligand
SpA	Spondylarthritis
SSC-H	Side scatter area
STAT	Signal transducer and transcription activator
T2DM	Type 2 diabetes
TCIs	Topical calcineurin inhibitors
Tcm	Central memory T cells
Tem	Effector memory T cells
TGF- β	Transforming growth factor-beta
Th17	T helper type 17 cells
Th22	T helper type 22 cells
TLOs	Tertiary lymphoid organs
TLR	Toll like receptor
TNF-a	Tumor necrosis factor alfa
TNFAIP3	Tumor necrosis factor alpha-induced protein 3
TNFR1	Tumor necrosis factor receptor 1
TNIP1	TNFAIP3-interacting protein 1
TRMs	Tissue-Resident Memory T cells
UV	Ultra-Violet
UVB	Type B ultraviolet
VCAM-1	Vascular cell adhesion molecule-1
VCAM-1	Vascular cell adhesion molecule-1
VDR	Vitamin D receptor
VEGF	vascular endothelial growth factor
VEGF	Vascular endothelial growth factor
VLDL	Very low-density lipoprotein

ABSTRACT

Background and aim:
Psoriasis is a chronic, immune-mediated inflammatory skin disorder associated with numerous comorbidities.
Medications for psoriasis, especially biologic agents, are designed to inhibit the inflammatory response. While these agents can clear skin lesions, discontinuing the treatment leads to the recurrence of psoriasis in the same locations. Indeed, even after effective treatment, cleared lesions leave behind a "molecular scar" composed of pathogenic immune cells, which can lead to a relapse after the cessation of therapy.
Currently, biologic agents are prescribed after inadequate response to topical or conventional systemic agents. However, evidence from rheumatoid arthritis and Crohn's disease has demonstrated that the early use of targeted therapies improves long-term outcomes.
In this study, we aimed to investigate the molecular and cellular signatures of psoriasis and assess whether an early intervention with biologic drugs might modify the natural course of the disease at both cutaneous and systemic levels.

Methods:
This is a single-center, open-label study involving eighteen patients with moderate to severe psoriasis treated with anti IL-23 and anti TNF-α biologic drugs according to the European Guidelines. Based on disease duration, patients were classified into early (within 5 years from onset) or late (after 5 years from the disease onset) intervention groups. Clinical evaluations, blood samples, and skin biopsies were taken before and after 24 weeks of treatment and analyzed via Luminex Multiplex assay, Multiparametric Flow Cytometry, immunofluorescence.

Results:
Early intervention with anti IL-23 and anti TNF-α led to a greater clinical improvement and lower disease severity. Both groups showed systemic inflammation through elevated serum levels of cytokines. A positive correlation was observed between IL-17A and IL-23p40 and disease severity. The treatment with both anti IL-23 and anti TNF-α normalized cytokine levels, with early-intervention group showing a significant drop in IL-17A. Multiparameter flow cytometry analysis of the T-cell compartment in skin biopsies revealed an increase in T-cell infiltration and permanence in the psoriatic skin as compared to non-lesional and post-lesional skin, with a predominance of the memory compartment, that was strongly decreased by the treatment. Tissue resident memory cells, which are believed to be involved in psoriasis memory and recurrence, were especially reduced in early- intervention group, with trends suggesting better outcomes with anti IL-23 treatment.
A unique T-cell subpopulation that expressed both naive and memory markers was identified within the psoriatic skin, along with the presence of aggregates of B and T cells, pointing to the presence of tertiary lymphoid organs (TLOs).

Conclusions:
Early intervention, particularly with biologics targeting the IL-23/Th17 axis, proved superior to late intervention in terms of improving clinical outcomes, mitigating the systemic inflammatory milieu, and modulating the "disease memory" within the skin.
Psoriatic skin exhibited intricate T-cell activity, hinting at its potential role as TLO.

1. INTRODUCTION

1.1 Psoriasis background

Psoriasis is a chronic skin condition that results from a multifaceted interaction of immunological, environmental, and genetic factors. It is a common immune mediated inflammatory disease (IMIDs) with a significant global burden.

1.1.1 Epidemiology

Psoriasis affects about 2-3% of the world's population, thus about 125 million people worldwide. However, the prevalence of psoriasis varies among different populations and ethnic groups. In general, psoriasis can manifest at any age, being more common in adults than in children, with a pick observed in early adulthood (20s to 30s) and another in late adulthood (50s to 60s) (Parisi et al., 2013). Systematic reviews have shown that psoriasis prevalence in children ranges from 0% in Taiwan to approximately 2.1% in Italy and that the rates among adults vary from 0.4% in Asian countries to 8.5% in Norway (Parisi et al., 2013). In the United States, the prevalence of psoriasis is estimated to be between 2-4%, while in Western Europe, it's around 1.5-2% (Armstrong et al., 2021; Parisi et al., 2013). The disease affects males and females at approximately equal rates (Armstrong et al., 2021).
The incidence of psoriasis showed increased rates over time. A study conducted in the United States, revealed an increase in the disease's incidence from 50.8 cases per 100,000 individuals during the years 1970 to 1974, to 100.5 cases per 100,000 from 1995 to 1999 (Icen et al., 2009). The incidence in children also showed an upward trend in the same timeframe, moving from 29.6 cases per 100,000 to 62.7 cases per 100,000 (Tollefson et al., 2010). However, it's debatable whether these data indicate a real increased incidence of the disease or simply reflect the progress in diagnostic skills over time (Icen et al., 2009).

1.1.2 Clinical Manifestations

There is a wide spectrum of cutaneous manifestations of psoriasis, with individual lesions varying from pinpoint to large plaques, or even generalized erythroderma.

1.1.2.1 Plaque Psoriasis (Psoriasis Vulgaris)

This is the most common form, occurring in 85-90% of all patients. It is characterized by well-demarcated, scaly and erythematous, infiltrated plaques, which appear mainly in some body locations, in particular symmetrically on the extensor surfaces of the limbs (knee and elbows) and/or on other mechanically stressed locations such as the lumbar region, but also on the scalp (Boehncke and Schön, 2015). However, any body location may be involved and the extension may range from limited, localized disease to extent disease, with the involvement of the majority of the body surface area. Plaques are usually asymptomatic; however, itch and pain may appear (Raychaudhuri et al., 2014). In a patient with psoriasis, new lesions may follow skin trauma, a phenomenon known as Koebner's reactive isomorphism. In suspected cases, the "Brocq's methodical scratching" of the skin revealing the 'drop of wax' sign (a whitening of the lesion surface due to lifted scales), the Duncan-Bulkley membrane (a clear, shiny surface revealed when scales are removed), and the Auspitz sign or 'dew of blood' (pinpoint bleeding from the lesion caused by the cutting off of the small blood vessels in the papillary layer of the dermis) may be helpful.

1.1.2.2 Guttate Psoriasis

This form typically occurs in children and young adults, often following a streptococcal upper respiratory tract infection or dermatitis. Recently, it has been reported to follow SARS-CoV-2

infection (COVID-19) (Gananandan et al., 2020; Rouai et al., 2021). It is characterized by an abrupt onset of small, droplet-shaped, red patches, typically on the trunk and proximal extremities (Boehncke and Schön, 2015). It is usually self-limiting within a few months, however in some cases it can progress to psoriasis vulgaris, nevertheless patients with history of guttate psoriasis are considered at risk of manifest psoriasis vulgaris during their lifetime (Pfingstler et al., 2016). Indeed, guttate and vulgaris psoriasis share close association with the PSORS1 genetic locus (Asumalahti et al., 2003).

1.1.2.3 Inverse (or Flexural) Psoriasis

Inverse psoriasis affects the skin folds such as the armpits, groin, under the breasts, and other areas where skin rubs against skin. The lesions are well-demarcated, smooth, shiny plaques but lack the scale typical of psoriasis vulgaris (Boehncke and Schön, 2015). Because of its tendency to maceration, it is often misdiagnosed as intertriginous bacteria of fungal infection (Micali et al., 2020).

1.1.2.4 Erythrodermic Psoriasis

This is a severe but rare type of psoriasis that leads to widespread, fiery redness over most of the body, often more than 80%, and may be associated with lymphadenopathy and pruritus. Several factors may precipitate the onset of erythrodermic psoriasis, including abrupt withdrawal of systemic treatment, severe sunburn, infections, certain medications such as lithium, and alcohol (Raychaudhuri et al., 2014). Erythrodermic psoriasis is associated with vasodilation, which can cause hypothermia, and extensive desquamation, linked to a reduction in skin barrier function, which may result in hypoalbuminemia, oedemas and, in severe cases, in cardiac, hepatic, and renal failure. It's crucial to be aware of these triggers to prevent the abrupt onset of severe variants of the disease.

1.1.2.5 Palmoplantar Pustolar Psoriasis (PPP)

The clinical manifestation of PPP often begins with reddening of the skin on palms and/or soles, followed by the appearance of multiple small, sterile pustules. Over time, these pustules may coalesce and turn into brownish scales as they dry out. Symptoms can also include pain, itching, and fissuring, making everyday tasks challenging for affected individuals. It is often associated with psoriatic nail disease and may be accompanied by psoriasis vulgaris. Triggering factors such as smoking, infection, stress, and certain medications have been implicated in disease onset (Menter et al., 2021).

1.1.2.6 Acrodermatitis continua of Hallopeau

This variant is characterized by a sterile, painful pustular eruption localized on the distal surface of the fingers and toes, particularly in the periungual and subungual regions. The pustules coalesce to form lakes of pus which, if not treated promptly, can lead to paronychia, onychodystrophy, onycholysis, and eventually osteolysis of the distal phalanges. This manifestation is a rare variant of pustular psoriasis and typically shows poor response to both topical and systemic treatments (Smith et al., 2019).

1.1.2.7 Von Zumbusch generalized pustular psoriasis (GPP)

GPP is rare and appears as a generalized eruption of sterile non-follicular subcorneal pustules arising on erythematous skin (Fujita et al., 2022). Triggers for GPP can include withdrawal from systemic corticosteroids, infections, drugs (lithium, chloroquine, beta-blockers, salicylates, tars), hypocalcemia (Fujita et al., 2022; Gooderham et al., 2019). Pregnancy can also trigger or exacerbate the condition in a form known as impetigo herpetiformis(Oumeish and Parish, 2006). GPP is characterized by the rapid onset of numerous small, sterile, non-infectious pustules over wide areas of reddened skin that may lead to a suberythrodermic state. The eruption of pustules is typically accompanied by systemic symptoms such as fever, fatigue, and malaise, fluid and electrolyte imbalance that require hospitalization (Gooderham et al., 2019). It may be associated with geographic tongue, polyarthritis and cholestasis (Viguier et al., 2004).

1.1.2.8 Psoriatic Arthritis (PsA)

PsA is a seronegative inflammatory arthritis that can affect up to 30% of individuals with psoriasis (Mease et al., 2014). This arthritis can be peripheral, axial, or both, presenting in several ways: as a symmetrical inflammation of many joints, as an asymmetric inflammation of few joints, as arthritis of the distal interphalangeal (DIP) joints, as a destructive arthritis known as arthritis mutilans, or as spondyloarthritis (SpA). These patterns often coexist. Other symptoms such as enthesitis, dactylitis, and tenosynovitis may also occur. PsA can lead to joint damage and disability over time if not treated effectively (Boehncke and Schön, 2015). Radiographic characteristics of PsA include an asymmetric distribution, involvement of distal interphalangeal joints, and in severe cases, bone erosions and neo-appositions that could lead to deformities such as the "pencil in cup" appearance in phalanges (Wiell et al., 2007). Ultrasound highlight signs of enthesopathy, even subclinical (Wiell et al., 2007), and magnetic resonance imaging (MRI) identifies subcortical bone edema at the site of enthesis, being crucial for the early diagnosis of PsA (Qi et al., 2021). PsA may also have systemic effects, including fatigue and eye inflammation (uveitis) (Fotiadou and Lazaridou, 2019). It has a chronic-relapsing pattern characterized by periods of remission interspersed with periods of exacerbation, yet the inflammation persists if left untreated. In 75% of patients skin psoriasis precedes the onset of PsA, in 10% of cases they present at the same time, and arthritis can sometimes precede skin manifestations (15% of cases) (Duarte et al., 2012).

1.1.3 Disease severity scales

The assessment of disease severity is important for guiding treatment decisions and monitoring treatment efficacy. Several validated scales are used in both clinical practice and research to evaluate psoriasis severity, each assessing different aspects of the disease:

Psoriasis Area and Severity Index (PASI): The PASI is the most commonly used tool for measuring the severity of psoriasis. It considers both the extension of the disease and the characteristics of the plaques. The percentage of body surface area involvement of the head, trunk, and upper and lower extremities is scored from 0 to 6 based on the extent of the disease (1=1-9%, 2=10-29%, 3=30- 49%, 4=50-69%, 5=70-89% and 6=90-100%). A severity score, ranging from 0 to 5, is given to the lesions' degree of redness, thickness, and scaling. Scores can range from 0 (no disease) to 72 (most severe disease). The PASI rating scale is frequently used to quantify the degree of improvement following therapy: PASI50 denotes a 50% improvement, PASI75 a 75% improvement, and PASI90 a 90% improvement (Feldman, 2005). When PASI > 10, psoriasis is regarded as severe.

Body Surface Area (BSA): The BSA measurement is a simple and quick tool used to assess the percentage of the body affected by psoriasis (Speeckaert et al., 2019). One hand's worth of psoriasis roughly equates to 1% of the BSA. Psoriasis is considered severe when BSA>10.

Dermatology Life Quality Index (DLQI): The DLQI is a questionnaire that assesses the impact of skin disease on a patient's quality of life over the previous week (FINLAY and KHAN, 1994). Notably, even if psoriasis is not a contagious disease, it leads to a severe disability and negatively impacts on patients' quality of life causing a severe economic and psychological burden. DLQI covers six domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Scores range from 0 (no impact on quality of life) to 30 (extremely large impact on quality of life), the disease is considered severe when DLQI >10 (Mazzotti et al., 2005).

Physician's Global Assessment (PGA): The PGA is a 5-point scale (clear, minimal, mild, moderate, or severe) that allows the physician to give an overall assessment of the patient's psoriasis severity without complex calculations (Langley and Ellis, 2004)

Psoriasis Global Assessment (PsGA): The PsGA is similar to the PGA but adds a 6th point on the scale for very severe psoriasis (Langley and Ellis, 2004).

These scales are often used together in clinical trials and practice to provide a comprehensive assessment of psoriasis severity and the impact of the disease on a patient's quality of life.

1.1.4 Histopathology

Although, in the vast majority of patients, the diagnosis of psoriasis can be made by physical examination including the scalp, nails, and anogenital skin; in doubtful cases, a biopsy correlated with the histological examination can be decisive.
The maturation process of keratinocytes in the epidermis of skin affected by psoriasis is expedited by a factor of ten when compared to healthy skin. As a result, this progression from the basal layer to the stratum corneum takes merely 4-5 days in total. In this scenario, the stratum corneum becomes thickened giving rise to *hyperkeratosis*, which leads to a buildup of cells and a thick, scaly appearance to the skin (Lowes et al., 2014). Furthermore, the normal process of keratinocyte differentiation cannot occur resulting in retention of nuclei in the upper layers and stratum corneum, termed *parakeratosis*. The increased skin turnover also leads to an irregular thickening of the stratum spinosum, named *acanthosis*, with an elongation of the rete ridges and finger-like extensions of the epidermis into the dermis, giving the epidermis a "saw-toothed" appearance(Hurt, 2012). A reduction of the normal granular layer (*hypogranulosis*) is usually associated (Hurt, 2012). In the epidermis, neutrophils derived from the papillary dermis collect forming the so-called *Munro microabscesses*. Moreover, there's an increased number of activated T cells, dendritic cells, and macrophages within the dermis. (Lowes et al., 2014).
The dermis underneath psoriatic lesions shows an increase in the number and size of blood vessels. These vessels are tortuous and have a characteristic elongated, "serpiginous" appearance. This vascular proliferation is driven by angiogenic growth factors like vascular endothelial growth factor (VEGF), which are produced by keratinocytes and immune cells in the lesion (Creamer et al., 2002).

It's important to note that these histological features can vary depending on the type and stage of psoriasis. Moreover, there can be overlap with other skin conditions, so the clinical context and presentation are important in making the correct diagnosis.

1.1.5 Risk Factors

Psoriasis is a complex disease, and its development is likely due to a combination of genetic predisposition and environmental factors.

1.1.5.1 Genetics

There is a clear genetic predisposition to psoriasis: approximately 40% of individuals with psoriasis or PsA have a family history of the disease (Solmaz et al., 2020), and that the disease occurs more frequently among monozygotic twins versus dizygotic twins (Lønnberg et al., 2013). Genome-wide association studies have identified multiple susceptibility loci for psoriasis, many of which contain genes involved in immune system regulation (Ellinghaus et al., 2010; Hüffmeier et al., 2010; Mahil et al., 2015; Nair et al., 2009; Stuart et al., 2010; Tsoi et al., 2012).
At least 12 major psoriasis susceptibility (*PSORS*) loci have now been identified, with PSOR1 on chromosome 6 containing the HLA-Cw6 allele being the most significant (Lowes et al., 2014). Indeed, there is a significant association between class I HLAs such as HLA-B13, HLA-B17, HLA-B57 and HLA-Cw6 and psoriasis. HLA-Cw*62 is particularly associated with early-onset psoriasis and guttate psoriasis (Mallon et al., 2000). HLA B17, B37 and B62 may can drive the susceptibility to the development of psoriasis and more severe PsA (Alenius et al., 2002)

1.1.5.2 Other Genetic Factors

Genome-wide association studies (GWAS) have identified numerous other susceptibility loci for psoriasis. These loci contain genes involved in the regulation of the immune response, skin barrier function, and inflammatory pathways, among others.

Examples include the IL-23R and IL12B genes, which code for components of the IL-23 cytokine signaling. In particular, polymorphism in the IL12B gene that encodes the p40 subunit, which is shared by both IL-12 and IL-23 and in the IL23R gene that encodes the IL-23 receptor, which binds to the p19 subunit of IL-23 have been associated with psoriasis susceptibility and progression (Cargill et al., 2007; Nair et al., 2009).

Although it has not been as strongly implicated in psoriasis as IL12B and IL23R, variants in IL23A encoding the p19 subunit of IL-23 have been associated with an increase in psoriasis risk in certain populations (Bojko et al., 2018).

Genetic variants in the tumor necrosis factor alpha-induced protein 3 (TNFAIP3) and its interacting protein TNIP1, could lead to overactive NF-κB signaling and an exacerbated inflammatory response, contributing to the development and progression of psoriasis (Ellinghaus et al., 2012; Hüffmeier et al., 2010; Nair et al., 2009). The gene known as TNFAIP3 is responsible for the creation of a critical ubiquitin-editing enzyme called A20. This enzyme plays a crucial role in ending NF-κB signaling, thus ensuring equilibrium within the immune system. On the other hand, the TNIP1 gene is responsible for encoding a protein that collaborates with A20 to prevent the activation of NF-κB.

Distinct mutations in the CARD14 gene, also involved in the NF-κB signaling pathway, have been associated with the development of familial plaque psoriasis and psoriasis with early onset (Jordan et al., 2012).

The Late Cornified Envelope (LCE) gene cluster, specifically the LCE3B and LCE3C genes, has been implicated in psoriasis susceptibility. This gene cluster is located within the Epidermal Differentiation Complex (EDC) on chromosome 1 and is involved in the terminal differentiation of the epidermis. In particular, a common deletion of two genes in this cluster, LCE3B and LCE3C (LCE3C_LCE3B-del), has been associated with an increased risk of developing psoriasis. The deletion is thought to lead to a defective skin barrier, thereby triggering an immune response that could lead to the development of psoriasis (de Cid et al., 2009). Research has suggested that this genetic deletion may be particularly associated with psoriasis triggered by environmental factors, such as physical trauma to the skin (the so-called 'Koebner phenomenon'), suggesting a gene-environment interaction in the pathogenesis of psoriasis (Riveira-Munoz et al., 2011).

Interleukin-1 beta (IL-1β) is a pro-inflammatory cytokine that has been implicated in the pathogenesis of psoriasis. Several studies have suggested that polymorphisms in the IL1B gene, located on chromosome 2, may influence susceptibility to psoriasis. For instance, a study on a Caucasian population reported that a single nucleotide polymorphism (SNP) in the IL1B gene (rs16944) was associated with a higher risk of psoriasis (Hébert et al., 2014). IL-1β is believed to contribute to the disease process by promoting inflammation and keratinocyte proliferation, key features of psoriasis. In addition, IL-1β can induce the production of other pro-inflammatory cytokines and chemokines, amplifying the inflammatory response in psoriatic skin (Cai et al., 2019).

1.1.5.3 Epigenetic Factors

Beyond the DNA sequence, epigenetic changes also play a role in psoriasis. Examples include DNA methylation, histone modifications, and microRNAs (miRNAs) alterations within the lesional skin and in PBMCs (Gao and Lu, 2023).

1.1.5.4 Smoking

The relationship between smoking and psoriasis is not entirely clear, however it seems that nicotine mediates its effect through the nicotinic acetylcholine receptors (nAChRs) present on keratinocytes, monocytes and dendritic cells, thus impacting cell proliferation and immune regulation (Naldi and Mercuri, 2009).

1.1.5.5 Infections

Some infectious agents can also trigger psoriasis. Streptococcus pyogenes causing sore throat is one of the best-known triggers, particularly for guttate psoriasis, while worsening of psoriasis has been linked to intestinal or skin colonization by Staphylococcus aureus, Malassezia, and Candida albicans (Teng et al., 2021). Both superantigen-driven polyclonal T lymphocyte activation and molecular mimicry have been proposed as potential mechanisms linking infections, particularly streptococcal infections, to psoriasis. Indeed, streptococcal M protein, given its molecular mimicry with keratin 17 (Valdimarsson et al., 2009), or other streptococcal antigens, structurally similar to peroxiredoxin 2 or heat shock protein, are potentially implicated (Besgen et al., 2010).

The prevalence of psoriasis in HIV-infected individuals is higher than in the general population. In these individuals, psoriasis can be severe and difficult to treat. This association suggests a role of immune activation and inflammation in the pathogenesis of psoriasis (Menon et al., 2010).

1.1.5.6 Stress

Stress is widely recognized as a potential trigger for psoriasis flare-ups, as well as a common consequence of living with this chronic skin disease. It is thought that stressors can dysregulating hypothalamic-pituitary-adrenal (HPA) axis activity affecting cortisol levels and eventually impairing inflammatory responses (Evers et al., 2010).

1.1.5.7 Obesity

Several research studies have reported that a higher body mass index (BMI) is associated with an increased risk of psoriasis, and it's also linked to the severity of the disease, indeed increased adiposity and weight gain were identified as strong risk factors for psoriasis A large cohort showing that women with a BMI of 30.0-34.9 had 1.48 times the risk of psoriasis, and those with a BMI of 35.0 or higher had 2.69 times the risk compared to those with a BMI below 25 (Setty, 2007). Moreover, weight loss has been associated with a decrease in the severity of psoriasis symptoms, further strengthening the link between BMI and psoriasis(Jensen et al., 2013) . The relationship between obesity and psoriasis is likely due to shared underlying inflammatory pathways and the impact of obesity on the body's immune function. Molecular mechanisms linking obesity and psoriasis will be discussed in the “comorbidities” section.

1.1.5.8 Alcohol

The relationship between alcohol and psoriasis is multifaceted, with several potential mechanisms contributing to the observed links. One proposed mechanism involves the impact of alcohol on keratinocyte proliferation. In fact, some studies in cell cultures have shown that ethanol can increase the proliferation of keratinocytes and can also increase the production of some cytokines, such as TNF-alpha and IL-6, promoting hyperkeratosis and the inflammation of the plaque (Farkas et al., 2003; Ockenfels et al., 1996).

1.1.5.9 Medications

Numerous molecules are known to be able to induce an exacerbation of psoriasis: some psychoactive drugs (lithium, carbamazepine, valproic acid), antihypertensives (beta-blockers, calcium channel blockers, ACE inhibitors, acetazolamide, clonidine), antibiotics (tetracyclines, ampicillin, penicillin), antimalarials, NSAIDs, interferon, digoxin, G-CSF, potassium iodide, progesterone and morphine (Basavaraj et al., 2010). However, the drugs most commonly implicated are beta-blockers, lithium, and antimalarials. It is known that interferon-based drugs, such as those used in the treatment of hepatitis C, melanoma and multiple sclerosis, can trigger or exacerbate psoriasis probably due to their immunomodulatory effect (Balak and Hajdarbegovic, 2017). Newly applied drugs such as immune checkpoint inhibitors, used to treat some types of cancer including melanoma and lung cancer, have been shown to cause or exacerbate psoriasis (Cutroneo et al., 2021; Nikolaou et al., 2021). A review

found that skin-related side effects are common in patients treated with programmed cell death 1 (PD-1) inhibitors, with approximately 4% of patients developing psoriasis-like skin lesions (Cutroneo et al., 2021)
Tumor necrosis factor-α (TNF-α) inhibitors, drugs used for the treatment of psoriasis, are occasionally linked to the development of psoriasis-like eruptions (Cutroneo et al., 2021; Nikolaou et al., 2021). The exact mechanism of these paradoxical reactions is not yet fully understood, but some theories suggest it could be due to a complex interplay of various immune responses, including shifts in cytokine profiles (e.g., increased production of interferon-α (IFN-α) or interleukin (IL)-23), the development of autoantibodies, or changes in T-cell subsets (Ko et al., 2009).

1.2 Etiopathogenesis of psoriasis

The development of plaques of psoriasis is a multistage process involving a dysregulated activation of innate and adaptive immune systems, alteration of the keratinocyte function, and inappropriate vascular structure proliferation. Briefly, various external factors like trauma and injury, infection, or medication can stress or damage keratinocytes (Nestle et al., 2009) leading to the release of endogenous DNA/RNA and antimicrobial peptides (AMPs) (e.g. LL-37), which form complex and activate plasmacytoid dendritic cells (pDC) via toll-like receptors (TLR)-7 or TLR-9 (Rendon and Schäkel, 2019) resulting in the production of type I interferons (IFN-α, IFN-β) (Kamata and Tada, 2022). Type I interferons stimulate the activation of myeloid dendritic cells (mDCs) to produce key psoriatic inflammatory cytokines, as TNF-α, IL-12 and IL-23 (Benezeder and Wolf, 2019) that facilitate the differentiation of naïve T cells into Th1, Th22 and Th17 subsets (Figure 1). Of note, LL37–RNA complexes can directly activate mDCs via TLR8 (Rendon and Schäkel, 2019) . Furthermore, macrophages also respond to LL37–RNA activation by secreting high amounts of TNF-α, IL-12, and IL-23 (Hänsel et al., 2011).

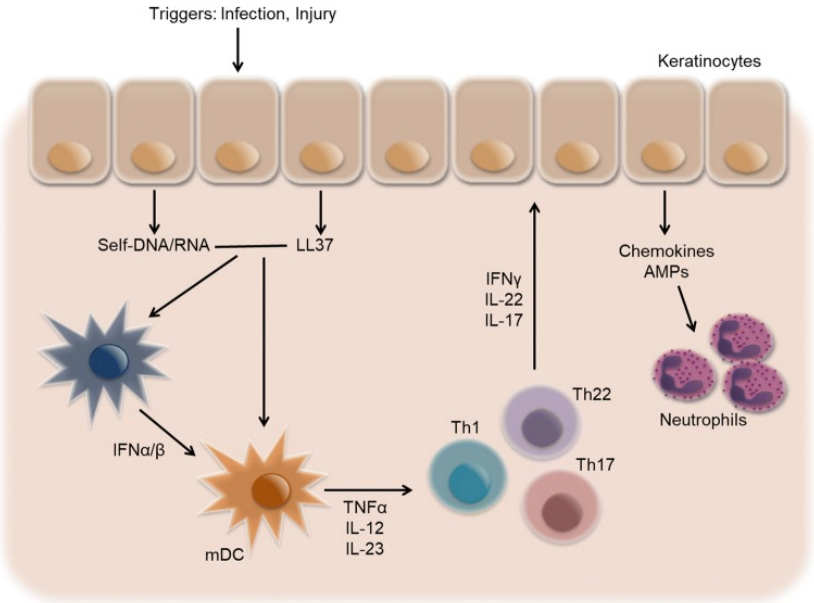

Figure1: Initiation phase of psoriasis. Various triggers can cause activation of keratinocytes and the release of nucleic acids and AMPs (e.g., LL-37), which form complexes and activate pDCs and mDCs. DCs promote differentiation of T cells into Th1, Th22, and Th17 subsets. Cytokines produced by these T cells such as IL-17, and IL-22 act on keratinocytes and cause hyperproliferation. Keratinocytes release AMPs and chemokines and attract neutrophils and other leukocytes (Benezeder and Wolf, 2019).

Cytokines produced by Th1, Th22 and Th17 cells including IFN- γ, IL-17 and IL-22 stimulate keratinocytes to proliferate and to differentiate abnormally, leading to the clinical manifestations of psoriasis, such as thick, scaly plaques (Benezeder and Wolf, 2019). Keratinocyte themselves perpetuate the cycle of inflammation, producing AMPs and chemokines (Girolomoni et al., 2015), which attract neutrophils and other leukocytes, and VEGF, which recruits and favors proliferation of endothelial cells, thereby promoting angiogenesis and creating highly vascular psoriatic plaques (Benezeder and Wolf, 2019) (Figure 2).

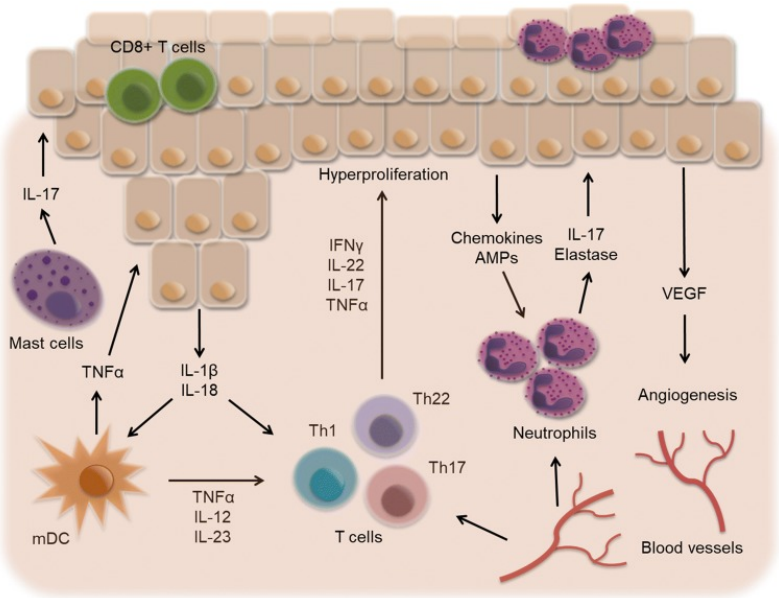

Figure 2: Chronic psoriatic lesion. In psoriasis, mast cells, neutrophils, mDCs, and T cells produce pro-inflammatory cytokines. Proliferating keratinocytes release IL-1β, IL-18, chemoattractants, and VEGF resulting in accumulation of neutrophils in the epidermis and increased angiogenesis (Benezeder and Wolf, 2019).

Recent research has highlighted the role of tissue-resident memory T cells (TRMs) in the pathogenesis of psoriasis. These are IL-17 and IL-22 producing cells that can persist long-term in the skin and, if reactivated, could contribute to disease recurrence, in the same body sites, after the cessation of the therapy (Gallais Sérézal et al., 2018). Indeed, even after long-term therapy, CD8+ TRMs do not lose their ability to produce IL-17A, after Il-23 stimulation (Whitley et al., 2022), driving inflammation and recruitment of circulating leukocytes into the tissue; while CD4+ TRMs produce IL-22 which can signal to keratinocytes and stimulate their proliferation (Cheuk et al., 2014). Although the role of innate cells has not been extensively studied, Langerhans cells (LCs) isolated from resolved psoriatic lesions can produce IL-23 after stimulation, which makes them another potential player in the restart of activation of “resting” TRMs and possible reappearance of psoriatic lesions (Benezeder and Wolf, 2019) (Figure 3).

Besides, several studies have shown that in macroscopically resolved skin, the expression levels of several gene products, mainly related to inflammatory pathways and skin structure, are not fully normalized after treatment (Brodmerkel et al., 2019; Suárez-Fariñas et al., 2011).

Taken together, these elements define what is called the "cellular and molecular scar" of psoriasis, indicating changes in gene expression and cellular functions that remain in the skin even after the active psoriatic lesions have clinically resolved. This idea suggests that even in the absence of visible inflammation, the skin is not completely 'normal' and is 'primed' for another bout of inflammation.

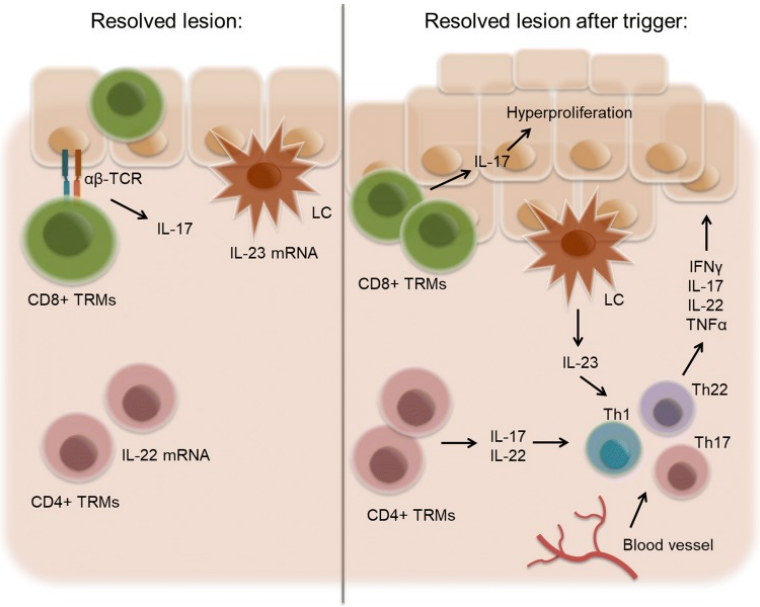

Figure 3: Model mechanism for disease recurrence in resolved lesions. In clinically healed lesions, CD4+ T cells remain in the dermis and express IL-22 mRNA. LCs residing in the epidermis express IL-23 mRNA. Epidermal CD8+ TRMs are able to produce IL-17. Upon disease trigger, LCs and T cells actively produce pro-inflammatory cytokines and cause recurrent inflammation (Benezeder and Wolf, 2019).

An in-depth description of the drivers implicated in the pathogenesis of psoriasis is now reported.

1.2.1 Antigens

The exact antigens involved in psoriasis are not fully understood and remain an ongoing research topic. Recent studies have suggested that some proteins may act as self-antigens by activating the immune system. AMPs are small proteins that play a crucial role in the innate immune response, helping to protect against a wide range of pathogens. In addition to their direct antimicrobial activity, AMPs can modulate the immune response, contributing to inflammation and wound healing. In the context of psoriasis, keratinocyte- derived antigens are upregulated in the early phases of the disease and may represent the starting point of the inflammatory cascade.

Among them, LL37 is a peptide derived from the larger protein cathelicidin, which is involved in the body's defense against bacterial infections. According to current opinion, LL-37 is an important player in the pathogenesis of psoriasis. Indeed, LL37 released by keratinocytes after an injury or an infection, it can form complexes with self-DNA or self-RNA, that trigger pDCs cells to produce type I interferons. In particular, LL37–DNA complexes stimulate pDCs through TLR9, whereas LL37 bound to RNA stimulates pDCs through TLR7. In addition, LL37–RNA complexes may directly act on mDCs via TLR8 (Rendon and Schäkel, 2019). β-defensins are another type of AMP overproduced in psoriatic skin. They can stimulate the production of inflammatory cytokines and chemokines, thus contributing to the inflammatory environment (Harder et al., 2001). Moreover, S100 proteins, including S100A7 (psoriasin), S100A8, and S100A9 are elevated in psoriatic skin and can also stimulate inflammatory responses (Ekman et al., 2017).

A more recent study identified ADAMTSL5 as a melanocyte autoantigen targeted by autoreactive CD8+ T cells in psoriasis. Indeed, in a mouse model, triggering ADAMTSL5-specific CD8+ T cells in the skin led to the development of psoriasiform skin inflammation (Arakawa et al., 2015).

Finally, lipid antigen PLA2G4D, able to activate lipid-specific autoreactive T cells, and keratin 17, characterized by the molecular mimicry with the M protein of Streptococcus pyogenes, could be implicated in the pathogenesis of the disease, as confirmed by their overexpression in psoriatic lesions (ten Bergen et al., 2020).

1.2.2 The innate immunity in psoriasis

1.2.2.1 Dendritic Cells (DCs)

pDCs are a rare subset of dendritic cells representing less than 0.4% of peripheral blood mononuclear cells. They can be identified by the expression of several cell surface markers including BDCA-2 (CD303), CD123 (the alpha chain of the IL-3 receptor), and BDCA-4 (CD304). Unlike conventional DCs, pDCs lack expression of many typical dendritic cell markers such as CD11c(Swiecki and Colonna, 2015). pDCs play a critical role in antiviral immunity due to their ability to produce large amounts of type I interferons (IFN-α and IFN-β) upon sensing of viral nucleic acids via TLR7 and TLR9. Besides their antiviral role, pDCs can present antigens to T cells and produce other cytokines such as IL-6, TNF-α and IL-12, affecting both innate and adaptive immunity(Gilliet et al., 2008). Abnormal functioning of pDCs has been implicated in systemic lupus erythematosus (Sisirak et al., 2014) and psoriasis. In fact, pDCs are significantly increased in early psoriatic lesions, while they are absent in normal skin (Wollenberg et al., 2002). In this context, it seems to be their ability to produce type I interferons to intervene in the early stages of plaque formation. Conversely, in cancer, pDCs often show a reduced ability to produce type I interferons and may contribute to immune evasion (Conrad et al., 2012). mDCs play a crucial role in initiating adaptive immune responses and are characterized by their ability to efficiently capture, process, and present antigens to T cells (Merad et al., 2013). After encountering the antigens, mDCs undergo a maturation process during which they upregulate the costimulatory molecules (such as CD80, CD86 and CD40) and major histocompatibility complex (MHC) molecules on their surface, allowing them to effectively activate the T cells. In addition to their antigen-presenting function, mDCs produce a variety of cytokines that can shape the type of immune response(Collin and Bigley, 2018). In humans, mDCs are generally classified into two major subsets: mDC1 (also known as CD1c+ DC or BDCA1+ DC) and mDC2 (also known as CD141+ DC or BDCA3+ DC). Each subset has distinct phenotypic characteristics and functional specializations. mDC1 cells are particularly efficient at presenting antigens to CD4+ T cells and in inducing Th1 responses, whereas mDC2 cells are specialized in cross-presenting antigens to CD8+ T cells (Haniffa et al., 2013) The number of mDCs is markedly elevated in psoriatic skin, particularly an inflammatory subset of mDCs (including DCs expressing TNF-alpha and iNOS [TIP-DC], 6-sulfo LacNAc DC [slanDC] and epidermal DC [eDCs]) (Farkas and Kemény, 2011; Hänsel et al., 2011; Lowes et al., 2005; Martini et al., 2017; Zaba et al., 2009). These are implicated in disease pathogenesis by producing pro-inflammatory cytokines such as TNF-α, IL-12 and IL-23, which can drive the differentiation of Th1 and Th17 cells and thus the production of IL-17 (Lowes et al., 2014; Zaba et al., 2009). mDCs also modulate keratinocyte functions through the production of IL-20 and act on the endothelium by inducing vasodilation through the production of and nitric oxide (Wang et al., 2006).

LCs are considered macrophages that retain the function of DCs and are mainly located in skin, oral, genitalia, respiratory epithelia (Guilliams et al., 2014). Within the skin, these stellate DCs, are located at the basal layer of the epidermis where they exist for a long time after migration and act as antigen presenting cells (APCs), holding a crucial role in inflammatory responses. They are characterized by the expression of Langerin (CD207) and CD1a and contain Birbeck granules, thought to play a pivotal role in endocytic processes (Yan et al., 2020). Research on the number of inflammatory cells in psoriasis has been debated, with different reports indicating an increase, decrease, or stability of LCs in the epidermis of patients with the condition. It is thought that LCs may induce the proliferation of CD4+T cells under inflammatory conditions, while CD4+T cells, CD8+T cells produce IL-17, IL-17A, IL-17F, IL-21, and IL-22 as cytokines of Th17 cells (Yan et al., 2020). The presence of pro-inflammatory LCs that trigger T cell activation in psoriasis aligns with the continuous expression of IL-23 in LCs in resolved psoriatic plaque (Martini et al., 2017).

1.2.2.2 Macrophages

Macrophages are involved in the innate immune response by recognizing and engulfing foreign particles, including bacteria, viruses, and other pathogens, and by releasing chemicals that attract

other immune cells to the site of infection and promote inflammation. While, in the context of the adaptive immune response, they act as APCs.
Depending on the signals they receive from the surrounding environment they can mainly differentiate into M1 (pro-inflammatory, fight against pathogens and promote tissue destruction) and M2 macrophages (anti-inflammatory, involved in tissue repair and wound healing).
Increased levels of circulating monocytes have been demonstrated in patients with psoriasis (Nguyen et al., 2018) with a bias towards the M1 phenotype (Lin et al., 2018). A considerable infiltration of macrophages has also been demonstrated in psoriatic skin (Leite Dantas et al., 2016), particularly at the dermal level, along the basement membrane (Boehncke et al., 1995), characterized by an increase in the M1/M2 ratio compared to normal skin (Kim et al., 2019). These cells contribute to the disease both by serving as antigen-presenting cells and by producing cytokines, such as TNF-α and IL-23 (Kamata and Tada, 2022). Of note, macrophages, not mDCs, have been identified as the most abundant source of IL-23 in psoriatic skin (Mehta et al., 2021). Their reduction in the skin after effective biologic therapy (Mehta et al., 2021) and the loss of skin with a psoriatic phenotype after their depletion in the mouse model (Wang, 2006) confirm the importance of their role.

1.2.2.3 Neutrophils

Neutrophils are found in high numbers in psoriatic skin lesions; in particular, in the initial phase of plaque formation, neutrophils migrate to the upper layers of the skin, where they collect to form Munro's microabscesses.
However, the exact role of neutrophils in the pathogenesis of psoriasis is not fully understood, but they are thought to contribute to inflammation and skin changes in several ways. These, in fact, release pro-inflammatory molecules such as cytokines (IL-17A) (Reich et al., 2015) and chemokines (IL-8) (Glowacka et al., 2010), which recruit further immune cells. Furthermore, their production of reactive oxygen species (ROS), together with degranulation and NET formation may contribute to disease pathogenesis (Chiang et al., 2019).

1.2.3 The adaptative immunity in psoriasis

The Th17 subset of CD4+ T cells and, to a lesser extent, Th1 and Th22 cells, are implicated in psoriasis. Although Th1 cells were previously thought to play the most important role; it is now known that the main actor is Th17 cells.

1.2.3.1 T helper type 17 cells

Th17 cells are a subset of pro-inflammatory T cells that play crucial roles in host defense against bacterial and fungal infections, particularly in mucosal surfaces, inflammation, and autoimmune and inflammatory disorders, including psoriasis, rheumatoid arthritis, multiple sclerosis and inflammatory bowel disease (McGeachy et al., 2019). In particular in psoriasis, Th17 cells are found in lesional skin and at elevated levels in the circulation in patients (Kagami et al., 2010; Lowes et al., 2008; Teunissen et al., 1998)
Th17 cells differentiate from naïve CD4+ T cells in the presence of the cytokines transforming growth factor-beta (TGF-β), IL-6 and IL-23 produced by inflammatory DCs and macrophages (Di Cesare et al., 2009). This induces the expression of the transcription factor RORγt, which is essential for Th17 cell development. Furthermore, the presence of IL-23 is crucial for the maintenance and expansion of Th17 cells (Bettelli et al., 2006).
Th17 cells are characterized by the production of the cytokines IL-17A, IL-17F, IL-21 and IL-22. IL-17A and IL-17F are particularly important in promoting inflammation by inducing the production of other inflammatory mediators, including cytokines (e.g., IL-6, TNF), chemokines (e.g., CXCL1, CXCL2), and AMPs (e.g. β -defensins) (Korn et al., 2009).

1.2.3.2 T helper type 1 cells

Th1 cells are a subset of CD4+ T cells that play a key role in mediating cellular immunity. They are mainly involved in immune responses against intracellular pathogens, such as viruses and some bacteria. The primary cytokines produced by Th1 cells are IFN-γ, TNF-α, and IL-2 (Abbas et al., 1996).

The differentiation of naïve T cells into Th1 cells is induced by the cytokine IL-12 and is marked by the expression of the transcription factor T-bet. Th1 cells exert their effects by activating macrophages and cytotoxic T cells, thereby enhancing the immune system's ability to kill intracellular pathogens.

In addition to their role in infectious diseases, Th1 cells have been implicated in the pathogenesis of various inflammatory and autoimmune diseases, including multiple sclerosis, type 1 diabetes, and rheumatoid arthritis (O'Shea and Paul, 2010). In the context of psoriasis, the Th1 pathway was initially thought to be the dominant immune response, indeed, increased levels of Th1 cells and related cytokines have been found in psoriatic skin lesions (Szabo et al., 1998). However, the discovery of the Th17 cell subset has shifted focus, with current understanding suggesting that both Th1 cells and Th17 cells play critical roles in the pathogenesis of psoriasis (Lowes et al., 2013).

1.2.3.3 T helper type 22 cells

Th22 cells are a subset of CD4+ T cells, which have been identified relatively recently compared to Th1 and Th17 cells. The differentiation of naïve CD4+ T cells into Th22 cells is driven by TNF-α. Th22 cells are mainly characterized by their production of IL-22 (Duhen et al., 2009).

The primary function of Th22 cells is thought to be tissue remodeling and repair, particularly in the skin. In fact, where they are involved in wound healing and contribute to the pathogenesis of various skin diseases, including psoriasis and atopic dermatitis (Eyerich et al., 2009).

In psoriasis, increased levels of Th22 cells and IL-22 have been observed in skin lesions, suggesting a critical role in the disease (Jiang et al., 2021). IL-22 produced by Th22 cells can stimulate keratinocyte proliferation and production of chemokines and proinflammatory cytokines driving the recruitment of neutrophils (Jiang et al., 2021).

1.2.3.4 T regulatory cells

Tregs are a subset of T cells that play crucial roles in maintaining immune homeostasis and self-tolerance (Sakaguchi et al., 2008; Wing and Sakaguchi, 2010). They achieve this by suppressing or downregulating the induction and proliferation of effector T cells (Sakaguchi et al., 2008; Wing and Sakaguchi, 2010). The most studied Tregs are those expressing the transcription factor Foxp3 (Foxp3+ Treg). Dysregulation or dysfunction of Tregs can lead to autoimmune disease and chronic inflammation.

In the context of psoriasis, on one hand, there is evidence to suggest that the number and function of Tregs may be impaired leading to overactive immune responses (Jorn Bovenschen et al., 2011); on the other hand, studies have found that Tregs can convert to IL-17-like cells under inflammatory conditions, which may contribute to disease progression (Goodman et al., 2009).

Furthermore, psoriatic inflammation is associated with relative resistance to Treg-mediated suppression, as cytokines such as IL-6 and TNF-α can interfere with Treg function (Sugiyama et al., 2005).

For these reasons it is probable that the dysfunction of Tregs in psoriasis could also lead in vivo to the reduced suppression and therefore to the hyperproliferation of effector T cells.

1.2.4 Keratinocytes

It is debated whether keratinocytes can represent the starting element of the inflammatory cascade of psoriasis. In fact, in genetically predisposed subjects, external agents, such as trauma or infection are able to induce the production of keratinocyte-derived AMPs, including beta-defensins, cathelicidins (e.g. LL-37) and psoriasin (S100A7) (Coimbra et al., 2012).

Moreove, keratinocytes, under the stimulation of IL-17 and IL-22 activate and proliferate and in turn release chemokines such as CCL20 and CXCR8 and further AMPs amplifying the inflammatory process (Coimbra et al., 2012).
Keratinocytes also participate in the pathogenesis of the disease by producing and releasing pro-angiogenic cytokines such as VEGF and IL-8, responsible for neoangiogenesis and abnormal vascular proliferation of psoriatic skin (Mahil et al., 2016).

1.2.5 Endothelial cells

In plaque, proangiogenic cytokines are able to activate endothelial cells (Heidenreich et al., 2009); leading to neo-angiogenesis; process including vasodilation, increased vessel permeability, destabilization of the pre-existing vessel, degradation of the extracellular matrix, proliferation and migration of endothelial cells, formation of a new lumen and maturation of the new vessel with recruitment of pericytes (Carmeliet, 2003; Klagsbrun and Moses, 1999). Furthermore, activated endothelial cells also express intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), Thy-1 and E- and P-selectins, thus facilitating the leukocyte migration to the skin (de Boer et al., 1994; Groves et al., 1991; Horrocks et al., 2008; Terajima et al., 1998; Wetzel et al., 2006).

1.2.6 Cytokines

1.2.6.1 Interferons

Type I IFNs (including IFN-α and IFN-β) induced in response to viral infections, act by inhibiting viral replication by stimulating the immune response. Type I IFNs are expressed in particular by pDCs following TLR7- and TLR9-mediated recognition of viral RNA and DNA(Ganguly et al., 2009; Lande et al., 2007). Type I IFNs are not found in normal skin, but are induced in virus-infected skin, as well as in skin wounds, finally in psoriatic skin where its production is sustained from the pDCs (Nestle et al., 2005). It is very likely that type I IFNs are involved in the initiation phase of psoriasis skin lesions, as pDCs have been shown to infiltrate early developing lesions, but are notably absent in chronic lesions (Baliwag et al., 2015). The role of type I IFNs in the triggering of psoriasis is confirmed by the fact that treatment with INF- α 2 is capable of inducing the disease or worsening pre-existing conditions (Afshar et al., 2013). Furthermore, topical treatment with imiquimod, which induces local production of IFN-α in the skin, stimulated the development of psoriasis in humans and psoriasis-like diseases in mice (van der Fits et al., 2009; Patel et al., 2011). However, during the phase I clinical trial for the treatment of chronic plaque psoriasis, an anti IFN-α antibody (MEDI-545) did not show efficacy (Bissonnette et al., 2010). A probable explanation is that type I IFN secretion appears to be critical in disease progression until it enters the activation phase of the adaptive immune response, becoming absent in chronic psoriatic lesions (Mohd Noor et al., 2022).
Psoriasis lesions have long been known to contain elevated levels of IFN-γ (Austin et al., 1999), mostly secreted by cutaneous T cells (Vollmer et al., 1994) and intradermal injection of IFN-γ has been shown to induce a psoriatic skin (Fierlbeck, 1990; Johnson-Huang et al., 2012). Probably, IFN-γ contributes to the cytokine storm in psoriasis by favoring the IL-12/IL-17 axis (Baliwag et al., 2015). However, the correlation between serum levels and disease severity appears to be conflicting (Mohd Noor et al., 2022).

1.2.6.2 Tumor necrosis factor-α

TNF-α considered a central cytokine in the development of psoriasis, rheumatic arthritis and inflammatory bowel disease (Bradley, 2008); but its role also extends to major depression, Alzheimer's disease and cancer (Balkwill, 2009; Morgan et al., 2018; Wang and Lin, 2008). This cytokine is involved in granuloma formation, an important part of the host defense against M. tuberculosis (Lin et al., 2007). It is produced mainly by macrophages, but also by a variety of other immune cells such as lymphocytes, natural killer cells and neutrophils. The primary function of TNF-

α is the regulation of immune cells and the inflammatory response. TNF-α is a critical mediator of acute phase reaction, promoting fever, loss of appetite, and acute phase protein production. Its ability to induce cell death by apoptosis and is essential for fighting infections and tumors. TNF-α exerts its effects by binding to two types of receptors: TNFR1 (p55/60) and TNFR2 (p75/80). Binding of TNF-α to its receptors initiates several signaling cascades, including the activation of NF-κB and MAP kinases, leading to the expression of genes involved in inflammation and cell survival (Locksley et al., 2001). In the context of psoriasis, it has well proven to be high in skin lesions (Uyemura et al., 1993) where it is produced by mDC, Th17, Th1 and from keratinocytes, which are themselves influenced by this molecule. TNF-α works synergistically with IL-17 amplifying the cytokine storm of psoriasis (Baliwag et al., 2015). Specifically, it stabilize IL-17 mRNA(Hartupee et al., 2007), and boost the expression of IL-17R on keratinocytes (Johnston et al., 2014); concurrently, IL-17A trigger to induce TNFR expression.

1.2.6.3 Interleukin-17

The IL-17 family consists of six ligands (IL-17A to IL-17F) and five receptors (IL-17RA to IL-17RE), with IL-17A and IL-17F sharing maximum homology and binding to the same 17RA and IL-17RC receptor complex (Gaffen, 2009) . IL-17 plays a key role in host defense against some pathogens, including Candida species, by stimulating the release of antimicrobial peptides and pro-inflammatory cytokines and chemokines (Baliwag et al., 2015). The role of IL-17 in psoriasis, but also in rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and Crohn's disease is suggested by its increased expression at sites of inflammation (Kryczek et al., 2008; Maddur et al., 2012; Zhu and Qian, 2012). Of note, IL-17A has been shown to be elevated in lesions of psoriasis and serum of patients with psoriasis (Fotiadou et al., 2015; Johansen et al., 2009). The main producers of IL-17 are Th17, but gamma delta T cells (γδ), some subsets of CD8+ T cells (Tc17), can also produce IL-17(Eyerich et al., 2009; Miossec et al., 2009). IL-17A appears to have the major role in psoriasis, followed by IL-17C and IL-17F (Mohd Noor et al., 2022). The binding of IL-17-A to the receptor compound composed of IL-17RA and IL-17RC activates an adapter protein called ACT1. This, in turn, activates downstream pathways including the NF-κB, MAPK and C/EBP pathways, leading to the production of pro-inflammatory cytokines, chemokines and antimicrobial peptides (Gaffen, 2009). The primary targets of IL-17 are epithelial cells, fibroblasts and keratinocytes, but it can also act on immune cells. IL-17 stimulates these cells to produce cytokines (such as IL-6 and TNF), chemokines (such as CXCL1 and CXCL2), and antimicrobial peptides (such as β-defensins), contributing to neutrophil recruitment and inflammation (Onishi and Gaffen, 2010).

1.2.6.4 Interleukin-12/IL-23

The IL-12 family of cytokines plays a crucial role in the regulation of innate and adaptive immune responses. It includes IL-12, IL-23, IL-27 and IL-35, each consisting of two subunits and exerting distinct effects on various immune cells. IL-12 and IL-23 seem to be implicated in the pathogenesis of psoriasis. Indeed, IL-23 has been shown to be increased in diseased skin compared to unaffected skin in subjects diagnosed with the disease (Chan et al., 2006; Lee et al., 2004; Piskin et al., 2004). Furthermore, injection of IL-23 into the skin is able to induce a psoriasis-like phenotype in mice (Chan et al., 2006; Rizzo et al., 2011; Zheng et al., 2007). Furthermore, as explained above, polymorphisms in the genes for IL23R, and the p40 and p19 subunits of IL-23 have been linked to psoriasis (Liu et al., 2008). IL-23 is composed of the p40 subunit of IL-12 and a single p19 subunit. It is mainly produced by mDCs and macrophages and (to a lesser extent) by keratinocytes while its receptors are commonly expressed on T cells, NK cells, neutrophils, macrophages and mast cells. IL-23 does play a significant role in the pathogenesis of psoriasis from the early onset to its sustenance mechanisms by inducing and maintaining differentiation in the Th17 sense (Oppmann et al., 2000).

IL-12 is a heterodimeric cytokine composed of the p35 and p40 subunits. It is mainly produced by antigen-presenting cells such as dendritic cells and macrophages. IL-12 plays a crucial role in the differentiation of naïve T cells into Th1 cells (Oppmann et al., 2000).
IL-12 family cytokines signal through heterodimeric receptors, which are associated with Janus kinases (JAKs). Activation of these receptors leads to the recruitment and phosphorylation of signal transducer and transcription activator (STAT) proteins, which dimerize and translocate to the nucleus to activate target genes. For example, IL-12 signals through STAT4 to promote Th1 responses (Teng et al., 2015), while IL-23 signals through STAT3 to induce Th17 responses by inducing transcription factor ROR-γt (Liu et al., 2020).

1.2.6.5 Interleukin-22

IL-22 is a cytokine produced mainly by immune cells, including Th17 and Th22. It helps improve barrier function and stimulates the production of antimicrobial proteins, thereby helping control bacterial infections on body surfaces (Basu et al., 2012). Interestingly, IL-22 is unique among cytokines in that it does not act on immune cells, but instead targets non-immune cells, such as epithelial cells and fibroblasts, on barrier sites (Wolk et al., 2004). In addition to its role in immunity, IL-22 has also been implicated in several inflammatory diseases, such as psoriasis, inflammatory bowel disease, rheumatoid arthritis, and systemic lupus erythematosus (Pan et al., 2013).
In psoriasis, IL-22-mediated signaling via STAT3 on keratinocytes support cell hyperproliferation, secretion of AMPs, and production of matrix metalloproteinases that support increased cell mobility (Wolk et al., 2006). Despite increased levels of IL-22 have been demonstrated in the blood of patients with psoriasis and in psoriatic plaques, an anti IL-22 monoclonal antibody failed in psoriasis, indicating this cytokine is not critical for maintenance of the disease (Hao, 2014).

1.2.7 Tissue resident memory cells

TRMs are a recently identified subset of non-circulating memory T cells that reside long-term in peripheral tissues (Clark, 2015). They are mainly found in epithelial barrier tissues, such as gastrointestinal, reproductive and respiratory tracts, and skin, where they offer a rapid and robust defense against pathogens (Park and Kupper, 2015). Indeed, during an initial infection, naïve T cells, upon recognizing their cognate antigen, become activated, proliferate and differentiate into effector T cells; which, after the clearance of the pathogen, mostly undergo apoptosis. However, a small fraction of these cells survives this contraction phase and differentiates into memory T cells to provide long-term immunity (Raphael et al., 2020). Central memory T cells (Tcm) predominantly reside in lymph nodes, ready to proliferate and differentiate into effector cells upon re-encountering the antigen. Effector memory T cells (Tem) are found in both circulation and peripheral tissues, prepared to exert immediate effector functions when faced with a familiar threat. Distinctly, TRMs persist in peripheral tissues, acting as sentinels to provide immediate on-site immune responses against reinfection. Interestingly, it's worth noting that while mostly TRMs develop following encounters with external pathogens, some may arise due to sensitization to self-antigens, thus being involved in the pathogenesis of autoimmune disorders (Clark, 2011; Park and Kupper, 2015) .
TRMs are characterized by the expression of several markers that distinguish them from circulating memory T cells. Although the exact profile can vary between different tissues and different species, some of the most commonly used markers for TRMs in humans and mice include CD69, CD103 and CD49 (Figure 4).

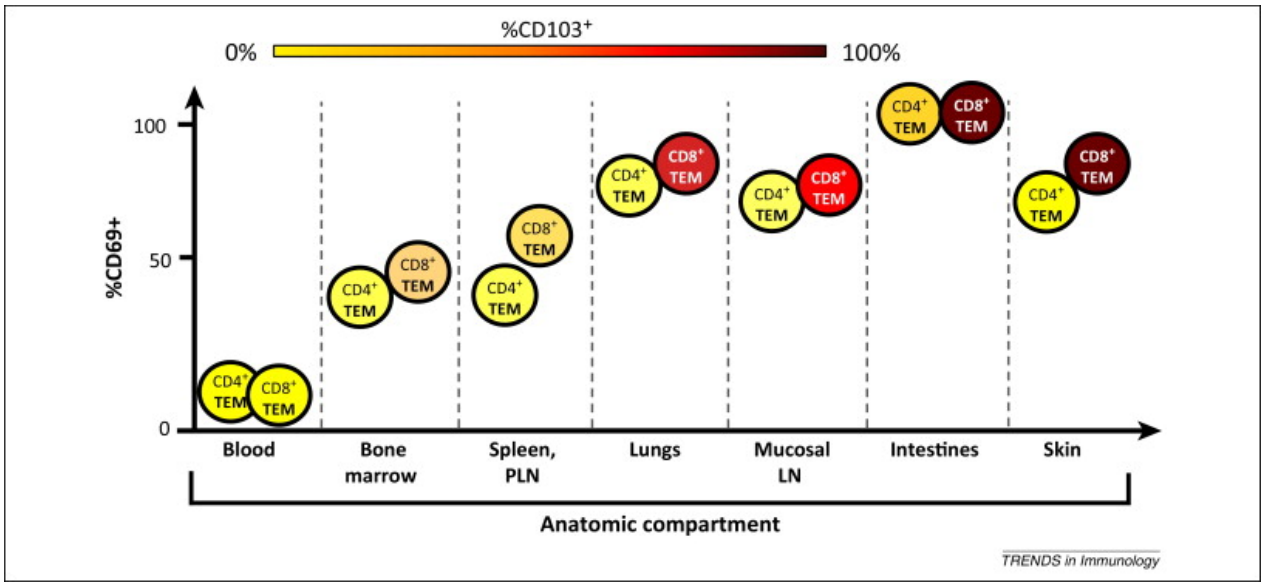

Figure 4: Variegation of TRM phenotypes in different tissue sites.
The variety of tissue-resident memory (TRM) cell characteristics in different tissues is demonstrated by the expression of the TRM markers CD69 and CD103 on CD4+ and CD8+ effector memory T cells (TEM) found in various tissues (indicated on the horizontal axis). The proportion of CD69+ cells is depicted based on their location on the vertical axis, while the proportion of CD103+ cells is shown by the color shading of each cell type, ranging from yellow (representing 0%) to deep red/brown (representing 100%). CD69 is not present on circulating cells and is gradually upregulated on TEM, with the highest levels of expression seen in mucosal sites. CD103 expression is highest in CD8+ TEM in mucosal tissues and lymph nodes that drain mucosal sites. Its expression varies in CD8+ TEM across different tissues, while CD4+ TEM typically show low or negligible CD103 expression (Thome and Farber, 2015).

CD69 is a marker for activated T cells, but it is also constitutively expressed on TRM cells. It helps retain TRM cells in tissues by counteracting the effects of S1P1, a receptor that promotes lymphocyte egress from tissues (Tokura et al., 2021). CD103 (integrin αE) and CD49a (integrin α1) are others common marker for TRMs that have been shown to bind and interact with E-cadherin and collagen, respectively (Tokura et al., 2021). The prevalent opinion suggests that CD69 and CD103 are key identifiers of TRMs, with the most frequently found TRMs cells displaying CD8, CD69, and CD103. Nonetheless, there have been reports of TRMs in certain organs like the intestine, female reproductive system, and kidney that do not exhibit CD103 expression. (Li et al., 2022)

Within the skin, all CD4+ and CD8+ TRMs express CD69, whereas CD103 is more strongly expressed by CD8+ compared to CD4+ cell (Thome and Farber, 2015) (Figure 4). CD4+ and CD8+ CD103+ TRM are enriched in the epidermis where they bind to E-cadherin, which is widely expressed by epithelial cells; whereas CD4+ and CD8+ CD103- cells are mainly located in the dermis (Thome and Farber, 2015; Watanabe et al., 2015; Willemsen et al., 2019) (Figure 5). Finally, CD49+ TRMs producing interferon-gamma have been identified in vitiligo; whereas CD49- TRMs producing IL-17 have been found in psoriatic skin (Cheuk et al., 2017).

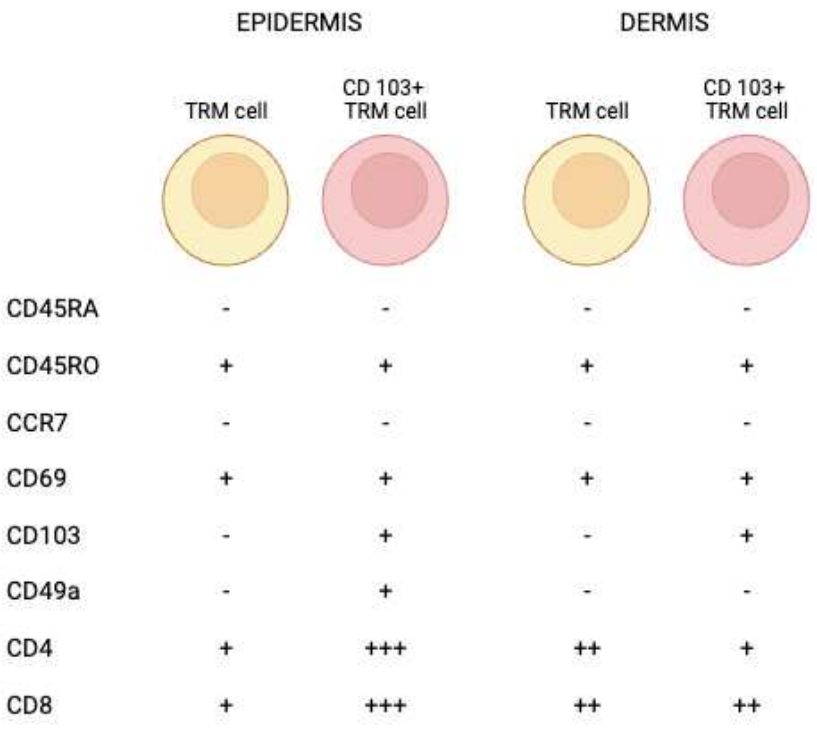

Figure 5: Key phenotypic properties and location of skin-resident T cells. Phenotypic characteristics of skin-resident memory T cells and distribution in human skin are shown. Human memory T cells are distinguished from naïve T cells by being CD45RO+ and CD45RA− (whereas naïve T cells show the CD45RO− CD45RA+ phenotype) (Farber et al., 2014; Raphael et al., 2020). The absence of CCR7 and expression of CD69 and CD103 distinguish TRM cells from circulating memory T cells. CD49a is found on epidermal CD69+ CD103+ CD8+ T cells only. CD69 and CD103 can be found on both CD4+ and CD8+ T cells, but at different levels. CD4+ T cells constitute approximately 75% of the lymphocytes present in both layers of the healthy human skin. However, there are twice as many CD103+ TRM cells (both CD4+ and CD8+) in the epidermis, while in the dermis, the majority of TRM cells are CD103−. −, no expression; + expression. Regarding CD4+ and CD8+: + represents low expression frequency; ++ medium expression frequency; +++ high expression frequency. * Fraction of CD69+CD4+ and CD69+CD103+CD4+ TRM cells of the total CD4+ TRM cell pool in either the epidermis or dermis are shown. **Fraction of CD69+CD8+ and CD69+CD103+CD8+ TRM cells of the total CD8+ TRM cell pool in either the epidermis or dermis are shown (adapted from Willemsen et al., 2019).

Indeed, in the skin, TRMs not only offer protection against Candida albicans, HSV and leishmania infections (Tokura et al., 2021) but are also implicated in numerous skin diseases, including vitiligo and psoriasis but also fixed drug eruption, alopecia areata, cutaneous T cell lymphomas, melanoma, lupus erythematosus and autoimmune bullous disease (Tokura et al., 2021).

In the context of psoriasis, the initial indication of TRMs' role came from the surprising discovery that blocking E-selectin, a molecule that prevents T cells from migrating from the blood into the skin, did not effectively treat psoriasis (Bhushan et al., 2002). Subsequently, research using xenograft models showed that when non-lesional skin grafts are implanted into immunosuppressed mice, they can result in the formation of plaque psoriasis, unlike grafts of healthy skin (Boyman et al., 2004). These lesions arise due to the stimulation and multiplication of resident T cells, which are transferred along with the non-lesional skin grafts. In 2011 Suárez-Fariñas (Suárez-Fariñas et al., 2011) pioneered the exploration of the "molecular scar" phenomenon in psoriasis. By using microarray analysis, they examined gene expression differences in skin samples taken from psoriasis lesions at baseline, after 12 weeks of treatment with etanercept, when psoriatic plaques had subsided, and in unaffected skin. They discovered that, even after treatment, the expression of 248 genes in skin samples that looked clinically and histologically normal remained different from the gene expression in unaffected skin, resulting in what they termed a "genomic residual disease profile". Five significant proinflammatory genes - IL-12p35, MX1, IL-22, IL-17, and IFN-γ - remained overexpressed by more than 25%, with their improvement ranging from 62-67%. They also found that genes associated with skin "structural" cell types did not return to baseline levels. Specifically, LYVE-1, WNT5A, RAB31, all associated with epidermal growth and differentiation, remained upregulated, while AQP9, a gene

associated with lipid metabolism and the formation of the skin's barrier function, remained downregulated. Lastly, they noted that although CD3+ cells seem to almost entirely disappear from the epidermis and dermis after treatment, CD8+ cells in the dermis only showed a 64% reduction, suggesting that these cells might contribute to the residual inflammatory signature of psoriasis. Following research discovered the existence of IL-17A+ CD8+ TRMs and IL-22+ CD4+ TRM persisting in the epidermis, representing a form of disease memory in clinically healed areas of psoriasis (Cheuk et al., 2014). Notably, a unique group of epidermal CD8+ T cells that co-express CD103, CCR6, and IL-23R were found to be significantly concentrated in healed lesions. This evidence suggests a potential "cellular scar" where CD8+ TRMs could trigger inflammation and draw circulating leukocytes into the tissue through IL-23-dependent IL-17A production (Whitley et al., 2022), while CD4+ TRMs could stimulate keratinocyte activation and the development of acanthosis through the production of IL-22 (Cheuk et al., 2014). Furthermore, the percentage of IL-17A-producing TRMs has been found to increase in relation to disease duration (years) (Vo et al., 2019) and individuals with a higher count of TRMs cells within their lesions tend to have thicker skin plaques and more severe manifestations of psoriasis in comparison to those with fewer TRMs (Kurihara et al., 2019; Sgambelluri et al., 2016). This indicates that TRMs not only contribute to the recurrence of psoriasis but also to its chronicity and severity, suggesting potential promising strategies with a therapeutic prompt intervention.

1.3 Comorbidities associated with psoriasis

Although, historically psoriasis has been considered as a skin-limited disease, recently, it is increasingly thought to be a systemic inflammatory disease, with several studies indicating an association between psoriasis and various comorbidities, that will be discussed in this paragraph (Kovitwanichkanont et al., 2020). The current opinion supports the idea that psoriasis-related inflammation may extend beyond the skin leading to the concept of "psoriatic march", or "inflammatory skin march" (Boehncke et al., 2011). In this context, skin may act as an endocrine organ and molecules produced within the psoriatic plaque could influence biological processes at distant sites (Piaserico et al., 2022). The systemic burden in psoriasis has been demonstrated by increased inflammatory laboratory biomarkers including C reactive protein (CRP), erythrocyte sedimentation rate (ESR), ICAM-1, TNF-α, VEGF and radiological tests with (18)F-fluorodeoxyglucose positron emission tomography computed tomography (FDG-PET/CT) that demonstrated numerous foci of inflammation within the skin, liver, joints, tendons, and aorta (Beygi et al., 2014; Garbaraviciene et al., 2009; Mehta, 2011; Montaudié et al., 2014; Sokolova et al., 2020; Suárez-Fariñas et al., 2012).

1.3.1 Cardiovascular disease (CVD)

People with psoriasis have an increased risk of CVD, myocardial infarction (MI), chronic heart failure (CHF), and cardiac arrhythmia. In particular, severe psoriasis confers the highest CV risk (compared with control subjects), including up to threefold increased risk of MI, 60% increased risk of stroke, and 40% increased risk of CV-related deaths (Samarasekera et al., 2013). Several studies, involving large sample sizes and complex multivariate models, have strongly suggested that severe psoriasis per se can be considered an independent risk factor of CVD (Abuabara et al., 2010; Li et al., 2012; Mehta et al., 2011; Ogdie et al., 2015; Prodanovich et al., 2009). Interestingly, psoriasis has been shown to impact early on the vascular compartment, leading to endothelial dysfunction and subclinical atherosclerosis that might predispose to cardiovascular events (Orlando et al., 2022). Indeed, exploring the microvascular compartment by Coronary Flow Reserve (CFR), a diagnostic parameter which evaluate the capacity of the coronary arteries to increase blood flow in response to demand, such as during physical exercise, it has been shown that people with psoriasis have reduced

CFR, even if they don't show any other signs of heart disease (Osto et al., 2012; Piaserico et al., 2019). Cardiologists have, therefore, included psoriasis in the European and American guidelines on CVD prevention as a 1.5 risk factor multiplier for CV risk (Piepoli et al., 2016), as well as a risk-enhancing factor for the start of statin treatment in nondiabetic adults with a CV intermediate risk (Grundy et al., 2019). In accordance, the Joint American Academy of Dermatology- National Psoriasis Foundation Guidelines recommend that patients with psoriasis should be advised of their increased cardiovascular risk and referred to the primary care physician or cardiologist (Elmets et al., 2019).
It has been hypothesized that chronic cutaneous inflammation directly could promote vascular inflammation leading to endothelial alterations, microvascular dysfunction and atherosclerotic plaque formation (Orlando et al., 2022). Briefly, Th1 and Th17 immune responses within the psoriatic plaque lead to the consequent overproduction of cytokines such as TNF-α, INF- α; INF- γ, IL-1, IL-6, IL-23 that may eventually establish a systemic inflammation able to negatively impinge on endothelium and microcirculation at distant site and thus contributing to atherosclerosis and finally to CVD (Orlando et al., 2022). In particular these cytokines may lead to e endothelial dysfunction inducing the expression of adhesion molecules, such as VCAM-1, ICAM-1, and E-selectin, on endothelial cells thus facilitating the attachment and subsequent migration of leukocytes into the arterial wall, a critical early step in atherogenesis (Erbel et al., 2009; Kölliker Frers et al., 2015; Libby, 2002). Moreover, they may effect on lipid metabolism promoting the formation of foam cells, by increasing LDL transcytosis in endothelial cells and by regulating the activity of macrophage scavenger receptor and foam cell formation (Hsu and Twu, 2000; Libby, 2002; Schuett et al., 2009; Taleb, 2016; Tedgui and Mallat, 2006; Zhang et al., 2014); can stimulate the expression of tissue factor, a key initiator of coagulation, thus promoting a prothrombotic state that contributes to the progression and complications of atherosclerosis (Kölliker Frers et al., 2015; Schuett et al., 2009) and can promote plaque instability, a key event in acute coronary syndromes, by stimulating the production of matrix metalloproteinases, enzymes that degrade the extracellular matrix and can weaken the fibrous cap of the atherosclerotic plaque, making it prone to rupture (Erbel et al., 2009; Gisterå and Hansson, 2017; Hansson et al., 2015; Schuett et al., 2009). Of note, interestingly, atherosclerosis shares some pathogenic mechanism within the psoriatic plaques: both are a Th1/Th17 disorder and exhibit increased TNFα (Boechat, 2020; Flammer and Ruschitzka, 2012).

Alongside with the direct link between psoriasis and CVD, both the diseases show to be more prone to traditional modifiable CV risk factors including hypertension, diabetes, hyperlipidemia, and obesity, all of which are combined and defined as metabolic syndrome (Piaserico et al., 2022) (Figure 6). Indeed, a “dose effect” of psoriasis on the metabolic syndrome and its components has been demonstrated (Langan et al., 2012).

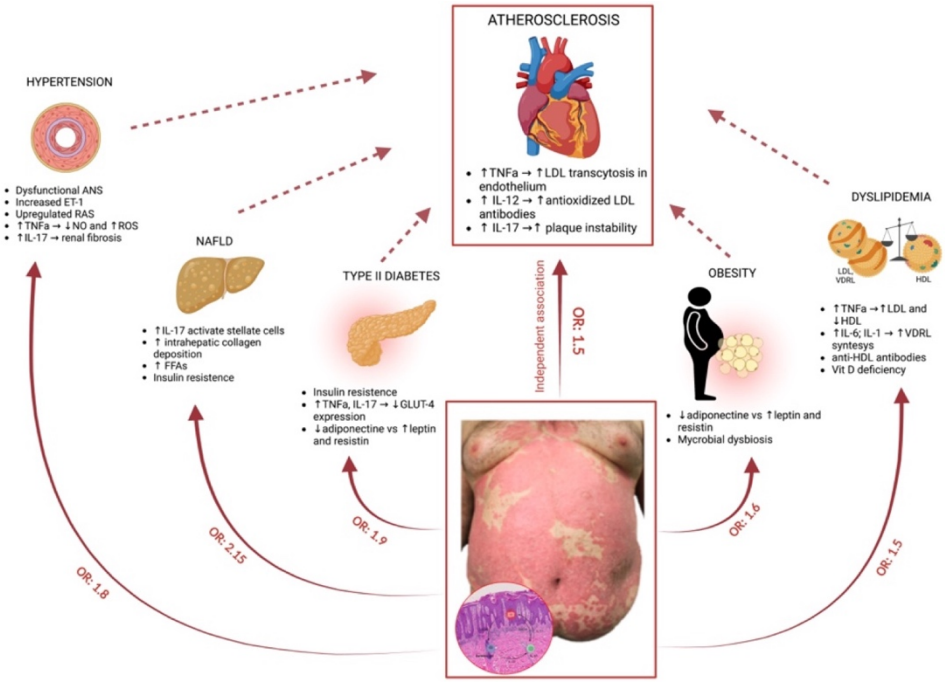

Figure 6: Molecular pathways involved in the link between psoriasis and its comorbidities.
Psoriasis *per se* is considered an independent risk factor for atherosclerosis. Moreover, psoriasis is also associated with a high prevalence of traditional modifiable CV risk factors, such as hypertension, diabetes, hyperlipidemia, obesity, and nonalcoholic fatty liver disease (NAFLD). Skin may act like an endocrine organs and molecules produced within the psoriatic plaque could influence biological processes at distant sites (Piaserico et al., 2022).

1.3.2 Hypertension

The prevalence of hypertension in patients with psoriasis is approximately 38.8% (Cohen et al., 2010), while it is estimated to be 31.1% in the general population (Mills et al., 2020). Many pathophysiological and molecular pathways have been explored to shed light on the link between psoriasis and hypertension. Among them, the role of the autonomic nervous system (ANS), involved in the regulation of blood pressure and heart rate, has been demonstrated to be impaired in patients with psoriasis (Halıgür et al., 2012; Mastrolonardo et al., 2006). Other evidence suggests that endothelin-1 may play a role in the development of hypertension among patients with psoriasis. Endothelin-1 is a mediator of vasoconstriction and increases blood pressure. It is synthesized by different cell types, including keratinocytes, and its expression appears to be increased in both skin and blood levels in patients with psoriasis (Bonifati, 1998). The role of the renin-angiotensin-aldosterone system, involved in vasoconstriction and blood pressure increase, was also investigated; showing that patients with psoriasis have higher renin activity and higher urinary aldosterone excretion (Ena et al., 1985). Moreover, heightened expression of the renin gene in the affected skin of patients with moderate to severe psoriasis, in comparison to unaffected skin from the same individuals, has been demonstrated (Suárez-Fariñas et al., 2012).
Finally, TNF-α contributes to increase the risk of hypertension and CVD through various mechanisms. In particular, it known to increase reactive oxygen species (ROS) levels and decrease nitric oxide production in blood vessels, which can lead to endothelial dysfunction, the initial step in the development of atherogenesis (Lee et al., 2017) and to an unbalanced microvascular dilation/constriction (Chen et al., 2015; Yoshizumi et al., 1993; Zhang et al., 2009).

1.3.3 Diabetes

Psoriasis and diabetes are two long-term health conditions that numerous studies have found to be significantly interconnected. Indeed, numerous community-based studies have revealed a higher incidence of type 2 diabetes (T2DM) in individuals with psoriasis compared to the average

population. This association appears to be proportionate to the severity of psoriasis, suggesting that the risk of diabetes escalates with the worsening of psoriasis. A meta-analysis by Armstrong et al.(Armstrong et al., 2013) found that patients with severe psoriasis have a 1.8 times higher risk of diabetes compared to those without psoriasis. TNF-α and IL-23/IL-17, as well as adipokines, have been shown to influence the regulation of insulin sensitivity (Davidovici et al., 2010; Donath, 2014). Notably, TNF-α impairs insulin signaling via serine phosphorylation of the IRS-1, thus leading to the reduction of GLUT-4 expression and subsequent decrease of glucose entry into cells (Hotamisligil, 2006). Adipokines are a large family of cytokines including adiponectin, leptin and resistin, which are generated and released from adipocytes (Fantuzzi, 2013). Adiponectin improves insulin sensitivity and leads to a decline in lipogenesis (Yamauchi et al., 2002). Conversely, leptin and resistin are considered insulin antagonist adipokines, as they inhibit insulin signaling pathways (Howard and Flier, 2006). The adipokine milieu in patients with psoriasis is similar to that of prediabetic subjects (Boehncke, 2018), who have lower adiponectin levels (Bai et al., 2018; Gerdes et al., 2012; Shibata et al., 2009) and increased leptin and resistin levels compared to healthy controls (Boehncke et al., 2007; Çerman et al., 2008). Interestingly, both TNF-α and IL-17 can influence the production of adiponectin, resistin and leptin by adipocytes (Gustafson et al., 2007; Zúñiga et al., 2010).

1.3.4 Hyperlipidemia

Epidemiological data demonstrate a higher prevalence of hyperlipidemia in individuals with psoriasis compared to the general population. A systematic review and meta-analysis by Armstrong et al. (Armstrong et al., 2013) concluded that psoriasis is associated with a 1.43 times higher risk of hyperlipidemia. The alteration of serum lipid composition appears to be, at least in part, a consequence of chronic systemic inflammation. In fact, TNF-α increases serum levels of small dense LDL and ox-LDL and lowers HDL concentrations. IL-6 and IL-1β induce VLDL synthesis and lower triglyceride clearance, further contributing to the production of small dense LDL and oxLDL (Shih et al., 2020).

Vitamin D deficiency is a common mechanism that could contribute to both psoriasis and dyslipidemia. Vitamin D, in fact, contributes to the integrity of the skin barrier and modulates the functioning of the skin immune system. In particular, it stimulates regulatory T cells, downregulates the expression of proinflammatory cytokines, and suppresses dendritic cell activation (Barrea et al., 2017). In line with this observation, vitamin D levels are lower in both psoriasis and psoriatic arthritis than in controls and are inversely correlated with inflammatory markers and disease severity (Grazio et al., 2015; Kincse et al., 2015; Orgaz-Molina et al., 2012). On the other hand, low levels of vitamin D have been correlated with an increase in triglyceride levels (Martins et al., 2007; Zittermann et al., 2011) and its supplementation has instead been shown to be associated with a significant decrease in LDL and total cholesterol (Dibaba, 2019), and in triglycerides (Lin et al., 1994; Zittermann et al., 2009). It has therefore been hypothesized that vitamin D may modulate lipid levels through calcium and PTH-mediated mechanisms (Zittermann et al., 2011), as well as by acting directly on gene transcription (Dibaba, 2019).

1.3.5 Obesity

Psoriasis and obesity are deeply related. Indeed, not only psoriasis is more common and more severe in patients with obesity, but also obesity is more prevalent in patients with psoriasis (Gisondi et al., 2007; Neimann et al., 2006), including children (Guidolin et al., 2018). In addition to the common lifestyle characterized by unhealthy diet, low physical activity and social isolation, the two pathologies share molecular dysregulations that explain they bidirectional association (Jensen and Skov, 2016; Sommer et al., 2006).

Psoriasis, through circulating proinflammatory cytochines, in particular TNFα, may stimulate the hypothalamic-pituitary axis, which is admittedly associated with central obesity (Oliveira et al.,

2015); moreover it may induce insuline resistance that contributes to the pathogenesis of obesity by generating hyperglycaemia and compensatory hyperinsulinemia (Rodríguez-Cerdeira et al., 2019). On the other hand, obesity itself is a risk factor for insulin resistance, which is linked with alterations of insulin-like growth factor (IGF) system and IGF-1 is known to stimulate the proliferation of keratinocytes (Rolski and Błyszczuk, 2020). Moreover, obesity leads to increased production of proinflammatory cytokines such as leptin which may lead to, polarization of Th1/Th17 axis in lymphocytes (Chiricozzi et al., 2016; Guo et al., 2022) and induce proliferation of keratinocytes, fibroblasts and endothelial cells in the skin, exacerbating the psoriatic milieu (Dopytalska et al., 2020). Adipose tissue is also implicated in the inflammation of psoriasis through the release of free fatty acids, which are able to promote keratinocyte activation (Guo et al., 2022).

1.3.6 Non -alcoholic fatty liver disease

Non -alcoholic fatty liver disease (NAFLD) is a condition characterized by the accumulation of excess fat in the liver not caused by alcohol consumption and is considered a hepatic manifestation of metabolic syndrome and is the most frequent cause of transaminase elevations in the Western world, affecting approximately one-third of the general population. It has a spectrum of manifestations ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) to cirrhosis (Adams, 2005; de Alwis and Day, 2008; Kotronen and Yki-Järvinen, 2008; Marchesini et al., 2005). Multiple studies have reported a higher prevalence of NAFLD in patients with psoriasis compared to the general population. This association is independent of shared risk factors like obesity, diabetes, and hyperlipidemia. A meta-analysis by Candia et al. (Candia et al., 2015) found that psoriasis patients have a 2.15 times higher risk of having NAFLD.
In addition to the important role of obesity, there appears to be a direct link between psoriasis and NAFLD (Balak et al., 2021). Indeed, NAFLD in the general population can also occur among individuals with a normal body mass index (BMI), labeled as "lean NAFLD" (Young et al., 2020). These patients generally show higher CRP levels than healthy subjects, suggesting that systemic inflammation could be one of the pathogenic factors of "lean" NAFLD. In fact, IL-6, IL-17 and TNF-α produced by the liver (hepatokines) and inflamed skin could have synergistic effects on these organs. This relationship between psoriasis and NAFLD has been referred to as the "hepatodermal axis"(Balak et al., 2021; Piaserico et al., 2022). Furthermore, IL-17 can induce hepatic stellate cell activation and subsequent collagen production (Ruiz de Morales et al., 2020). Thus, IL-17 facilitates the progression from simple fatty liver disease to steatohepatitis (Balak et al., 2021; Ruiz de Morales et al., 2020).

1.3.7 Inflammatory Bowel Disease

Psoriasis and Inflammatory Bowel Disease, which includes Crohn's disease and ulcerative colitis, are both chronic inflammatory conditions, and there is evidence to suggest a link between the two. A meta-analysis by Wu et al. (Wu et al., 2012) found that psoriasis was associated with a significantly increased risk of Crohn's disease and ulcerative colitis. Both psoriasis and IBD are characterized by a dysregulated immune response, leading to chronic inflammation in the skin and gut, respectively. T-helper cells, specifically Th17 cells, and their associated cytokines, such as IL-23, IL-17, and TNF-alpha, play crucial roles in the pathogenesis of both diseases (Lowes et al., 2014).

1.3.8 Psychosocial disorders

It is well established that the burden of psoriasis extends beyond physical symptoms and can significantly impact mental health. Numerous studies have shown a higher prevalence of mental health disorders, such as depression, anxiety, and suicidal ideation, among individuals with psoriasis compared to the general population. The severity of psoriasis seems to be related to the risk of mental health disorders. For instance, a meta-analysis by Dowlatshahi et al. (Dowlatshahi et al., 2014) found

that individuals with psoriasis have a 1.5 times higher risk of depression, a 1.3 times higher risk of anxiety, and a 1.4 times higher risk of suicidality compared to those without psoriasis.
The link between psoriasis and mental health disorders may be related to both psychosocial and physiological factors. On one hand, the visible nature of psoriasis can lead to stigma, low self-esteem, and social isolation, which can contribute to the development of mental health disorders. On the other hand, chronic inflammation associated with psoriasis might contribute to mental health disorders through immune-mediated pathways. Supporting this hypothesis is the fact that high levels of proinflammatory cytokines such as TNFα, IL-6, prostaglandin E2, CRP, IL-1 and IL-12 have been found in major depression (Haapakoski et al., 2015; Miller and Raison, 2016). Furthermore, there is evidence of the positive impact of biologics on psychiatric comorbidity in patients with both psoriasis and other chronic inflammatory diseases (Carrascosa and Ballesca, 2017; Fleming et al., 2015).

These interconnections strengthen the hypothesis that inflammatory agents, which originate in psoriasis plaques, might function similarly to hormones. This means they could influence biological processes in locations far removed from the plaque itself, affecting cells beyond the skin.

1.4 Current treatment of psoriasis

Psoriasis is a lifelong condition with no cure, so the goals of treatment are to reduce inflammation and scale, slow excessive growth of skin cells, and relieve symptoms. Drugs used in the therapy of psoriasis mainly work by blocking the inflammatory cascade and the growing understanding of the pathophysiology of psoriasis has led to the development of various therapeutic options ranging from topical drugs to systemic drugs and, more recently, to targeted biologic agents.
The choice of treatment depends on the extent and severity of the psoriasis, patient age, comorbidities, quality of life considerations, and patient preferences. Even if limited, psoriasis of the hand, foot, or face or genitalia can be debilitating functionally or socially and may deserve a more aggressive treatment approach.
The first line of treatment, in case of mild psoriasis (BSA<10, PASI<10), is represented by topical drugs, while for severe disease (BSA >10, DLQI >10) it is advisable to suggest phototherapy or systemic treatments. Biological drugs are recommended in cases of severe disease (BSA>10, PASI>10, DLQI>10) and are used when traditional systemic drugs are ineffective or contraindicated.

1.4.1 Topical treatments

They are usually the first line of treatment, particularly for mild to moderate psoriasis (PASI<10).

1.4.1.1 Topical corticosteroids

Topical corticosteroids are the most commonly used treatment for psoriasis, especially in cases of mild to moderate disease. Their mechanism of action is anti-inflammatory, anti-proliferative, immunosuppressive and vasoconstrictive. These effects are mediated by the interaction with intracellular corticosteroid receptors which regulate the transcription of numerous genes, in particular those coding for proinflammatory cytokines (Mehta et al., 2016) .
Topical steroids range from ultra-high potency (such as clobetasol propionate) to low potency (hydrocortisone), and several formulations, including creams, ointments, lotions, and gels. They can be used in combination with other treatments such as vitamin D analogues, phototherapy or systemic therapies (Callen et al., 2003).
They exhibit rapid efficacy, with a noticeable benefit already after a week or two. However, long-term use may lead to atrophy, development striae, perioral dermatitis, acne and rosacea. Furthermore, when used on a large body surface it can lead to systemic side effects such as Cushing's syndrome, osteonecrosis of the femoral head, cataracts and glaucoma (Menter et al., 2009a).

1.4.1.2 Vitamin D analogues

Vitamin D analogues, such as calcipotriene (calcipotriol), have been effectively used for the topical treatment of psoriasis. They are known to have antiproliferative, pro-differentiative, and immunomodulatory effects. They act by binding to the vitamin D receptor (VDR) in skin cells, which helps regulate cell growth and differentiation. Furthermore, vitamin D analogues have been found to have immunomodulatory effects, reducing the production of skin inflammation-related cytokines(Bhat et al., 2022).Topical vitamin D analogues are generally well-tolerated, with the main side effect being skin irritants (Menter et al., 2009a). They can be used alone or in combination with other treatments such as topical corticosteroids. The combination of vitamin D and a corticosteroid has been shown to be more effective than either component alone and may allow for lower doses of corticosteroids to be used (Lebwohl et al., 1996).

1.4.1.3 Topical retinoids

Topical retinoids, particularly tazarotene, have been widely used in the treatment of psoriasis due to their effectiveness and generally good tolerability profile. Retinoids are vitamin A derivatives that modulate cellular proliferation, differentiation, and inflammation(Duvic et al., 1997). It binds to all retinoic acid receptors (RARs), but it shows selectivity for RARβ and RARγ, modulating gene expression to normalize the abnormal epidermal proliferation and differentiation seen in psoriatic skin (Duvic et al., 1997).

It can be used alone or in combination with other treatments such as corticosteroids or vitamin D analogues. The most common side effects of tazarotene are local skin reactions, including burning, itching, redness, and peeling. These reactions are generally mild to moderate, and they tend to lessen with continued use as the skin adapts to the medication. While topical retinoids are an effective treatment for psoriasis, they are not recommended for use in pregnant women or women planning to become pregnant due to the risk of birth defects.

1.4.1.4 Tacrolimus e pimecrolimus

Topical calcineurin inhibitors (TCIs), such as tacrolimus and pimecrolimus, inhibit the activation of T-cells and the release of inflammatory cytokines. They are used effectively in inverse psoriasis. Indeed, their potential benefit lies in the lack of local side effects that are typically associated with long-term use of topical corticosteroids, such as skin atrophy. However, the use of TCIs in psoriasis is off-label and is generally recommended as a second-line or adjunctive treatment. Furthermore, the US Food and Drug Administration (FDA) has issued a black box warning due to a potential risk of malignancy with TCI use, although the clinical significance of this warning remains controversial (Ring et al., 2008).

1.4.1.5 Salicilic Acid

Salicylic acid, a keratolytic agent, encourages the shedding of the skin's epidermal layer, thereby aiding in the elimination of scales related to psoriasis. Often, it is employed alongside other treatments, such as topical corticosteroids or vitamin D analogs, where it boosts their penetration into the skin, thus amplifying their therapeutic effects. (Lebwohl, 1999). Skin irritation is a potential side effect, and it usually correlates with the dosage. When used on extensive body areas, it may lead to salicylate toxicity, symptoms of which can include nausea, tinnitus, hyperventilation, and in more extreme instances, altered mental status. (Menter et al., 2009a).

1.4.2 Phototherapy

Phototherapy involves exposing the skin to ultraviolet light under medical supervision and is commonly used for moderate to severe psoriasis (PASI>10).

Phototherapy is a well-established, effective treatment modality for various types of psoriasis. It involves exposure of the skin to specific wavelengths of ultraviolet (UV) light, and it can help reduce the speed of skin cell growth, inflammation, and scaling(Zhang and Wu, 2018).
UVB exposure causes a reduction of DNA synthesis in cutaneous keratinocytes and lymphocytes and an upregulation of P53, important in the control of the cell cycle which is shortened in psoriasis (Hemne et al., 2017).
The most frequently used form of phototherapy, Narrow Band UVB (NB-UVB), emits light in a small range within the UVB spectrum (311-312 nm). UVB light can directly induce DNA damage in the skin cells, leading to the formation of pyrimidine dimers. This damage can trigger a cascade of events including cell cycle arrest, apoptosis (programmed cell death), and immunosuppression, all of which can help clear psoriatic plaques. It also reduces the activity of immune cells, including T lymphocytes, and alters cytokine profiles, which helps reduce inflammation (Wong et al., 2013).
In PUVA therapy, psoralen intercalates into DNA and, upon exposure to UVA light, forms covalent bonds with thymidine bases, leading to DNA cross-linking. This can inhibit the proliferation of keratinocytes and induce their apoptosis. Additionally, it modulates immune response by affecting the activity and function of Langerhans cells, T cells, and other immune cells in the skin (Wong et al., 2013).
The 308-nm Excimer laser delivers a targeted beam of NB-UVB light. The mechanism is thought to be similar to that of UVB phototherapy, inducing apoptosis of T cells and other inflammatory cells in psoriatic plaques (Wong et al., 2013). While effective, phototherapy can also lead to side effects including skin aging and an increased risk of skin cancer with prolonged use. UVB-nb has a reduced carcinogenicity compared to PUVA and is less erythemagenic than broadband UVB.

1.4.3 Systemic Treatments

Systemic treatments are used for moderate to severe psoriasis (PASI>10) or psoriasis that is resistant to other treatments. These include:

1.4.3.1 Methotrexate

Methotrexate is a folic acid analog and works by inhibiting dihydrofolate reductase, a crucial enzyme in DNA synthesis and cell proliferation. Indeed, by inhibiting DNA synthesis, MTX limits epithelial hyperplasia, enhances apoptosis of activated T cells and inhibits neutrophil chemotaxis(Czarnecka-Operacz and Sadowska-Przytocka, 2014; Elango et al., 2014). Furthermore, the drug is responsible for decreasing the synthesis of a range of proinflammatory cytokines such as TNF-α and IL-1(Czarnecka-Operacz and Sadowska-Przytocka, 2014). MTX is especially helpful for both people with psoriasis vulgaris and those with PsA. The recommended dosage is 5 to 15mg/week followed 24 hours later by folate supplementation.
The most common side effects are nausea, fatigue and liver damage. Less common but potentially serious side effects include lung disease, bone marrow suppression, and potential harm to the fetus in pregnant women. Patients being treated with methotrexate require regular blood tests to monitor liver and bone marrow toxicity(Nast et al., 2020).

1.4.3.2 Cyclosporin

Cyclosporine induces immunosuppression by inhibiting the first phase of activation of T lymphocytes. In fact, it binds cyclophyllin: the CsA-cyclophyllin complex competitively inhibits calcineurin leading to the blockade of the nuclear transcription factor of activated T cells (NF-AT). This blockade leads to lowering of IL-2 and IFNγ levels, with inhibition of T cell activation. Because of its rapid action, CsA is very useful in the management of acute crises, as a bridge to other therapies, and in the rapid treatment of forms not responsive to other treatments (Nast et al., 2020). The dosage ranges from 3 to 5 mg/kg/day. Side effects include nephrotoxicity, hypertension, increased

triglyceride levels, gingival hyperplasia, tremors, hypomagnesaemia, hyperkalemia, numerous drug interactions, skin cancers, and lymphomas. Regular monitoring of blood pressure and kidney function is essential for patients taking this drug (Nast et al., 2020). CsA has been included in category C as regards its use in pregnancy therefore, although it is not teratogenic, it should only be used if strictly necessary(Menter et al., 2009b)

1.4.3.3 Acitretin

Acitretin is an oral retinoid that is used primarily in the management of psoriasis, especially in its severe forms such as pustular and erythrodermic psoriasis. It is a synthetic derivative of vitamin A, and its mechanism of action involves normalizing the growth cycle of skin cells and decreasing skin inflammation. It effective in the treatment of psoriasis, especially when used in combination with other therapies such as phototherapy. The usual dose range of acitretin is 25 mg every other day to 50 mg daily (Nast et al., 2020). Side effects are dryness of the skin and mucous membranes, hair loss, elevated liver enzymes, and hyperlipidemia. t is also teratogenic and so is not recommended for use in women of childbearing potential unless adequate contraceptive measures are in place. Of note, acitretin is teratogenic; it is only indicated in men and in women of nonreproductive potential. Pregnancy is contraindicated for three years after discontinuing the drug (Lam et al., 2008)

1.4.4 Biologic therapies

These medications work by specifically targeting key inflammatory molecules in the immune response that drives psoriasis. There is ample evidence of superiority in terms of efficacy and long-term tolerability of the new targeted therapies; however, their high cost is an important limitation. Indeed, in the clinical practice, they are used only in moderate to severe psoriasis, if traditional topical or systemic treatments have failed or if they are contraindicated (Nast et al., 2020; Sbidian et al., 2022, 2021) .

1.4.4.1 TNF-alpha inhibitors

1.4.4.1.1 Infliximab (IFX)

Infliximab is a chimeric monoclonal antibody approved for the treatment of moderate to severe plaque psoriasis and other inflammatory conditions such as rheumatoid arthritis and inflammatory bowel disease. Clinical trials have shown that up to 80% of patients achieve a 75% reduction in Psoriasis Area and Severity Index (PASI 75) after 10 weeks of treatment(Reich et al., 2005). Infliximab is given by intravenous infusion, typically given at 0, 2, and 6 weeks and then every 8 weeks thereafter. It is generally well tolerated, but like other anti TNF-α agents, it has been associated with an increased risk of infections, including the potential risk of reactivation of latent tuberculosis. Other less common adverse events include infusion reactions, development of autoantibodies, and a potential increased risk of malignancies (Menter et al., 2007).

1.4.4.1.2 Etanercept (ETA)

ETA is a fusion protein approved for use in psoriasis vulgaris and PsA. Standard dosing for etanercept for adults is subcutaneous injection of 50 mg twice weekly for the initial three months of therapy, followed by a 50 mg injection once weekly for maintenance therapy. Approximately half of the patients treated with etanercept achieve a 75% reduction in the Psoriasis Area and Severity Index (PASI 75) after 12 weeks of treatment(Papp et al., 2005). Treatment with ETA does not lead to the development of neutralizing antibodies(Hsu et al., 2014) .

1.4.4.1.3 Adalimumab (ADA)

It is a fully human antibody that binds to both free and cell membrane-bound TNFα. ADA is approved for the treatment of psoriasis vulgaris and PsA. The recommended dosage is 80mg, followed by 40mg after one week and then 40mg every 2 weeks as maintenance. Efficacy may be reduced over time by the development of neutralizing antibodies. The safety profile of adalimumab is consistent with that of other TNF inhibitors. More serious but less common side effects include potential reactivation of latent tuberculosis, a slightly increased risk of malignancy and demyelinating disease (Gharib et al., 2022).

1.4.4.1.4 Certolizumab

Certolizumab pegol is a PEGylated Fab' fragment of a humanized TNF inhibitor monoclonal antibody. Clinical trials have demonstrated significant improvements in psoriasis area and severity index (PASI) scores, with many patients achieving a 75% or even 90% reduction in PASI scores (Gottlieb et al., 2018). Standard dosing for certolizumab is 400 mg every other week. A potential advantage of certolizumab pegol is minimal transfer across the placenta; unlike other anti-TNF biologics, certolizumab pegol does not bind the neonatal Fc receptor because it lacks the IgG Fc.

1.4.4.2 Inhibitors of IL-23 and related cytokines

1.4.4.2.1 Ustekinumab

Ustekinumab is a human monoclonal antibody that binds to the shared p40 protein subunit utilized by the cytokines interleukin-12 (IL-12) and interleukin-23 (IL-23), effectively blocking their action. In the Phase III PHOENIX-1 and PHOENIX-2 studies, for example, approximately two-thirds of patients achieved a 75% reduction in Psoriasis Area Severity Index (PASI 75) at week 12, a response that is was largely maintained with continued therapy every 12 weeks (Leonardi et al., 2008). It is administered subcutaneously at week 0-4 and then every 12 weeks at a dosage of 45mg in patients <100Kg and 90mg in patients >100Kg. Common adverse effects include upper respiratory tract infection, headache, and fatigue.

1.4.4.2.2 Guselkumab

Guselkumab is a fully human IgG1 lambda monoclonal antibody that binds to the p19 subunit of interleukin (IL)-23 and inhibits its interaction with the IL-23 receptor. The mechanism of action in psoriasis is thought to involve inhibition of IL-23 signaling. Recommended dosing for guselkumab is 100 mg at weeks 0, 4, and then every 8 weeks. Guselkumab is also effective for psoriatic arthritis. Guselkumab was effective for psoriasis in phase 3 randomized trials (VOYAGE trials) (Blauvelt et al., 2017; Reich et al., 2017a) and showed greater long-term efficacy than secukinumab in a phase 3 trial (ECLIPSE trial)(Reich et al., 2019a).

1.4.4.2.3 Tildrakizumab

Tildrakizumab is a humanized IgG1/k monoclonal antibody that selectively targets interleukin-23p19, a key regulator in the pathogenesis of psoriasis. It is approved for the treatment of adults with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy. The recommended dose is 100 mg administered subcutaneously at weeks 0 and 4 and every 12 weeks thereafter. Phase 3 studies (reSURFACE 1, reSURFACE 2) support the superiority of tildrakizumab over placebo and etanercept (Reich et al., 2017b).

1.4.4.2.4 Risankizumab

Risankizumab is a humanized monoclonal antibody that specifically targets the p19 subunit of the cytokines IL-23 and IL-39 (Krueger et al., 2015). Recommended dosing for risankizumab is 150 mg at week 0 and week 4, then every 12 weeks. Risankizumab is also effective for psoriatic arthritis. Risankizumab had greater efficacy than ustekinumab and placebo in phase 3 trials (Gordon et al.,

2018). Risankizumab was more effective for plaque psoriasis than adalimumab in a randomized trial (Reich et al., 2019b). Adverse effect rates were similar between risankizumab and adalimumab groups. In a long-term study, the IMMerge trial, risankizumab was put head-to-head with secukinumab. The findings suggest that while secukinumab might show quicker improvement in psoriasis, risankizumab's performance was on par with secukinumab at the 16-week mark and surpassed it by week 52 (Warren et al., 2021).

1.4.4.3 Inhibitors of IL-17 pathway

1.4.4.3.1 Secukinumab

Secukinumab is a human monoclonal antibody that selectively binds to and neutralizes interleukin-17A (IL-17A) [1]. In the ERASURE, FIXTURE and CLEAR clinical trials, the majority of patients treated with secukinumab achieved clear or nearly clear skin (PASI 90) as early as week 12 and this response was maintained with continued treatment (Langley et al., 2014; Thaçi et al., 2015). Standard dosing for plaque psoriasis is 300 mg given subcutaneously once weekly at weeks 0, 1, 2, 3, and 4 followed by 300 mg every four weeks. Doses of 150 mg are sufficient for some patients. Secukinumab has also been shown to be effective in the treatment of psoriatic arthritis and ankylosing spondylitis (Mease et al., 2015). The most common side effects reported in clinical studies included upper respiratory tract infections, diarrhea and headache. However, no significant increase in the rate of serious infections, malignancies, or major adverse cardiovascular events has been reported in clinical trials (Langley et al., 2014; Mease et al., 2015). Studies have shown that these drugs may not be effective for Crohn's disease and may even exacerbate symptoms (Fobelo Lozano et al., 2018).

1.4.4.3.2 Ixekizumab

Ixekizumab is a high-affinity monoclonal antibody that selectively targets interleukin-17A (IL-17A). In clinical trials, a large percentage of patients achieved clear or almost clear skin within 12 weeks of treatment. The efficacy of ixekizumab was superior to placebo and etanercept in head-to-head trials (Griffiths et al., 2015). Ixekizumab is administered via subcutaneous injection every two weeks for the first twelve weeks, and then every four weeks. IIxekizumab is generally well-tolerated. The most common side effects are mild upper respiratory tract infections. An increased risk of fungal infections due to the role of IL-17 in defense against fungi (Griffiths et al., 2015)

1.4.4.3.3 Brodalumab

Brodalumab, a monoclonal antibody that inhibits the IL-17 receptor A, is highly effective in treating psoriasis. The suggested regimen is 210 mg administered during weeks 0, 1, and 2, followed by the same dose every fortnight. The effectiveness of brodalumab in treating moderate to severe plaque psoriasis is reinforced by phase 3 randomized trial data (Lebwohl et al., 2015). There was a notable statistical advantage of the 140 mg brodalumab dose over ustekinumab in achieving PASI 100 in the AMAGINE-3 trial at week 12, an advantage that was not seen in the AMAGINE-2 trial. Instances of mild to moderate Candida infections were more common in the brodalumab groups compared to the ustekinumab and placebo groups. Similarly, neutropenia was observed more often in the brodalumab and ustekinumab groups than in the placebo group. It's also important to note that two patients on brodalumab committed suicide during the crossover and open-label phases of the AMAGINE-2 trial.

1.4.4.4 Other immunosuppressive agents

1.4.4.4.1 Fumaric acid esters

Fumaric acid esters (FAE), in particular dimethyl fumarate (DMF), molecules used as a systemic treatment for psoriasis for several decades, especially in European countries(Reich et al., 2009). The mechanism of action of FAEs in psoriasis is not fully understood. They are thought to exert immunomodulatory effects by downregulating inflammatory cytokines and shifting overall from a proinflammatory Th1/Th17 response to an anti-inflammatory/regulatory Th2 response (Brück et al., 2018). AEDs are generally well tolerated, with the most common side effects being gastrointestinal discomfort and flushing, which can usually be managed by slowly increasing the dose. The association with mild lymphopenia has been reported (Ermis et al., 2013). They represent a useful treatment option for patients with moderate to severe psoriasis, particularly those who are not candidates for biologic therapies or who prefer oral medication.

1.4.4.4.2 Oral small molecules

1.4.4.4.2.1 Apremilast

Apremilast is an oral small molecule phosphodiesterase 4 (PDE4) inhibitor that acts within cells to modulate a network of proinflammatory and anti-inflammatory mediators involved in psoriasis(Papp et al., 2015; Paul et al., 2015) . The most common adverse events are diarrhoea, nausea and vomiting, which tended to occur within the first 2 weeks of treatment and subsided thereafter. Due to its safety, oral administration and efficacy profile, apremilast may be a useful treatment for patients with psoriasis who are not candidates for biologic therapy, as the risk of serious infections, malignancies or major adverse cardiovascular events does not appear to be increased (Papp et al., 2015; Paul et al., 2015).

2. AIMS OF THE STUDY

Psoriasis can significantly impact on patient's physical, emotional, and social well-being. The objective of the treatment is not only clearing skin lesions but also to prevent disease recurrence, aiming to alter its clinical course. Moreover, the suppression of systemic inflammation may prevent the onset of comorbidities (Girolomoni et al., 2015).

However, to date, the treatment of psoriasis in the first period after the onset of the disease is highly conservative and frequently based on topical agents or phototherapy. Treatment with systemic agents, in particular biologic drugs, generally begins only when topicals have proved unsuitable or ineffective.

Nonetheless, the use of targeted therapies from the very early stages of treatment has been shown to improve long-term patient outcomes in other IMIDs. Indeed, experience from rheumatoid arthritis, Crohn's disease and multiple sclerosis has shown that early intensive treatment can significantly improve long-term outcomes in disease activity by hindering immune pathways that finally lead to the establishment of a chronic inflammation (Girolomoni et al., 2015).

Regarding psoriasis, this concept is supported by a sub-analysis of two secukinumab extension studies (ERASURE and FIXTURE) where shorter disease duration correlated with a longer relapse-free period (Iversen et al., 2018). Moreover, in the VOYAGE study it has been demonstrated that patients treated with guselkumab with a shorter disease duration may more readily achieve long-term, drug-free disease control than patients with a longer disease duration (X Liu, 2019). Finally, very recent data from the ongoing GUIDE study showed that the proportion of super responder patients to guselkumab, defined as sustained complete skin clearance from Week (W) 20 to W28 of treatment, was higher in patients with a shorter disease duration (Schäkel et al., 2023).

In this context, we hypothesize that an early targeted systemic treatment approach -*early intervention*- can improve the control of skin symptoms, modify the course of the disease at a skin and systemic level and reduce the risk of recurrence, as compared to a *late intervention*. In particular, *early intervention* with IL-23 inhibitors, that target the primary pathway responsible for psoriasis, might be beneficial in controlling TRMs levels, thus, resulting in a prolonged therapeutic effect that might alter the course of the disease.

In detail, the aims of the project are:

To identify significative differences in the severity of the disease and clinical improvement after 24 weeks of treatment with biologic drugs between *early psoriasis (EP*) patients (disease duration<5 years) and *long-standing psoriasis (LP*) patients (disease duration >5 years) with moderate-severe psoriasis (PASI>10); thus, evaluate whether, an early treatment -*early intervention*- with biologics drugs is superior to a late treatment -*late intervention*-.

To characterize cytokine/chemokine milieu in peripheral blood of patients moderate-severe psoriasis (PASI>10) at baseline (T0) and changes (quantitative and qualitative characterization) after 24 weeks of treatment (T3) with biologics drugs by luminex multiplex assay; thus, to evaluate the presence of differences in the modulation of the cytokine milieu between *early intervention* vs *late intervention*.

To characterize immune cellular features within the blood and the skin of patients with moderate-severe psoriasis (PASI>10) at baseline (T0) and changes (quantitative and qualitative

characterization) after 24 weeks of treatment (T3) with biologics drugs by fluorescence activated cell sorting (FACS)-based analysis; thus, to evaluate the presence of significative differences in the modulation of skin pathogenic TRM frequencies between *early intervention* vs *late intervention* and between treatment with anti TNF-α and anti IL-23 drugs.

To evaluate the association between immune cellular number/phenotype and cytokines/chemokine milieu within the psoriatic plaque and the peripheral blood with 1) severity of the disease, 2) comorbidities and 3) duration of the disease.

3. PATIENTS AND METHODS

3.1 Participants, study design, and data collection

This is a single-center, open-label study in adult subjects (aged > 18 years) with moderate-to-severe plaque psoriasis (PASI >10) attending the Regional Centre for Psoriasis of the Dermatology Clinic at University of Padova and eligible to treatment with biologic drugs according to European Guidelines for the treatment of psoriasis (Nast et al., 2020).
Overall, 18 adult patients clinically diagnosed with moderate-severe psoriasis were enrolled in the study between September 2021 and March 2023. All patients were diagnosed with psoriasis and the severity of the disease was classified following the PASI score. 5 age and sex-matched participants were considered as a control group.
Patients was characterized as follows:
• *early intervention*: 7 patients with new onset psoriasis (<5 years) and naïve to phototherapy / systemic drugs -*early psoriasis (EP)*;
• *late intervention*: 11 patients with chronic psoriasis (> 5 years) and intolerance/inadequate response to phototherapy or traditional disease modifying antirheumatic drugs -*long-standing psoriasis (LP)*-.
Patients were screened before the beginning of clinical trials by blood sample in order to exclude major contraindications to use of biology drugs. Screening analyses included: complete blood count, serum values of liver enzymes, bilirubin, glucose, creatinine, complete urine test, HCV, HBV and HIV serological test and Quantiferon test.
Patients met all inclusion criteria of the study: ability and willingness to give his/her written informed consent; male and female subjects older than 18 affected by moderate to severe psoriasis (PASI>10); patients eligible to treatment with biologic drug for psoriasis; willing and able to comply with the protocol requirements for the duration of the study. We exclude patients showing the following exclusion criteria: subjects with non-plaque form of psoriasis (e.g..pustular, guttate, erythrodermic psoriasis); pregnant or breast-feeding women, or women who are planning pregnancy; patients with any contraindication to the treatment with biologic drug for psoriasis; patients concomitantly treated with phototherapy/systemic treatments.

For reaching the objectives of the protocol, the study design has been planned as shown in Figure 7:

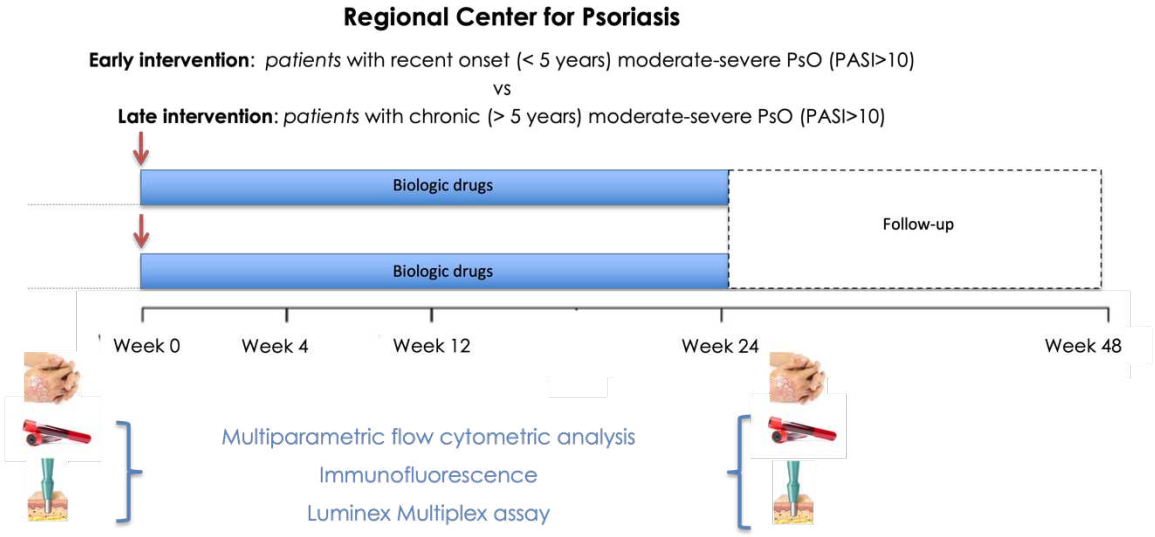

Figure 7: Experimental protocol design.

Complete clinical evaluation was performed at starting time, at week 4, 16 and 24 and 48. Complete blood count, serum values of liver enzymes, bilirubin, glucose, creatinine, complete urine test was repeated at week 4, 16 and 24 and 48.
Before initiating treatment, patients underwent a peripheral venous blood sample (5 ml) and two punch skin biopsies (4 mm) in the Dermatology Clinic. One skin biopsy was performed on psoriasis lesions and one skin biopsy was obtained from normal skin that was collected at least 10 cm from the edge of the lesion. After 24 weeks of treatment, a venous blood sample and one skin biopsy on the healed target area was repeated. Resolved psoriasis lesions were identified with help of photographs, hyperpigmentation, or reliable patient history.
Venous blood samples and skin biopsies were analyzed in Professor Viola's laboratories. The percentage and positioning of selected T cell subsets in the skin samples was investigated as following: FACS (wet); immunohistochemical / immunofluorescence analysis (on fixed/frozen embedded samples). Peripheral blood (PB) cells were analyzed by FACS immediately after blood sample collection; serum was used for cytokine/chemokine dosage. Cytokine/chemokine profiling in patient sera was evaluated by Luminex Multiplex assay.

3.2 Ethical commitment

The study was performed according to the ethical guidelines of the Declaration of Helsinki (7th revision). The study was approved by the Ethics Committee and the general authorization issued by the Data Protection Authority. Cod CESC n. 4972/AO/20. All the patients gave their written informed consent, and all analyses were carried out on anonymized data as required by the Italian Data Protection Code (Legislative Decree 196/2003) and the general authorization issued by the Data Protection Authority.

3.3 PBMC isolation and plasma collection

Peripheral blood (PB) from enrolled controls and psoriasis patients was collected in EDTA tubes and stored at 4 °C prior to processing for PBMC isolation and plasma collection. Peripheral blood mononuclear cells (PBMC) were isolated by density-gradient sedimentation using Ficoll–Paque PLUS (GE Healthcare, Germany) according to the manufacturer's protocol. Briefly, Ficoll-Paque media PLUS was added to the centrifuge tube and PB was carefully layered onto the Ficoll-Paque media solution. After centrifugation, plasma was removed from the top layer using a sterile serological pipette, avoiding disrupting the mononuclear cell interphase and stored at -80 °C until use. Post-purification the isolated PBMC were divided in two approximately equal part, one was directly used for the FACS analysis and the other cryopreserved in cell recovery media containing 10% DMSO (Gibco), supplemented with 90% heat-inactivated HyClone™ Fetal Bovine Serum (FBS; GE Healthcare, Germany) and stored in liquid nitrogen. Plasma was then carefully removed from the 2/3 of the top layer using a sterile serological pipette until the mononuclear cell interphase, portioned and aliquots were stored at −80 °C until the analysis.

3.4 Skin storage and lymphocyte isolation from skin

4 mm punch biopsy were split in two parts, one was paraffin embedded or OCT frozen and stored at -80° until the analysis and the other was directly digested to isolate lymphocytes and preform FACS. Briefly, after removing adipose tissue with disposable scalpel and minced with scissors and scalpel, enzymatic digestion was performed in gentleMACS C tubes (Miltenyi Biotec, Auburn, CA, USA) containing 500µL of enzyme mix (Whole skin dissociation kit, Miltenyi Biotec_without enzyme P), which were incubated in a water bath at 37° C overnight. At the end of the incubation, enzymes were inactivated with complete RPMI medium. Samples were then mechanically dissociated with gentleMACS Dissociator (Miltenyi Biotec) for about 1 minute and shortly centrifugate to collect pellets, which were then resuspended in 4 ml of RPMI. Sample was filtered through 70 µm cell strainers and cell suspension was centrifugate at 300g for 10 minutes al 4° to collect lymphocytes. The final samples were resuspended in 350 µL of FACS buffer with 7 µL of Fc block before sorting.

3.5 Luminex assay

In total 47 analytes (sCD40L, EGF, Eotaxin, FGF-2, Flt-3 ligand, CX3CL1, G-CSF, GM-CSF, CXCL1, IFNα2, IFNγ, IL-1α, IL-1β, IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, CXCL8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17A, IL-17E/IL-25, IL-17F, IL-18, IL-22, IL-27, CXCL10, CCL2, CCL7, M-CSF, CCL22, CXCL9, CCL3, CCL4, PDGF-AA, PDGF-AB/BB, TGF-α, TNF-α, TNF-β, VEGF-A) were analyzed by Luminex assay (Millipore, Billerica, USA) in the plasma from controls and 18 patients before treatment and 11 patients after treatment. The diluted standard and quality control were used according to the manufacture's instruction. Briefly, the plate was washed and the diluted standard, quality control and samples were prepared according to the manufacturer's instructions and added to the appropriate wells. Analyte-specific dyed beads were then added to each well and the plate was incubated overnight in shaking. Wells were emptied and washed, then detection antibodies were added to each well. After an incubation of 1 hour at room temperature (RT), Streptavidin-Phycoerythrin was added and the plate was incubated for 30 minutes at RT. Wells were then washed, Sheath Fluid PLUS was added and beads were resuspended by shaking. The plate was read on Luminex 200™. Analysis was performed using xPONENT 3.1 software.

3.6 Flow Cytometry Analysis

PBMC and skin lymphocytes characterization was performed by FACS, using preconfigured lyophilized reagent tubes (BD Lyotube TM 8-color CD4 and CD8 bundle, (BD Biosciences San Jose, CA, USA including CD4 specific and CD8 specific "Lyotubes") supplemented with fluorochrome-conjugated antibodies (Table II).

Table II. Antibodies for FACS lymphocytes characterization.

CD4 Cocktail				CD8 Cocktail			
Antigen	Fluorophore	Clone	Manufacturer	Antigen	Fluorophore	Clone	Manufacturer
CD95	FITC/BB515	*	BD Pharmigen	CD95	FITC/BB515	*	BD Pharmigen
CD3	PerCP-Cy5.5	*	BD Pharmigen	CD3	PerCP-Cy5.5	*	BD Pharmigen
CCR7	PE	*	BD Pharmigen	CCR7	PE	*	BD Pharmigen
CD28	PE-Cy5	555730	BD Pharmigen	CD28	PE-Cy5	555730	BD Pharmigen
CD25	PE-Cy7	*	BD Pharmigen	CD69	PE-Cy7	*	BD Pharmigen
CD127	Alexa-Fluor 647	*	BD Pharmigen	CD127	Alexa-Fluor 647	*	BD Pharmigen
CD45	APC-H7	*	BD Pharmigen	CD45	APC-H7	*	BD Pharmigen
CD45RA	V450	*	BD Pharmigen	CD45RA	V450	*	BD Pharmigen
CD4	V500-C	*	BD Pharmigen	CD8	V500-C	*	BD Pharmigen
CCR4	BV650	744140	BD Pharmigen	CCR4	BV650	744140	BD Pharmigen
CD45RO	BV711	563722	BD Pharmigen	CD45RO	BV711	563722	BD Pharmigen
HLA-DR	BV786	564041	BD Pharmigen	HLA-DR	BV786	564041	BD Pharmigen

* BD Lyotube TM 8-color CD4 and CD8 bundle, (BD Biosciences San Jose, CA, USA including CD4 specific and CD8 specific "Lyotubes")

PBMC and cells collected from skin biopsies were washed in PBS (5 min and 400g) and red blood cells were lysed with ACK lysing solution (Lonza) and the final samples were incubated with Purified Human FC block [BD Biosciences], diluted 1:50 in FACS Buffer for 20 minutes at 4°C to reduce the unspecific binding of primary antibodies. Lyotubes were then rehydrated with 100 µl the previous resuspension and the fluorochrome-conjugated antibodies were added with a dilution 1:50 in FACS buffer. Cells were marked through incubation for 30 minutes at 4°C in the dark, washed with FACS buffer and fixed in FACS buffer/4%PFA for 15 minutes. After a final wash with FACS buffer and centrifugation at 400g for 5 minutes, cells were resuspended in 200 µl FACS buffer and acquired on a BD FACSCelesta™ Cell Analyzer (BD Biosciences, San Diego, CA).
For the functional assay of skin lymphocytes, cells were stained for surface phenotypic marker followed by permeabilization and intracellular cytokine staining (Table III).

Table III. Antibodies for FACS functional analysis of skin lymphocytes.

Antigen	Fluorophore	Catalog n.	Manufacturer
IL-2	FITC/BB515	554565	BD Pharmigen
CD3	PerCP-Cy5.5	332771	BD Pharmigen
CD45RA	PE	555489	BD Pharmigen
TNFa	PE-CF594	562784	BD Pharmigen
CD4	PE-Cy7	557852	BD Pharmigen
IL-12	APC	554576	BD Pharmigen
CD45	APC-H7	560178	BD Pharmigen
IL-17a	V450	562933	BD Pharmigen
CD8	V500	561617	BD Pharmigen
CD45RO	BV711	563722	BD Pharmigen
IFNg	BV786	563731	BD Pharmigen

The fixation and permeabilization was performed with the BD Cytofix/Cytoperm™ Fixation/Permeabilization Solution Kit according to the manufacturer's instructions. Briefly, after permeabilization, the cells were washed with BD Perm/Wash™ buffer and then were resuspended in 100 µL BD Perm/Wash™ buffer followed by incubation with cytokine antibodies.
Control samples included unstained and single fluorochrome-stained cells for accurate compensation and data analysis. Results were analyzed with FlowJo software.

3.7 Gating strategy

Intact cells were gated based on forward scatter area (FSC-H) and side scatter area (SSC-H) followed by single cell gating. Subsequent gating analysis allowed the identification of CD45+ lymphocytes, CD3+ T-cells, CD4+ helper T-cells or CD8+ cytotoxic T-cells (Figure 8).

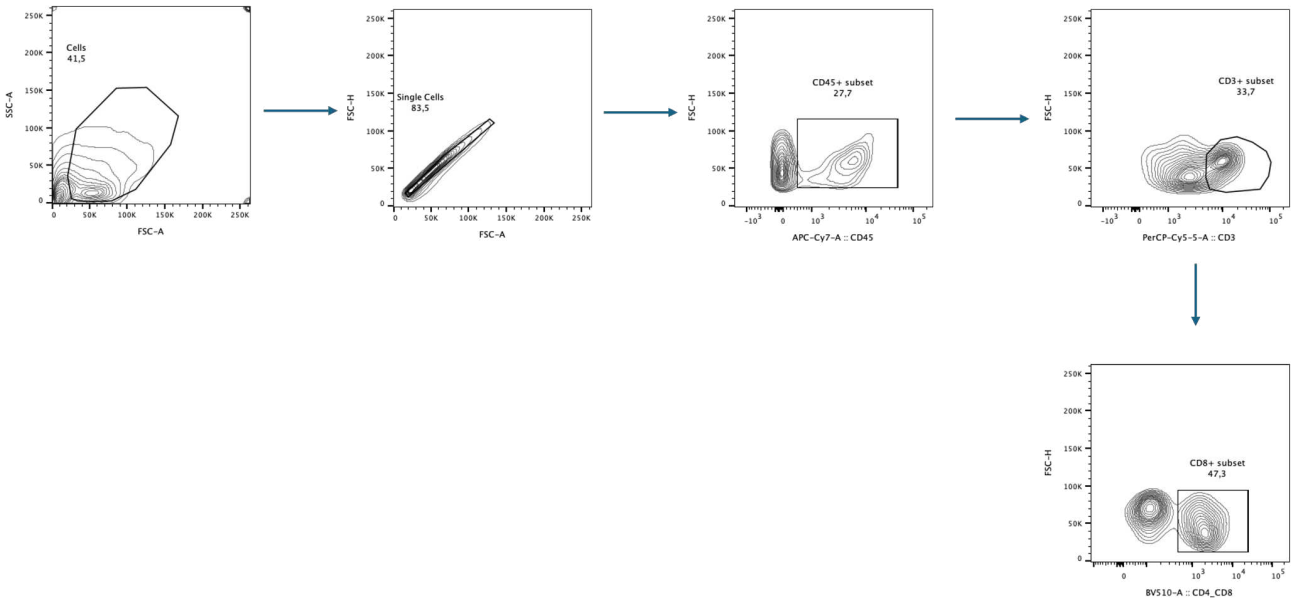

Figure 8: Gating strategy for the identification of T cell subsets.

CD4+ T cells and CD8+ T cells were analyzed for the expression of CD45RA and CD45RO markers to determine whether they were naïve or memory cells (Figure 9).

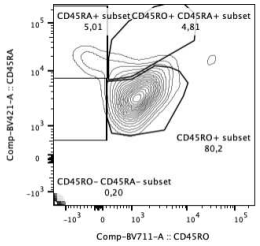

Figure 9: Gating strategy for the identification of naïve and memory cells.

In humans, heterogeneous expression of the lymph node homing receptor CCR7 defines additional functional subsets of CD45RA+ and CD45RO+ T cells. Naive T cells are primarily CD45RA+CCR7+. There is also a subset of CD45RA+ T cells that are CCR7 negative, which are designated terminally differentiated effector T cells (designated Temra cells). CD45RO+ memory T cells are subdivided into two subsets: CCR7+ ‘‘central memory’’ (Tcm) cells, which migrate to lymphoid tissue, and CCR7- ‘‘effector memory’’ (Tem) cells, which circulate to nonlymphoid sites. We used coordinate analysis of CCR7 and CD45RA expression by CD4+ T cells and CD8+ T cells to precisely define naive, Temra, Tcm, and Tem cell subsets. Therefore, we combined multiparameter analysis of CD45RA and CCR7 with CD69, as a marker of tissue residence, to obtain a picture of Tissue-resident memory T cells (TRM) CD8- (reasonably CD4+) and CD8+ T cell subsets. TRMs were identified as CD45RA-CCR7-CD69+ cells (Figure 10).

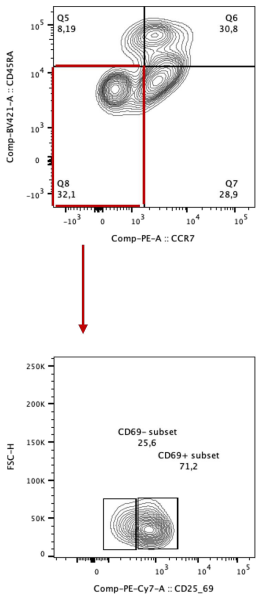

Figure 10: Gating strategy for the identification of Temra, naïve, Tcm, Tem and TRM cells.

3.8 Multiplex immunohistochemistry

Multiplex immunohistochemistry (mIHC) on 4 µm thick FFPE sections of non-lesional and lesional skin tissue was performed using the Opal-TSA technology (Akoya Biosciences). The sections were deparaffinised, rehydrated and stained with the antibody panel reported in Table III on the automated BOND RX immunostainer (Leica Biosystems). Multiplex antibody staining was conducted with serial cycles of 20' antigen retrieval at >95°C with pH 6 or 9 solutions, 30' to 60' incubation with primary antibodies, 10' incubation with Opal polymer HRP-labeled secondary antibodies and 10' incubation with Opal reagents. The slides were all counterstained with spectral DAPI.
The following antibodies were used in the same panel: anti-human CD45RA (4KB5 clone, Abcam, 1:300), anti-human CD4RO (UCHL1 clone, Abcam, 1:1000), anti-human CD8 (C8/144B clone, Dako, 1:200), anti-human CD4 (4B12 clone, ThermoFisher Scientific, 1:10), anti-human CD20 (L26 clone, Dako, 1:400), Pan-cytokeratin (AE1/AE3 clone, Dako, 1:100). The slides were treated with the ProLong™ Diamond Antifade Mountant (Invitrogen) and imaged with a 20X objective on a Mantra 2™ Quantitative Pathology Workstation (Akoya Biosciences). Images were acquired through the Mantra Snap program (1.0.4 version) and analyzed using the InForm software program (2.4.8 version).

3.9 Data quantification and statistical analysis

The sample size per group was estimated from literature data. We expected to detect a 30% difference between the percentage of TRMs within the T cell population between patients with new onset psoriasis and patients with chronic psoriasis (Vo et al., 2019). Consequently, the sample size estimated with a t-test, with a sample power of 80% and a α error of 0.05 was 7 patients per group (14 overall). Statistical analyses were done in Prism 8.4 (GraphPad, USA). Statistical analyses were carried out using packages of the R statistical software. Indicators such as mean, standard deviation, minimum, median and maximum were calculated for the continuous variables, while the categorical data were presented through frequencies (n, %). Gaussian distribution of data was assessed before performing statistical analysis by applying the D'Agostino-Pearson omnibus normality test and Shapiro-Wilk normality test. Differences in data sets were evaluated by application of T-test, Mann-Whitney test, Kruskal-Wallistest, Multiple Mann-Whitney tests or Mann-Whitney test and 2-way ANOVA with Sidak's multiple comparisons and Pearson's chi-square test according to the different experiments. Correlations between variables and the corresponding p-values were evaluated through

the Spearman correlation coefficients. Differences were considered statistically significant at confidence levels $p < 0.01$ or $p<0.05$.

4. RESULTS

4.1 Early treatment with biologic drugs promotes greater clinical clearance in psoriatic patients

A total of 18 patients were enrolled in the study, 7 (38.8%) classified as EP and 11 patients reporting a disease duration greater than 5 years (LP) (61.1%). 5 patients were treated with anti IL-23 (27.8%) drugs and 13 patients treated with anti TNF-α (72.2%). At baseline (T0) we collected the skin biopsies and the venous peripheral blood from all patients; after 24 weeks (T3) of the indicated treatment we obtained the samples of 11 patients. 7 patients refused to repeat the investigations; however, they continued the clinical follow-up. Demographics, disease characteristics, and treatment choices are shown in Table IV.

Table IV: Demographic characteristics of patients.

Patient Code	Age	Gender	Disease Duration	PASI T0	PASI T3	PASI reduction (%)	Treatment
#1	60	M	30y	25	6	75	tildrakizumab
#2	44	M	3m	25	1	95	adalimumab
#3	60	M	9y	35	0	100	adalimumab
#4	67	M	4m	18	5	70	adalimumab
#5	21	M	7y	18	3	83	adalimumab
#6	40	M	4y	15	0	100	tildrakizumab
#7	40	M	4y	15	0	100	tildrakizumab
#8	25	F	3m	25	2	92	adalimumab
#9	60	M	20y	15	3	80	adalimumab
#10	52	F	20y	25	16	36	adalimumab
#11	39	F	5y	10	6	40	tildrakizumab
#12	26	M	11y	32	11	66	certolizumab
#13	37	M	30y	35	3	91	adalimumab
#14	44	M	24y	18	7	61	adalimumab
#15	64	F	1y	30	0	100	tildrakizumab
#16	45	F	16y	25	19	24	adalimumab
#17	36	M	11y	13	8	38	adalimumab
#18	48	M	16y	25	15	40	adalimumab

M, male; F, female; y, years; m, months; PASI, Psoriasis Severity Index; T0 baseline; T3 24-week treatment; PASI reduction (%), reduction of PASI between T0 and T3 expressed as percentage (%).

As shown in Table V, the patient cohort had a mean age of 44.89 years (±13.61) and was predominantly composed by male patients (72%). EP and LP patients had similar age (42.00±12.54 vs 44.54±13.46) and baseline PASI values (19.71±7.11 vs 24.18±7.64); however, EP patients showed lower PASI at T3 than LP patients ($p<0.05$). Furthermore, a greater fraction of EP patients achieved PASI 90 as compared to patients with LP (71.4% vs 18.2%; $p<0.05$). Finally, we observed a noticeable difference in reaching PASI 100 between the EP patients (42.85%) and LP patients (0.09%), even though the difference was not statistically significant (Table V).

Table V. Patient demographics and disease characteristics of EP vs LP patients.

	Pso duration ≤5 y (EP) (n=7)	Pso duration >5 y (LP) (n=11)	Overall (n=18)	EP vs LP *(p value)*
Sex, n (%)				*p*=0.025
Female	3 (42.80)	2 (18.80)	5 (27.80%)	
Male	4 (57.14)	9 (81.82)	13 (72.20%)	
Age at baseline,y; mean ± SD	42(±12.54)	44.45 (±13.46)	44.89 (±13.61)	*p*= 0.704
Disease duration, m,mean± SD	25.43(±25.36)	211.68 (±95.89)	139.2(±119.80)	*p*= 0.022
PASI T0; mean ±SD	19.71(±7.11)	24.18(±7.64)	22.44(±7.56)	*p*=0.232
PASI T3; mean± SD	2.00(±2.51)	8.273(±6.21)	5.83(±5.90)	*p*=0.023
PASI 90 n (%)				*p*=0.024
PASI 90 (yes)	5(±71.42%)	2(18.18%)	7(38.89%)	
PASI 90 (no)	2(±28.57%)	9(81.81%)	11(61.10%)	
PASI 100				*p*=0.092
PASI 100 (yes)	3(42.85%)	1(0.09%)	4(22.22%)	
PASI 100 (no)	4(57.14%)	10(90.90%)	14(77.77%)	
PASI Reduction, (%); mean ± SD	85.29(±22.63)	63.09(±25.30)	71.72(±26.10)	*p*=0.041

Demographic and disease characteristics of early psoriasis (EP), long-standing psoriasis (LP) patients and of overall population. Unpaired t test and Chi^2 test was used to compare demographic and disease characteristics of EP and LP patients. P-values are provided.
M, male; F, female; y, years; m, months; PASI, Psoriasis Severity Index; T0 baseline; T3 24-week treatment; PASI reduction (%), reduction of PASI between T0 and T3 expressed as percentage (%).

To assess the influence of disease duration on other clinical parameters, we conducted a correlation analysis. No association was found between the duration of psoriasis and patient's age or PASI at T0 (Figure 11 a,b); on the contrary, disease duration positively correlated with PASI at T3 (Figure 11c) and negatively correlated with the percentage of improvement of PASI score between T0 and T3 (Figure 11 d).

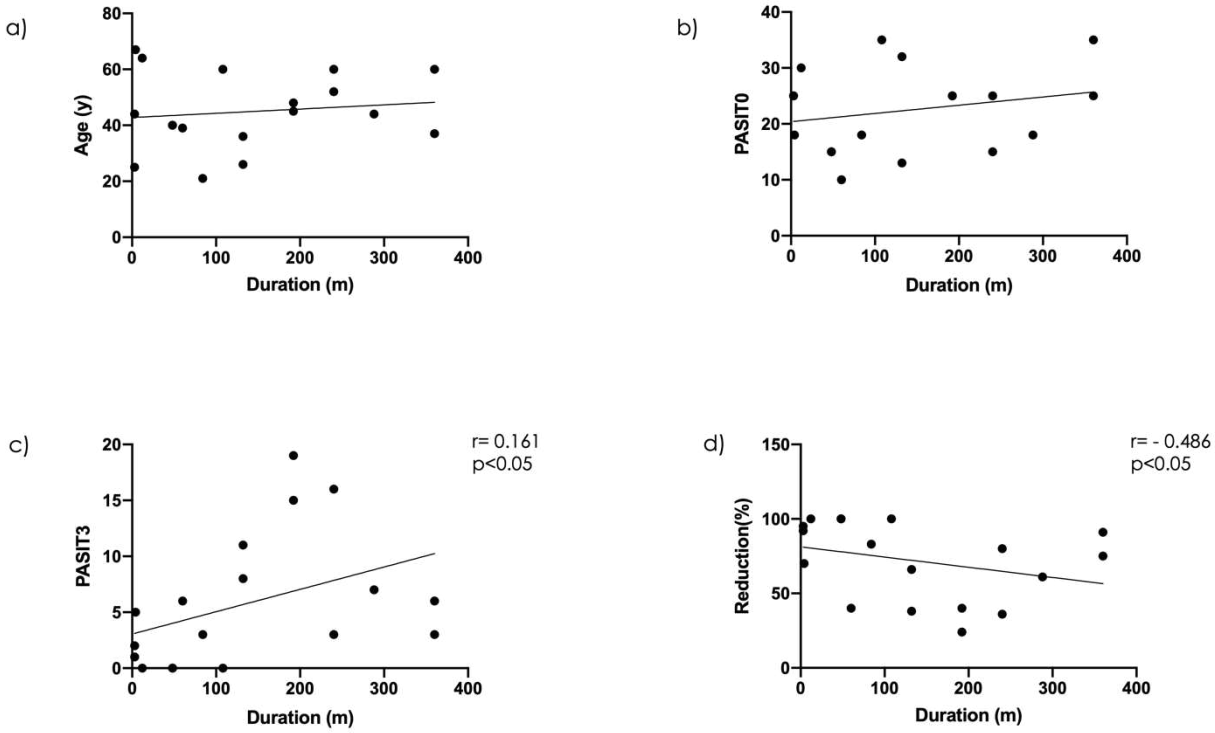

Figure 11. Disease duration impacts on the clinical improvement of psoriasis after treatment.
Correlations between disease duration and the following parameters were analyzed in psoriasis patients: a) age, b) PASI T0, c) PASI T3 and d) improvement of PASI between T0 and T3.
Correlations were assessed by Spearman's rank correlation test. Significant associations are indicated with R values together with the p-values.
y, years; m, months; PASI, Psoriasis Severity Index; T0 baseline; T3 24-week treatment; PASI reduction (%), reduction of PASI between T0 and T3 expressed as percentage (%).

4.2 The IL-23/Th17 axis impacts on disease severity and clinical responses and is intensely suppressed starting treatment early in the course of the disease

In order to assess crucial cytokines in the blood serum of individuals with psoriasis and evaluate the impact of early intervention vs late intervention with biologics on the blood inflammatory milieu, we analyzed the level of selected cytokines/chemokines in the plasma of psoriatic patients before and after anti IL-23 and anti TNF-α treatments (16 patients before the treatment and of 11 patients after the treatment) by Multiplex cytokine array. A total of 47 analytes were analyzed (sCD40L, EGF, Eotaxin, FGF-2, FLT-3 ligand, CX3CL1, G-CSF, GM-CSF, CXCL1, IFNα2, IFNγ, IL-1α, IL-1β, IL-1ra, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, CXCL8, IL-9, IL-10, IL-12/23 (p40), IL-12 (p70), IL-13, IL-15, IL-17A, IL-17E/IL-25, IL-17F, IL-18, IL-22, IL-27, CXCL10, CCL2, CCL7, M-CSF, CCL22, CXCL9, CCL3, CCL4, PDGF-AA, PDGF-AB/B,, TGF-α, TNF-α, TNF-β, VEGF-A). The concentrations of the previously mentioned analytes were compared with those found in 5 healthy controls. Table VI reports the values of chemokines and cytokines in the blood of patients and controls. Mann-Whitney test was employed to compare cytokine concentrations between the two groups. In comparison to healthy controls, patients with psoriasis showed elevated levels of various inflammatory markers: IL-17A ($p=0.025$), IL-23p40 ($p=0.048$), and MDC ($p=0.008$) demonstrated statistically significant increases, while IL-6 ($p=0.031$) was also significantly elevated. Notably, Eotaxin ($p=0.075$), G-CSF ($p=0.081$), MCP-1 ($p=0.091$), and TNF-α ($p=0.075$) displayed trends toward higher levels, and IL-10 showed a trend toward a decrease, nearing statistical significance ($p=0.057$) (Table VI). These trends, even if they did not reach the conventional threshold for statistical

significance, are of clinical interest for understanding the disease, especially given the limitations of our small sample size

Table VI: Levels of chemokines/cytokines analyzed in the serum of psoriasis patients and controls with Luminex multiplex assay.

	Psoriasis Patients Baseline (n=16)			**Controls (n=5)**			*p value*
	I Quartile (pg/ml)	Median (pg/ml)	II Quartile (pg/ml)	I Quartile (pg/ml)	Median (pg/ml)	II Quartile (pg/ml)	
sCD40L	530.50	1212.00	2118.00	781.5	1041.00	1144.00	0.735
EGF	11.99	25.41	56.83	18.80	19.82	40.93	0.100
EOTAXIN	62.72	82.58	104.60	39.34	57.87	71.40	**0.075**
FGF-2	11.31	38.50	78.34	4.97	21.66	45.24	0.348
FLT-3L	4.173	6.705	8.73	2.34	5.51	7.01	0.354
Fractalkine	67.01	83.02	109.80	51.52	82.12	89.96	0.652
G-CSF	25.62	31.42	39.87	13.82	17.74	36.19	**0.081**
GM-CSF	nd	nd	nd	nd	nd	nd	
GROa	4.76	12.09	17.91	7.07	16.14	19.69	0.780
INFa2	5.96	15.68	35.69	9.10	11.3	17.79	0.754
INFg	nd	nd	nd	nd	nd	nd	
IL-1a	0.16	4.96	9.85	3.90	6.18	12.71	0.560
IL-1b	nd	nd	nd	nd	nd	nd	
IL-1RA	1.95	4.15	6.86	1.62	2.17	6.52	0.505
IL-2	nd	nd	nd	nd	nd	nd	
IL-3	nd	nd	nd	nd	nd	nd	
IL-4	0.43	0.76	1.67	0.57	0.89	2.86	0.553
IL-5	2.19	3.39	5.43	1.36	1.96	4.19	0.230
IL-6	0	1.20	3.20	0	0	0	**0.031**
IL-7	nd	1.23	2.31	0.80	0.99	1.30	0.800
IL-8	1.41	1.89	2.47	1.50	1.90	3.04	0.701
IL-9	nd	6.27	13.48	nd	4.47	43.35	0.663
IL-10	0.00	0.95	2.75	0.92	5.66	7.99	**0.057**
IL-12/23p40	22.62	41.62	54.71	20.18	21.23	21.94	**0.048**
IL-12p70	nd	nd	nd	nd	nd	nd	
IL-13	nd	nd	nd	nd	nd	nd	
IL-15	0.00	0.41	1.50	0	0.14	2.15	0.529
IL-17A	0.06	1.63	5.95	0	0	0	**0.025**
IL-17E/25	668.70	857.90	1831.00	569.70	869.20	1271.00	0.899
IL-17F	nd	nd	nd	nd	nd	nd	
IL-18	61.53	158.50	273.60	44.01	85.33	131.90	0.109
IL-22	nd	nd	nd	nd	nd	nd	
IL-27	596.10	843.10	1161.00	630.10	635.80	638.90	0.148
IP-10	109.90	137.20	173.70	117.60	153.50	167.80	0.866
MCP-1	227.70	342.10	389.60	184.40	233.30	273.20	**0.091**
MCP-3	1.20	12.17	18.37	7.49	12.23	21.29	0.818
M-CSF	1.74	18.44	50.17	0	0	30.42	0.226
MDC	494.20	710.30	840.10	311.30	455.00	484.20	**0.008**
MIG/CXCL9	937.90	1094.00	1735.00	652.60	1006.00	1341.00	0.354
MIP1a	nd	9.80	22.76	0.40	8.79	29.11	0.946
MIP1b	13.10	17.84	18.23	10.17	14.52	28.94	0.968
PDGF-AA	299.70	483.30	693.60	521.60	690.80	853.05	0.179
PDGF-AB/BB	7297.00	15786.00	19137.00	11296.00	16333.00	21821.00	0.719
TGF-a	nd	nd	nd	nd	nd	nd	
TNF-a	11.39	13.75	17.88	7.96	8.69	12.46	**0.075**
TNF-b	nd	nd	nd	nd	nd	nd	
VEGF-A	18.96	46.55	87.75	19.59	42.28	61.03	0.596

Chemokines/cytokines concentrations in the serum of psoriasis patients at baseline and healthy controls are expressed as pg/ml. Values are presented as median, I quartile and II quartile. Mann-Withney test was used to compare chemokines/cytokines levels between psoriasis patients and controls. P-values are provided. Nd, not detected.

Next, we assessed the correlation between age, the disease severity, the duration, the clinical response and serum biomarkers before and after the treatment (Figure 12a). IL-23p40 positively correlated with the baseline PASI and with the T3-PASI (Figure 12a). Interestingly, patients with a greater clinical skin improvement after treatment showed lower levels of IL-23p40 at T3 (Figure 12b). IL-17A correlated with baseline PASI as well as MDC and MCP-1 (Figure 12a). Furthermore, IL-17A correlated with IL-23p40 levels (Figure 12a). Eotaxin, IL-6 and TNF-a were shown to be positively related with patient age either before and after the treatment, but did not show any direct relationship with clinical parameters (Figure 12 a,b).

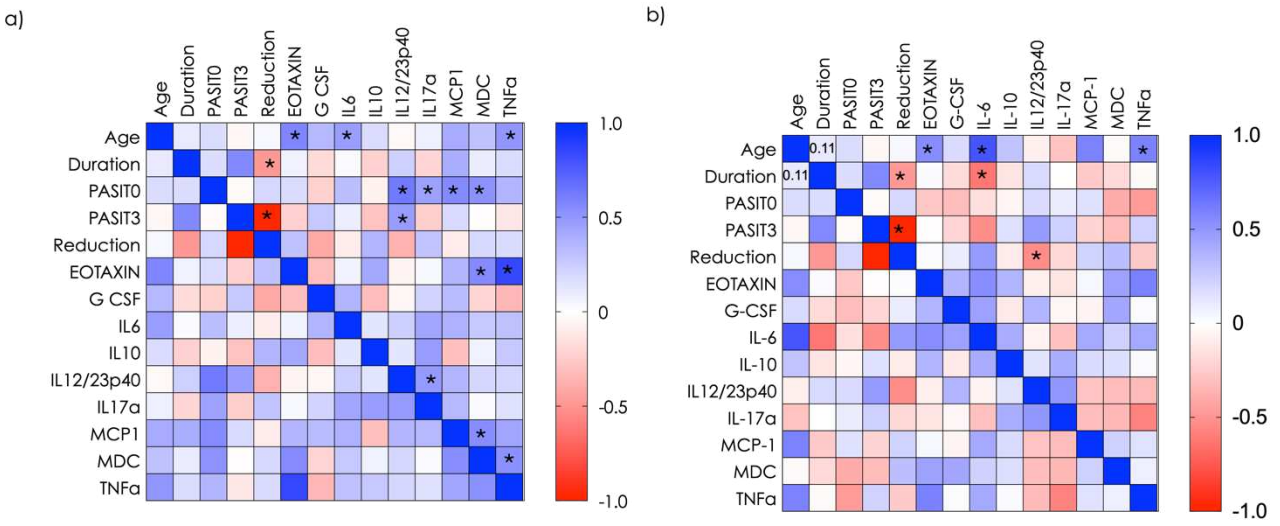

Figure 12.: IL-23/Th17 axis impact on disease severity.
Serum cytokines were analyzed at baseline and after 24 weeks of treatment by Luminex Multiplex Assay.
a) Correlations of baseline serum levels of eotaxin, tumor necrosis factor (TNF-α), interleukin-(IL-) 12/23p40, IL-17A, IL-10, IL-6, chemoattractant protein-1 (MCP-1), macrophage-derived chemokine (MDC) and granulocyte colony-stimulating factor (G-CSF) with age, duration of the disease, PASI at baseline (PASI T0), PASI at W24 (PASI T3), % of PASI reduction after treatment are analyzed by Spearman's correlation test. Statistically significant relationships are given in the corresponding square. *$p < 0.05$
b) Correlations of W24 serum levels of eotaxin, tumor necrosis factor (TNF-α), interleukin-(IL-) 12/23p40, IL-17A, IL-10, IL-6, monocyte chemoattractant protein-1 (MCP-1), macrophage-derived chemokine (MDC) and granulocyte colony-stimulating factor (G-CSF) with age, duration of the disease, PASI at baseline (PASI T0), PASI at W24 (PASI T3), % of PASI reduction after treatment are analyzed by Spearman's correlation test. Statistically significant relationships are given in the corresponding square. *$p < 0.05$

We also evaluated the levels of eotaxin, G-CSF, IL 17A, IL-23p40, MCP-1, MDC, IL-10, IL-6, and TNF-α in EP and LP patients before and after the treatment. As shown in Figure 13, we didn't find significant differences in the levels of these cytokines between EP and LP patients neither before nor after the treatment. However, patients with earlier psoriasis showed lower mean expression of IL-12/23p40, MCP-1, and IL-6; conversely, eotaxin, G-CSF, IL-10, IL-17A, MDC and TNFα appeared higher in EP patients. At T3 the concentration of eotaxin, G-CSF, IL 17A, IL-23p40, MCP-1, MDC, IL-6, G-CSF, TNF-α decreased and IL-10 increased compared to baseline, regardless the disease duration, following the biologic treatment. However, the reduction did not reach significance with the exception of IL-17A in EP patients (Figure 13).

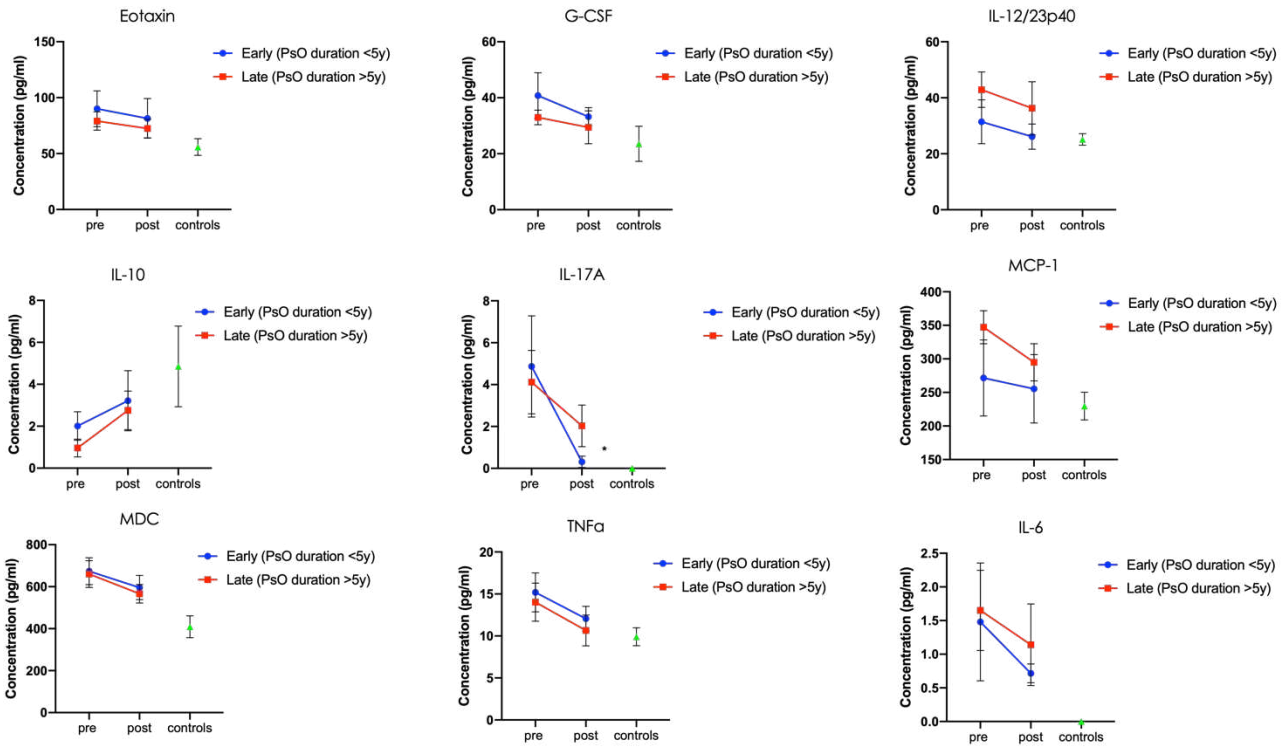

Figure 13: Impact of the treatment in EP and LP patients on cytokines/chemokines levels.
Change in serum levels (pg/ml) of eotaxin, granulocyte colony-stimulating factor (G-CSF), interleukin-(IL-) 12/23p40, IL-10, IL-17A, chemoattractant protein-1 (MCP-1), macrophage-derived chemokine (MDC), tumor necrosis factor (TNF-α) and IL-6 from baseline to W24 by disease duration. Plotted are averaged concentration (± SEM) for each group and time point. Sidak's multiple comparison test was performed. * $p<0.05$ vs T0.

Finally, we investigated the impact of anti TNFα and anti IL-23 medications on the serum levels of eotaxin, G-CSF, IL-17A, IL-23p40, MCP-1, MDC, IL-10, IL-6, and TNF-α (Figure 14). Overall, by week 24, there was a trend towards reduced cytokine expression in both the anti IL-23 and anti TNF-α treatment groups. This observation, however, did not attain statistical significance. Notably, IL-10 stood out from this pattern, showing increased levels after the treatment. This aligns with the observation that psoriasis patients had lower levels of IL-10 compared to the control group (Figure 14).

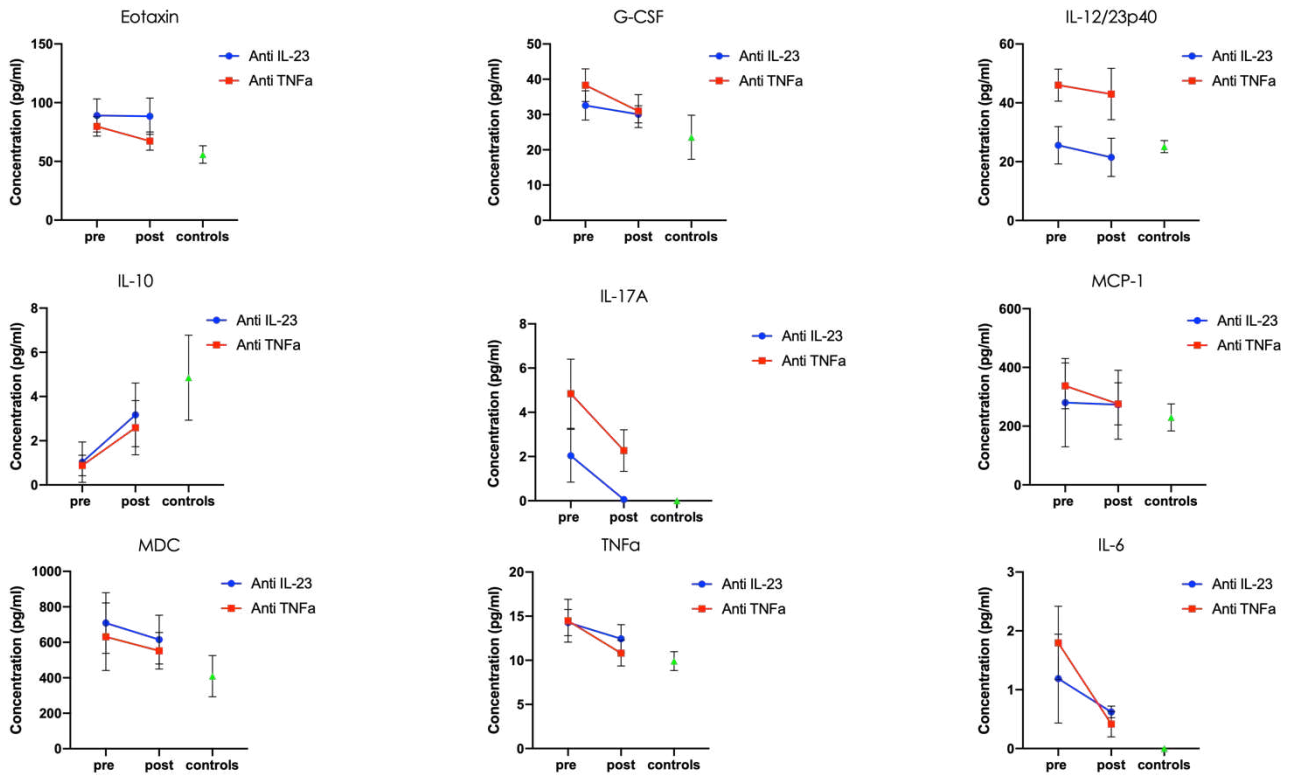

Figure 14: Impact of anti IL-23 drugs and anti TNF-α drugs on cytokines/chemokines levels.
Change in serum levels (pg/ml) of eotaxin, granulocyte colony-stimulating factor (G-CSF), interleukin-(IL-) 12/23p40, IL-10, IL-17A, chemoattractant protein-1 (MCP-1), macrophage-derived chemokine (MDC), tumor necrosis factor (TNF-α) and IL-6 from baseline to W24 by treatment. Plotted are averaged concentration (± SEM) for each group and time point. Sidak's multiple comparison test was performed.

Epidemiological evidence has demonstrated that psoriasis patients have an increased risk of cardiovascular disease (CVD). Interestingly, by exploring the Coronary Flow Reserve (CFR), which assesses the ability of coronary arteries to increase blood flow in response to an increased metabolic demand, it was found that psoriasis patients exhibit an impaired coronary microcirculation. Moreover, changes in the CFR are directly associated with the severity of psoriasis, as measured by the PASI score. Although it's believed that the spread of inflammation from psoriatic plaque beyond the skin can lead to endothelial damages, microvasculature impairment and the formation of atherosclerotic plaques, the exact agents driving this connection are still being researched (Orlando et al., 2022).
Studies have indicated that fractalkine, also known as CX3CL1, is elevated in individuals with psoriasis as well as those with CVD. Interestingly, psoriasis patients show even greater fractalkine levels than subjects with a history of major cardiovascular events (MACE) (Li RJ et al., 2014).
Given these findings, we focused on the potential role of this chemokine in the crosstalk between psoriasis and CVD (Figure 15). To this aim, we compared fractalkine serum levels between patients with psoriasis and previous history of MI, HF or impaired coronary microcirculation (assessed by CFR), patients with no history of CVD and controls. Remarkably, the former group presented markedly elevated chemokine levels (Figure 15a). Interestingly, we noticed that, although fractalkine did not appear to increase in psoriasis patients as compared with controls, patients with greater disease severity (PASI) exhibited greater serum levels of this chemokine (Figure 15c). Nevertheless, by performing the correlation of fractalkine levels with the CFR values, known to be directly related to PASI, we showed that it was more expressed in patients with an impaired coronary microvascular circulation (Figure 15b).

We also investigated the impact of therapy on this molecule, demonstrating that both anti TNFα and anti IL-23 were able to bring it back to similar levels compared to controls, although an early treatment appeared to be more effective (Figure 15 d,e).

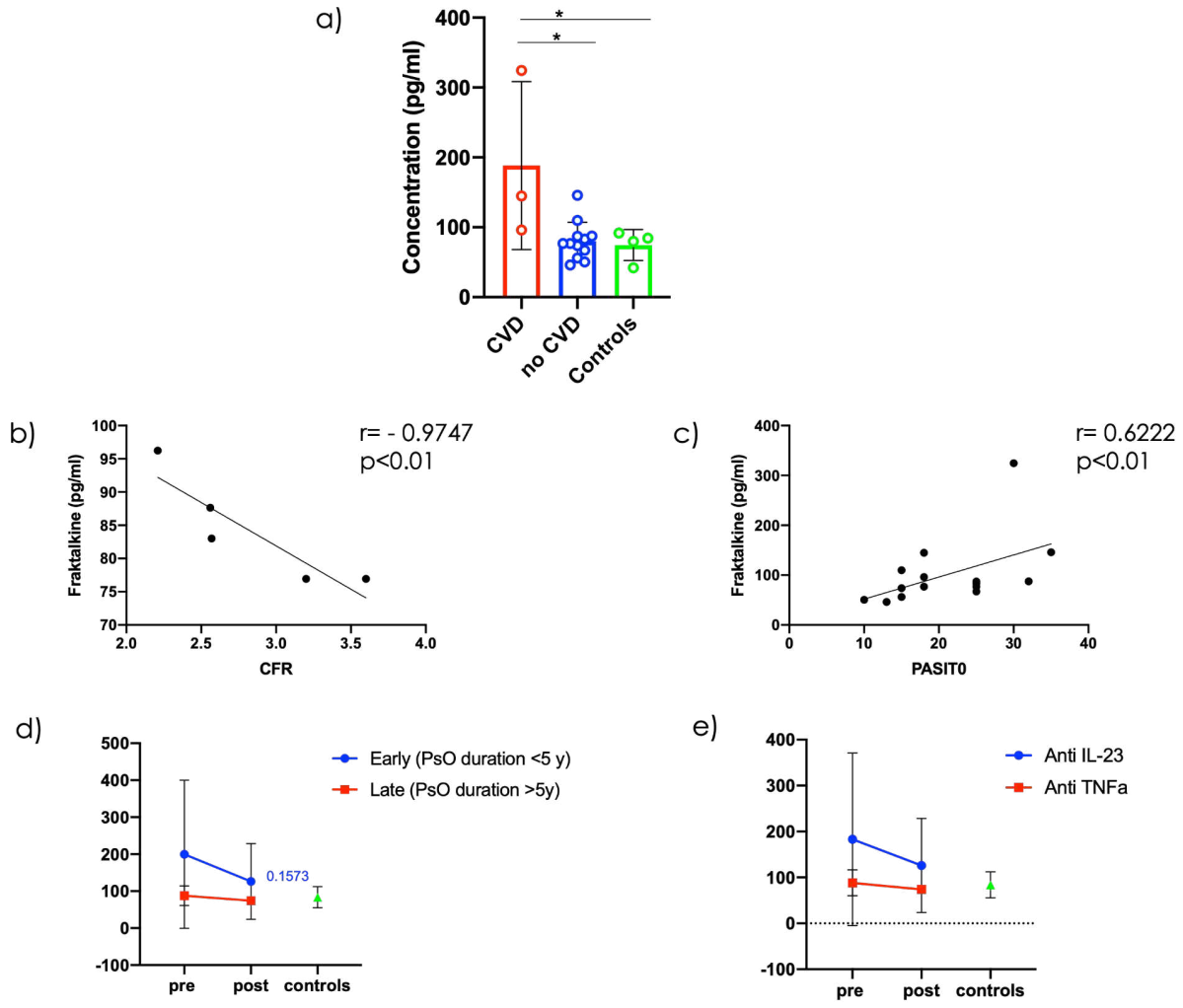

Figure 15: Fraktalkine is elevated in the serum of psoriasis patients with a history of cardiovascular diseases and is modulated by biologic drugs.
a) Mean concentration (±SD) reported in pg/ml of fractalkine in the serum of psoriasis patients with history of cardiovascular disease (CVD), psoriasis patent with no history of CVD and controls. Kruskal-Wallis test for multiple comparisons with Dunn's *post hoc*. *p < 0:05
b) Correlations of serum levels of fraktaline (pg/ml) with coronary flow reserve (CFR) and c) PASI at baseline (PASIT0) assessed by Spearman's rank correlation test. R values are indicated together with the p-values.
d) Change in serum levels fractalkine (pg/ml) from baseline to W24 by disease duration and e) different treatment. Plotted are averaged concentration (± SD) for each group and time point. Sidak's multiple comparison test was performed.

4.3Clinically healthy skin shows a pre-lesional pattern

Psoriasis is largely considered an organ-specific T cell-driven inflammatory disease. Indeed, T cells play a dominant pathogenic role in the initiation and maintenance of psoriasis, as well as in in the recurrence of the disease upon discontinuation of therapy (Benezeder et al. 2019).
In keeping with this, a multiparametric flow-cytometry analysis was performed to characterize the local and systemic immune T cells landscape of psoriatic patients. With this purpose, peripheral blood (PB) together with samples of non-lesional skin and psoriatic skin were collected at baseline (18 patients). Furthermore, PB and post-lesional skin samples were collected at T3 (11 patients).

We first considered the percentage of both CD4+ and CD8+ T cell subsets within the gate of CD45+ CD3+ cells with respect to the total cells count (the gating strategy is reported in the material and method section). We did not observe significant differences in patients' blood levels of CD3+, CD4+ and CD8+ T cells before and after the treatment with both anti TNF-α and anti IL-23 drugs (Figure 16 a,b); however, variation in lymphocyte percentage were identified in the skin. In detail, a higher frequency of T lymphocytes (CD3+ events) was recorded in psoriatic skin in comparison to non-lesional skin, with a significant difference in both CD4+ and CD8+ T cell subsets (Figure 16 c,d). Interestingly, anti TNF-α and anti IL-23 treatment reduced the number of infiltrating T cells, bringing them to levels even lower than those found in non-lesional skin. (Figure 16c). Indeed, even though the non-lesional skin exhibited lower lymphocyte counts than the psoriatic skin, it had higher counts than the post-lesion skin. This indicates that the non-lesional skin could be in a preliminary activation stage, exhibiting characteristics of a pre-lesional state.

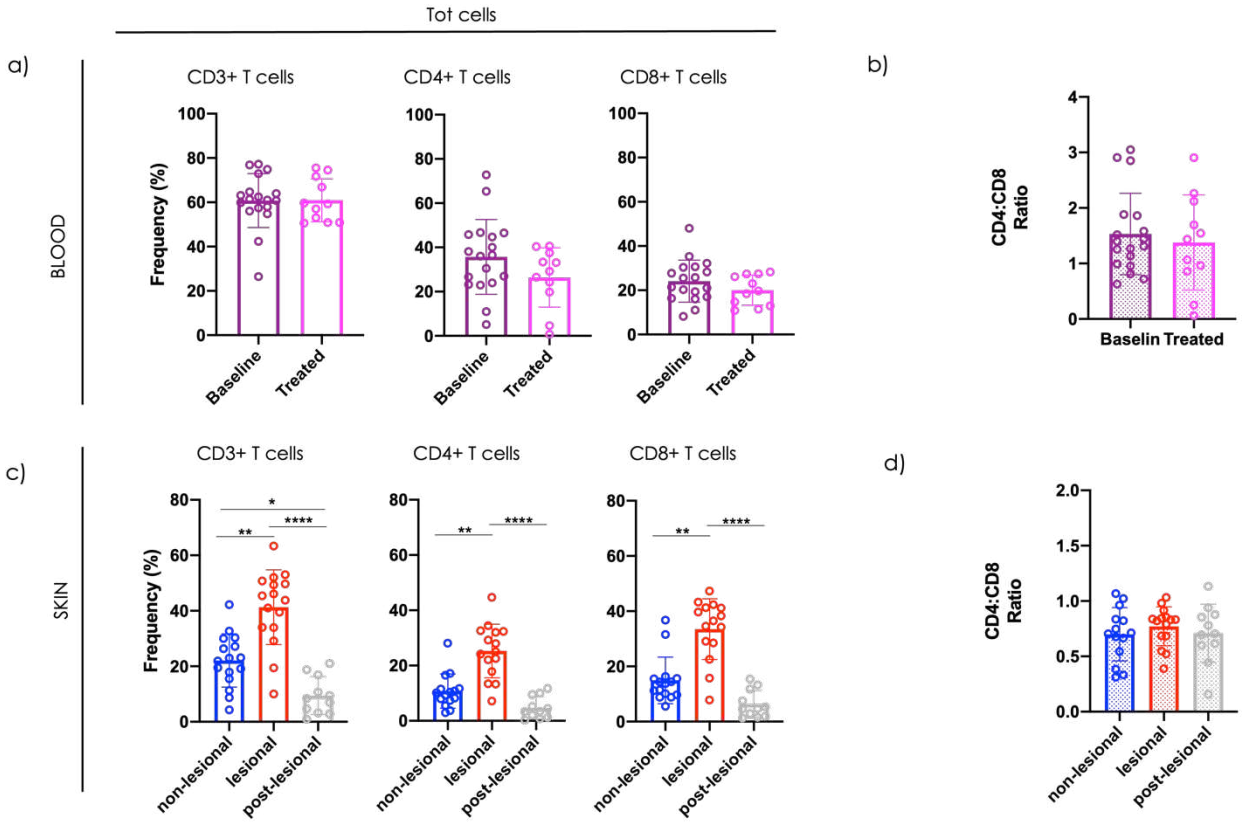

Figure 16. Lymphocyte Subset Frequency in psoriatic patient's peripheral blood and skin samples.
Lymphocytes were isolated from the skin and peripheral blood samples of patients indicated in Table 1 and analyzed by flow cytometry.
a) Changes in the mean frequency (±SD) of CD3+, CD4+ and CD8+ T cells within total cells in blood samples before and after the treatment.
b) CD4+ and CD8+ T cell subset composition in peripheral blood samples calculated as the mean ratio CD4+:CD8+ T cell frequency ± SD within total cells. Nonparametric Mann–Whitney U test.
c) Changes in the mean frequency (±SD) of CD3+, CD4+ and CD8+ T cells within total cells among non-lesional, lesional and post-lesional skin.
d) CD4+ and CD8+ T cell subset composition in non-lesional, lesional and post-lesional skin samples calculated as the mean ratio CD4+:CD8+ T cell frequency ± SD within total cells. Kruskal-Wallis test for multiple comparisons with Dunn's *post hoc*. *p < 0:05, ****p <0.0001

4.4 Memory T Cells Predominate throughout the skin and enhance with disease severity

To achieve a complete picture of memory and naive compartments distribution, the proportion of CD45RO+ memory and C45RA+ naïve CD4+ and CD8+ T cells in the PB and in the skin of psoriatic patients before and after the treatment was analyzed by FACS. Indeed, the expression of the CD45RO

isoform is a well-known marker used to phenotypically identify memory CD4+ and CD8+ T cells and, on the contrary, CD45RA isoforms are expressed by naïve and terminally differentiated effector cells (Sathaliyawala et al., 2013). In accordance with previous studies (Langewouters et al. 2008), the analysis in the blood revealed a higher percentage of CD45RO+ cells in comparison to CD45RA+ cells within CD4+ T cells compartment (Figure 17a). Conversely, CD45RA+ cells were more abundant within the CD8+ T cells (Figure 17b). The skin showed a preponderance of CD45RO+ memory T cells: CD45RO+ memory T cells predominate in non-lesional, lesional and post-lesional skin, exceeding the frequency of CD45RA-expressing subsets within CD4+ and CD8+ T cell subsets (Figure 17 c,d).

Intriguingly, although these results demonstrated that human memory T cells predominate in the skin of all psoriatic patients, their frequency varied with the severity of the disease. Indeed, by performing a correlation analysis we demonstrated that there is an increase of memory CD4+T cells (Figure 17e) and CD8+T cells (Figure 17f) in patients with higher PASI.

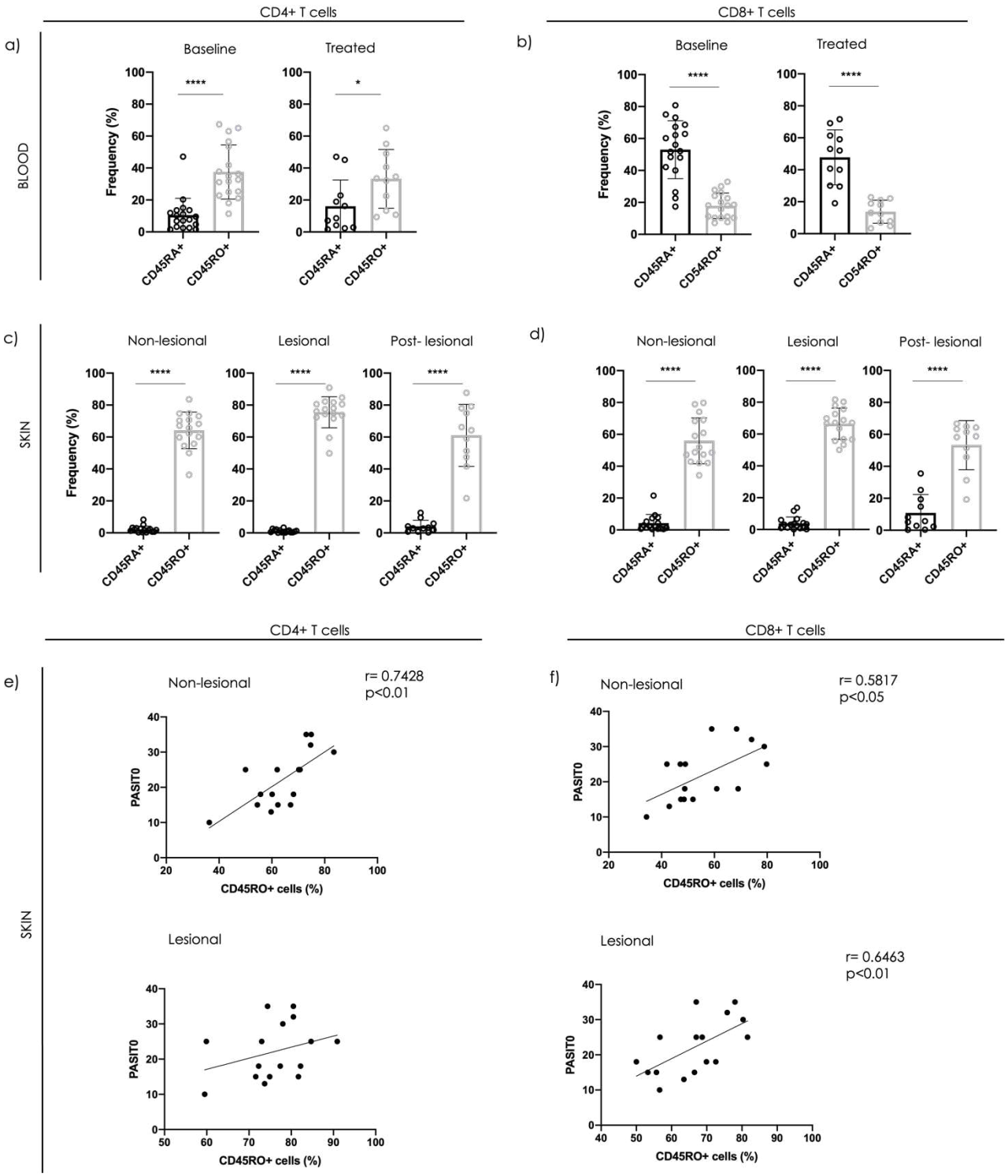

Figure 17. Distinctive blood and skin distribution of CD45RA+ naïve and CD45RO+ memory CD4+ and CD8+T Cell subsets and disease-severity dependence.

a) Frequency of CD4+ and (b) CD8+ CD45RO+ and CD45RA+ cell subsets in the peripheral blood before and after the treatment expressed as mean ± SD. Nonparametric Mann–Whitney U test. *p < 0:05, **p<0.01, *** p<0.001,****p <0.0001

c) Frequency of CD4+ and (d) CD8+ CD45RO+ and CD45RA+ cell subsets in non-lesional, lesional and post-lesional skin expressed as mean ± SD. Nonparametric Mann–Whitney U test. *p < 0:05, **p<0.01, *** p<0.001,****p <0.0001

e) Correlations of CD4+ and (f) CD8+ CD45RO frequency in non-lesional and lesional skin and psoriasis severity at baseline (PASI T0) assessed by Spearman's rank correlation test. Significant associations are indicated with R values together with the p-values.

Therefore, we evaluated whether the enrolled treatment directly affects the frequency of naive and memory T cells within the peripheral blood and skin of patients. Although we didn't appreciate significant differences in the proportion of memory and naïve T cells (either within CD4+ and CD8+ T cells) before and after the treatment in the peripheral blood (Figure 18 a,b), relevant differences were identified in psoriatic skin. Within the CD4+ T cell subset, the lesional skin showed significantly higher levels of CD45RO+ cells compared to non-lesional skin and, interestingly, the treatment allowed for the rescue of these cells, bringing them back to levels comparable to non-lesional skin. Concurrently, post-lesional skin showed a significant increase of CD45RA+ cells (Figure 18c). A similar trend was observed within the CD8+ T cells (Figure 18d).

These results pointed to a crucial involvement of T cells, in the psoriatic immune response, with a consistent accumulation of memory T cells in the lesional skin. Importantly, memory T cell subset were consistently molded by therapeutic treatments.

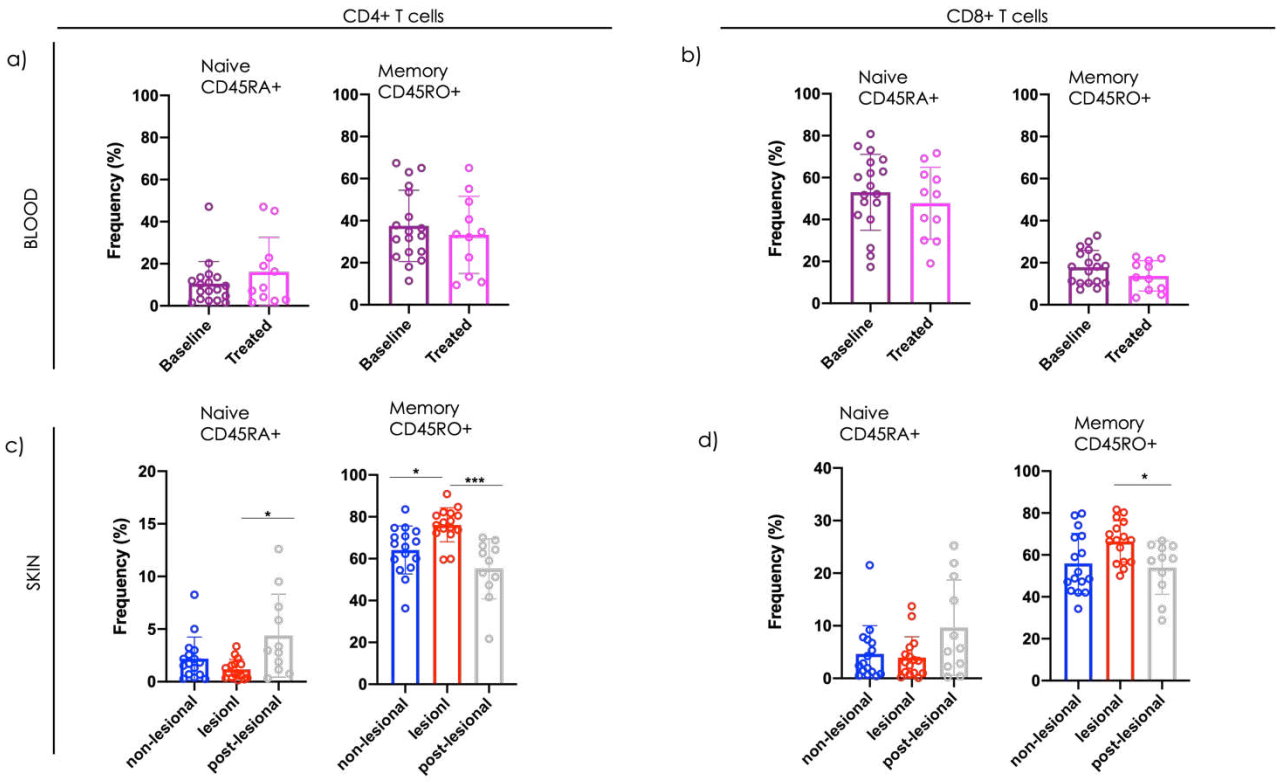

Figure 18. Treatment ability to modulate the CD45RA+ naïve and CD45RO+ memory cell compartments within the blood and the skin. Lymphocytes isolated from peripheral blood and skin were analyzed for CD45RO expression to delineate memory cells from CD45RA-expressing subsets representing either naive or terminal effector cells.
a) Mean frequency (±SD) of CD45RA+ and CD45RO+ CD4+ and b) CD8+ T cells in the blood at baseline and after the treatment. Nonparametric Mann–Whitney U test. *p < 0:05, ****p <0.0001
c) Mean frequency (±SD) of CD45RA+ and CD45RO+ CD4+ and d) CD8+ T cells in non lesional, lesional and post-lesional skin. Kruskal-Wallis test for multiple comparisons with Dunn's *post hoc*. *p < 0:05, ****p <0.0001

4.5Distinct Composition and Compartmentalization of CD4+ and CD8+ Effector and Memory Subsets

In humans, further functional subsets of CD45RA+ and CD45RO+ T cells are defined by the expression of the lymph node homing receptor CCR7. Naive T cells are indeed primarily CD45RA+CCR7+. There is also a subset of CD45RA+ T cells that are CCR7 negative, which are designated terminally differentiated effector T cells (designated Temra cells). CD45RO+ memory T cells are subdivided into two subsets: CCR7+ ''central memory'' (Tcm) cells, which migrate to

lymphoid tissue, and CCR7- ‘‘effector memory’’ (Tem) cells, which circulate to nonlymphoid sites (Sathaliyawala et al., 2013). We used coordinate analysis of the CCR7 and CD45RA expression in both the CD4+ and CD8+ T cell subsets to precisely define Temra, naïve, Tcm, and Tem cell subsets in the PB and and in non-lesional, lesional, post lesional skin of psoriatic patients before and after the treatment.

In healthy individuals' blood, naïve cells seem to be the primary subtype within both CD4+ and CD8+ categories (Sathaliyawala et al. 2013). In keeping with this observation, within the blood of our patients, naïve cells were more abundant in CD8+ T cells; on the contrary, Tcm appeared to prevail in the CD4+ T cells (Figure 19 a,b). Despite treatments not modifying these proportions, a decline of Tem was seen post-treatment (Figure 19 c,d), becoming pronounced in the CD4+ T cells compartment (Figure 19c).

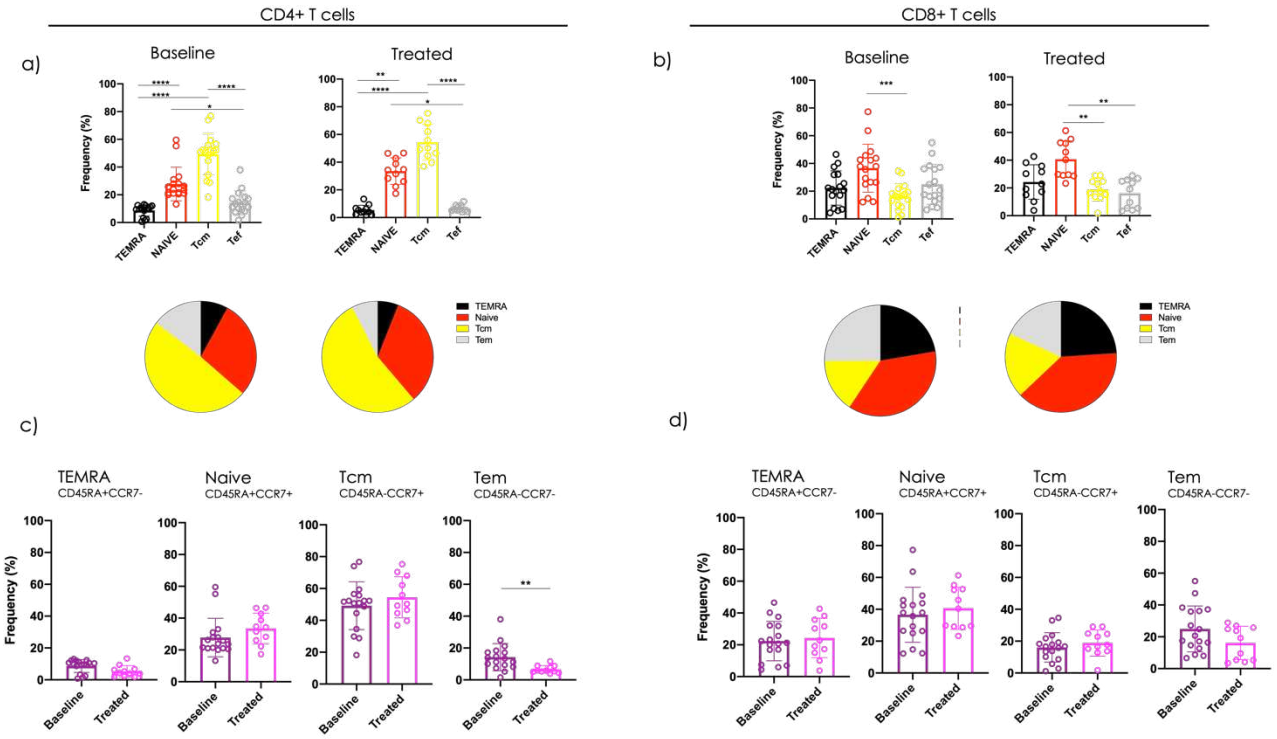

Figure 19. Blood distribution and subset composition of TEMRA, Naive, Tcm and Tem CD4+ and CD8+T cells before and after the treatment.
a) Frequency of CD4+ and (b) CD8+ Temra (black), naïve (red), Tcm (yellow), and Tem (gray) cell subsets in the peripheral blood before and after the treatment. Small graphs show frequency of each subset in blood at T0 and T3 expressed as mean ± SD. Bottom: Pie charts show average frequency of each subset (naive, Temra, Tcm, Tem) within CD4+ (a) or CD8+ (b) T cells in blood at T0 and at T3. Kruskal-Wallis test for multiple comparisons with Dunn’s *post hoc*. *p < 0:05, **p<0.01, *** p<0.001,****p <0.0001
c) Changes in the mean frequency (±SD) of CD4+ and (d) CD8+ of naïve, Temra, Tcm and Tem between T0 and T3 in the peripheral blood. Nonparametric Mann–Whitney U test. *p < 0:05, **p<0.01, *** p<0.001,****p <0.0001

Focusing on the skin compartment, we observed that Tem cells were the predominant population within CD4 and CD8+ cells in both psoriatic skin and non-lesional skin, thus confirming that, even before the clinical onset of the disease, apparently healthy skin shows a pre-lesional pattern. Of note, in the lesional skin, CD8+ Tcm cells were more abundant than Temra and naive cells, yet they were still less numerous than Tem cells (Figure 20 a,b).

Post-lesional skin showed Tem and Tcm cells in comparable amounts, with both being notably more prevalent than Temra in both the CD4+ and CD8+ compartments (Figure 20 a,b). Within the CD8+ subset, Tem cells continued to outnumber naïve cells (Figure 20b).

Remarkably, the treatment caused a substantial reduction of the Tem cells, bringing their frequencies even below those in non-lesional skin. Concurrently, both CD4+ and CD8+ Tcm and naïve T cells saw a significant increase at T3 (Figure 20 c,d) .

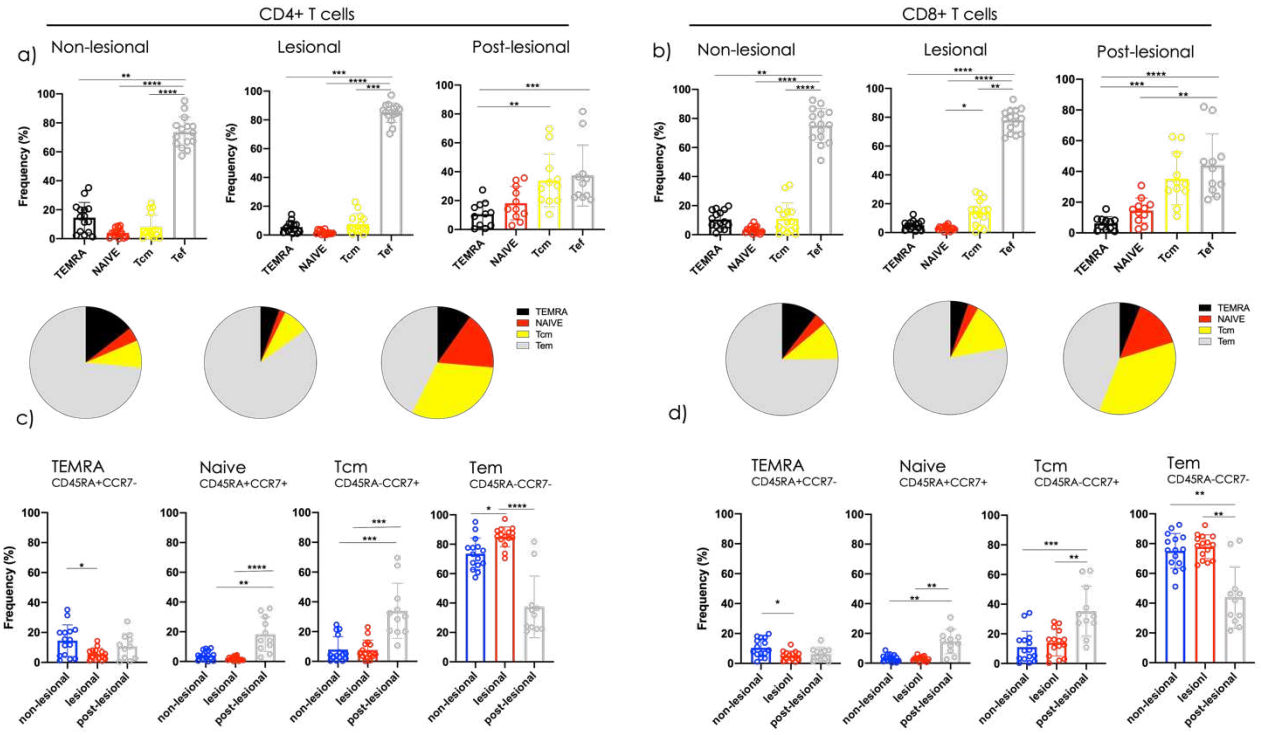

Figure 20. Skin distribution and subset composition of TEMRA, Naive, Tcm and Tem CD4+ and CD8+T cells before and after the treatment, a) Frequency of CD4+ and (b) CD8+ naïve (red), Temra (black), Tcm (yellow), and Tem (gray) cell subsets in the peripheral blood before and after the treatment. Small graphs show frequency of each subset in blood at T0 and T3 expressed as mean ± SD. Bottom: Pie charts show average frequency of each subset (naive, Temra, Tcm, Tem) within CD4+ (a) or CD8+ (b) T cells in non-lesional, lesional and post-lesional skin. Kruskal-Wallis test for multiple comparisons with Dunn's *post hoc*. *p < 0:05, **p<0.01, *** p<0.001,****p <0.0001
c) Changes in the mean frequency (±SD) of CD4+ and (d) CD8+ naïve, Temra, Tcm and Tem between non-lesional, lesional and post-lesional skin. Kruskal-Wallis test for multiple comparisons with Dunn's *post hoc*. *p < 0:05, **p<0.01, *** p<0.001,****p <0.0001

In both psoriatic and non-psoriatic skin, the memory cells compartment seemed to be predominantly composed of Tem cells (Figure 20 a,b). Consistently, post-treatment, Tef cells mirrored the overall trend observed in memory CD45RO+ cells (Figure 18 c,d), experiencing a substantial decrease (Figure 20 c,d). Of note, a similar trend was observed in the blood for overall memory cells and Tef cells (Figure 18 a,b and Figure 19 c,d), exhibiting a notable post-treatment decrease within the CD4+ subset (Figure 19c). In contrast, skin Tcm cells display an opposite pattern, witnessing a notable increase due to the therapy, similar to the behavior of naïve T cells (Figure 20 c,d).

4.6Tissue resident memory cells reduction is greater after early treatment with biologic drugs

Further analyzing the memory T cell compartment, we focused on tissue resident memory cells (TRMs), as they are known to play a crucial role in the psoriasis disease's "memory" (Benezeder et al. 2019). Indeed, these cells remain in the clinically healed post-lesional skin even after long-term treatment and, upon exposure to specific triggers or discontinuation of therapy, they can quickly reactivate and initiate an inflammatory response, leading to the recurrence of psoriatic lesions in previously affected areas (Benezeder et al. 2019).

To obtain a picture of TRMs CD8- (reasonably CD4+) and CD8+ T cell subsets within the non-lesional, lesional and post-lesional skin before and after the treatment, we combined multiparameter analysis of CD45RA and CCR7 with CD69, as a marker of tissue residence (Farber et al., 2014),

Specifically, we focused on CD45RA-CCR7-CD69+ cells, which are indicative of the TRM cell population within both the dermis and epidermis.
As shown in Figure 21, we observed that up to 70-80% of CD8- and CD8+ T cells in psoriatic skin were TRMs. Further exploring, we found that CD8- and CD8+ TRMs were similarly represented in non-lesional and psoriatic skin, and showed a remarkable contraction in healed skin.

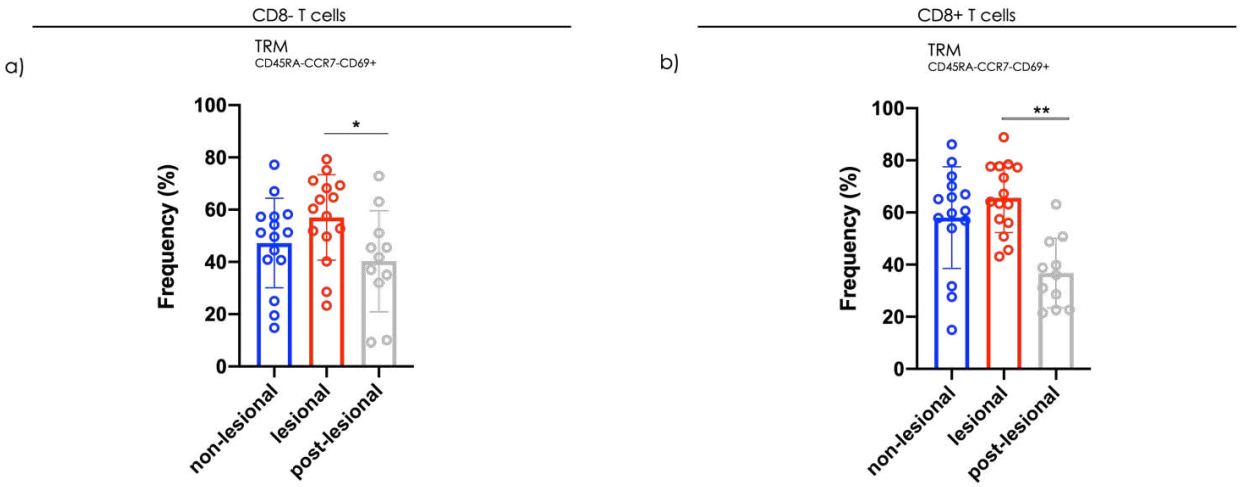

Figure 21. Distribution of TRMs within the skin.
FACS analysis of TRMs (CD45RA-CCR7-CD69+) expression in non-lesional and lesional skin at baseline and post-lesional skin after 4 weeks of treatment.
a) Mean frequency (±SD) of CD69+ T cells gated on CD45RA+ CCR7- CD4+ and b) CD8+ T cells in non lesional, lesional and post-lesional skin. Kruskal-Wallis test for multiple comparisons with Dunn's *post hoc*. *p < 0:05, ****p <0.0001

In order to evaluate the impact of the disease duration on TRMs frequencies, we compared EP and LP patients (Figure 22), noting a trend towards an increase in TRMs with the duration of the disease. Moreover, within the CD8+ T cell compartment, EP patients not only had fewer TRMs in post-lesional skin but also witnessed a more pronounced decline in TRMs after treatment compared to LP group (Figure 22b).

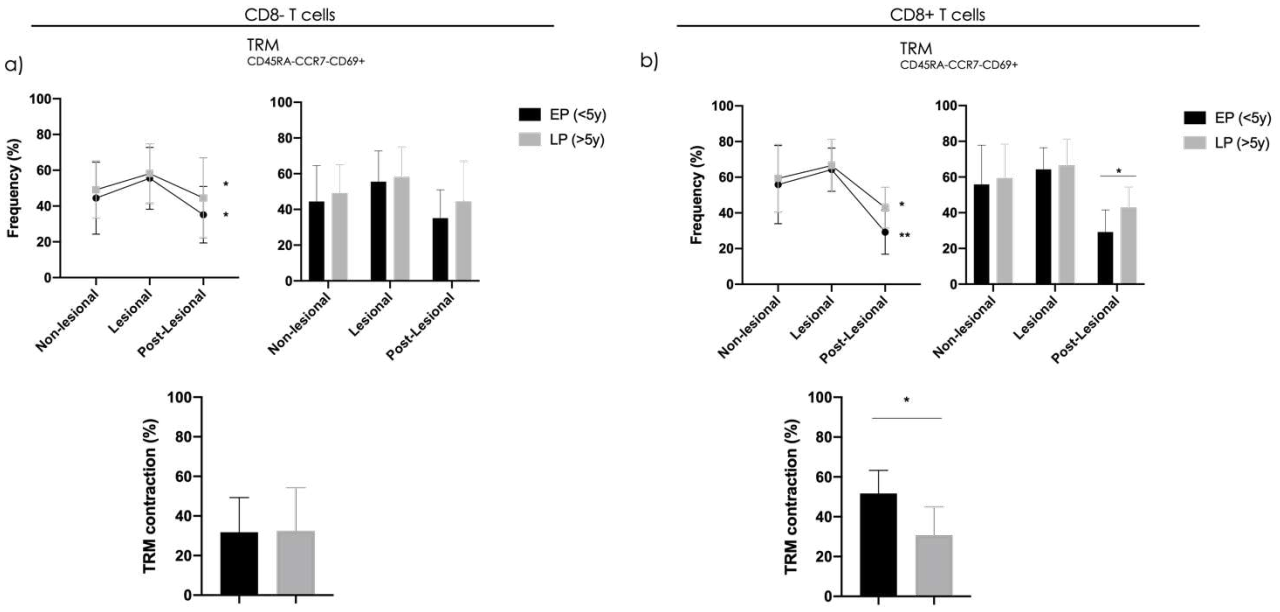

Figure 22. Distribution of TRMs within the skin with respect to disease duration.
a) Comparison of the mean frequency (±SD) of CD4+ and (b) CD8+ TRM cells in non-lesional, lesional and post lesional skin between EP and LP patients. Bottom: Comparison of the mean percentage of TRMs contraction (±SD) at W24 compared to baseline in CD4+ (c) and CD8+ (d) T cells between EP and LP patients. Nonparametric Mann–Whitney U test.

We therefore analyzed the different impact of the treatment with anti IL-23 and anti TNF-α on TRMs. Although our sample treated with anti IL-23 was limited to three subjects, there was a discernible impact on TRM numbers, though it wasn't statistically significant (Figure 23). Specifically, within the CD8+ subset, the decline in TRMs in post-lesional skin compared to lesional skin was more pronounced in patients receiving anti IL-23 treatment than those on anti TNF-α, resulting in fewer TRMs in the post-lesional skin for the former group (Figure 23b).

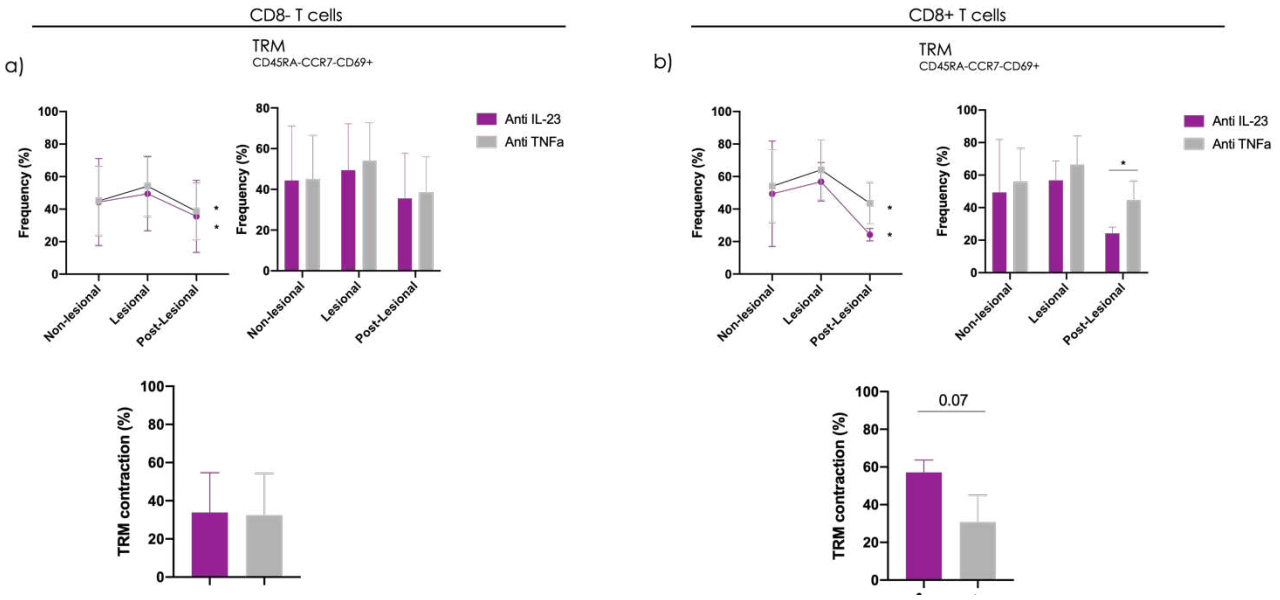

Figure 23. Impact of the treatment with anti TNFα and anti IL-23 on TRM cells.
a) Comparison of the mean frequency (±SD) of CD4+ and (b) CD8+ TRM cells in non-lesional, lesional and post lesional skin between the treatment with anti IL-23 and TNF-a. Bottom: Comparison of the mean percentage of TRMs contraction (±SD) at W24 compared to baseline in CD4+ (e) and CD8+ (f) T cells between anti IL-23 and anti TNF-α treatments. Nonparametric Mann–Whitney U test.*p < 0:05

4.7Psoriasis patient's skin contain a double-positive CD45RA+RO+ population typically associated to lymphoid organs

In a parallel setting, exploring the expression of CD45RA and CD45RO markers, we noticed that within the skin, but not in the blood, of our patients there was a subpopulation expressing both markers. These cells were found to be more abundant within lesional skin than in non-lesional skin and showed to be modulated by the therapy (Figure 24 a,b); in particular these changes reached the significance in the CD8+ T cells (Figure 24b).

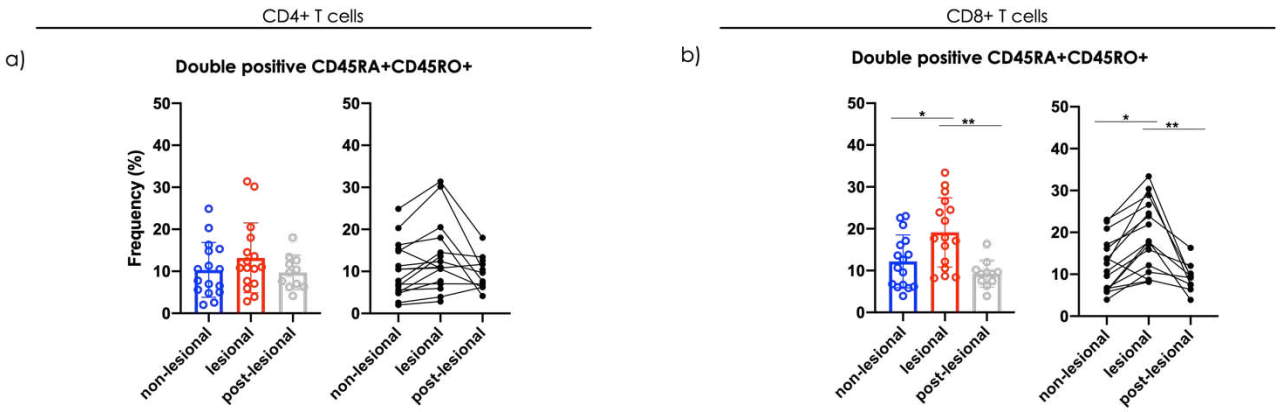

Figure 24. Psoriasis patient's skin contains a double positive CD45RO+RA+ population that is modulated by the treatment.
FACS analysis of CD45RA and CD45RO expression uncovered a double positive CD45RA+RO+ population in the skin of psoriatic patients.
a) Mean frequency (±SD) of CD45RA+RO+ CD4+ and b) CD8+ T cells in non lesional, lesional and post-lesional skin.

In order to better characterize the role of CD45RA+RO+ we performed a functional analysis of their intracellular cytokine's profile, evaluating the expression of IL-12, IL-17A, INF-γ; IL-2, TNF-α, known for their proinflammatory role. CD45RO+RA+ CD4+ and CD8+ T cells mainly expressed INF-γ and TNF-α in non-lesional, lesional and post-lesional skin (Figure 25 a,b). Notably, there are no significant differences in expression across these three skin conditions (Figure 25 c,d).

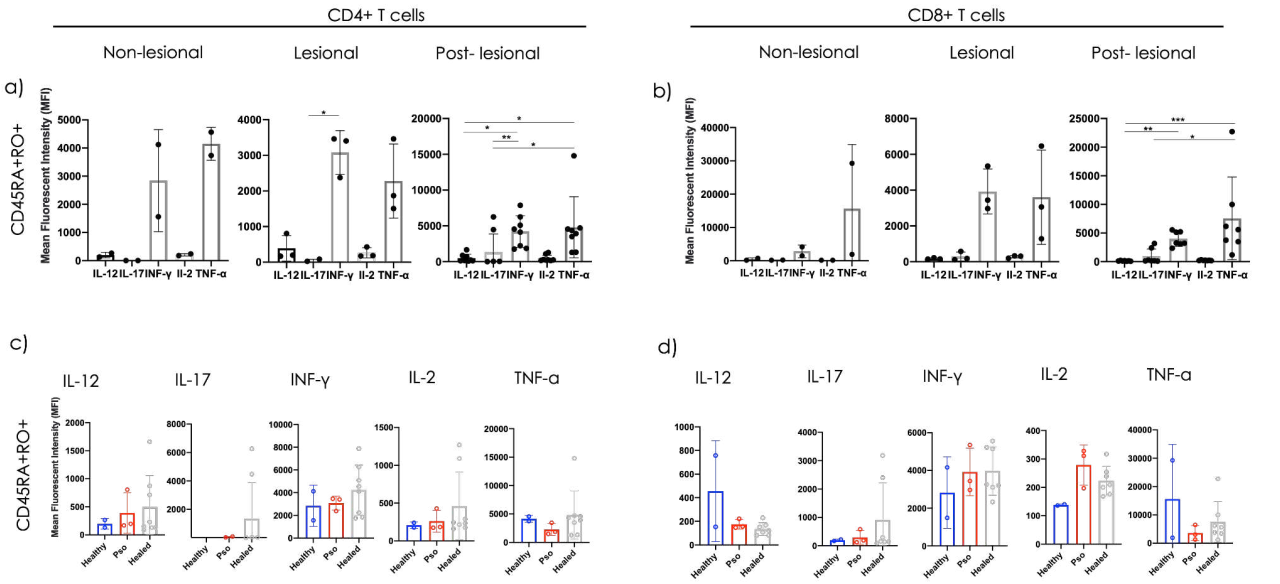

Figure 25. Functional profile of double positive CD45RA+CD45RO+ CD4+ and CD8+ T cells within the skin of psoriatic patients.
a) Mean fluorescent intensity (±SD) of intracellular profile of IL-12, IL-17A, INF-; IL-12, TNF-α in CD45RA+RO+ CD4+ and b) CD8+ T cells.
c) IL-12, IL-17A, INF-; IL-12, TNF-α production by CD45RA+RO+ CD4+ and d) CD8+ T cells in non-lesional, lesional a and post-lesional skin.
Kruskal-Wallis test for multiple comparisons with Dunn's *post hoc*. $p < 0,05$, ** $p<0.01$, ****$p <0.0001$

To gain a deeper understanding of these cells in relation to CD45RA+ naive and CD45RO+ memory T cells, we assessed and compared the cytokine expressions among these subsets. Our observations revealed that naive cells predominantly expressed TNF-α (Figure 26 a,b), while memory cells chiefly produced INF-γ (Figure 26 c,d).

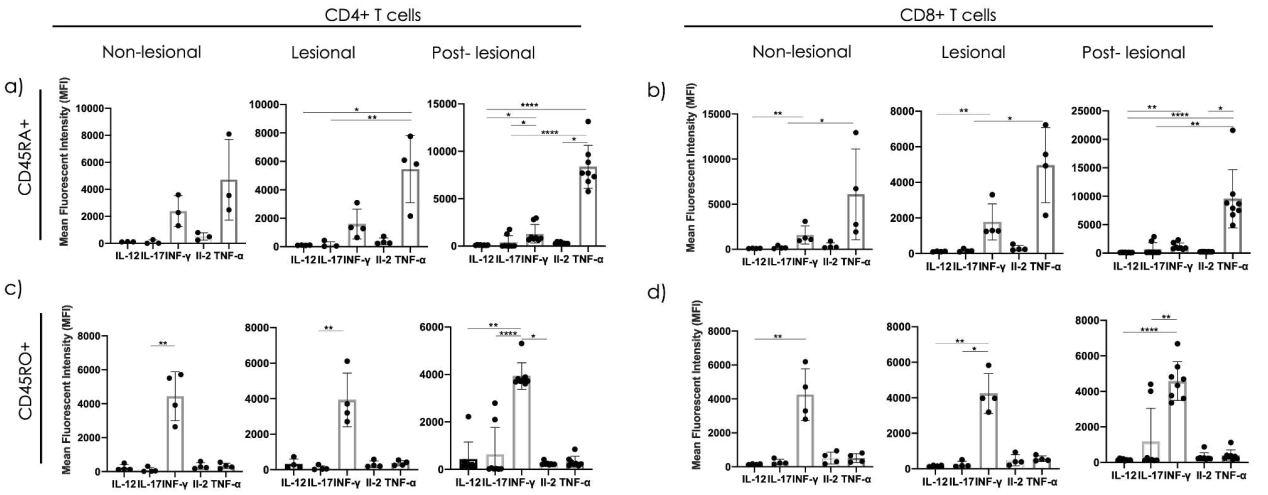

Figure 26. Functional profile of CD45RA+ and CD45RO+ in the skin of psoriasis patients.
a) Mean fluorescent intensity (±SD) of intracellular IL-12, IL-17A, INF-; IL-12, TNF-α in CD45RA+ CD4+ and b) CD8+ T cells in non-lesional, lesional and post-lesional skin.
c) Mean fluorescent intensity (±SD) of intracellular IL-12, IL-17A, INF-; IL-12, TNF-α in CD45RO+ CD4+ and b) CD8+ T cells in non-lesional, lesional and post-lesional skin.
Kruskal-Wallis test for multiple comparisons with Dunn's post hoc. $p < 0,05$, ** $p<0.01$, ****$p <0.0001$

Thus, we focused on the production of INF-γ and TNF-a comparing the mean expression of these cytokines by CD45RO+RA+ with respect to CD45RO+ and CD45RA+ and the entire CD4+ and CD8+ T compartment. It was evident that in both the CD4+ and CD8+ compartments, TNF-α was primarily produced by naïve and CD45RA+RO+ cells (Figure 27 a,b); on the other hand, INF-γ was primarily expressed by double positive CD45RA+RO+ cells and memory cells (Figure 27 c,d).

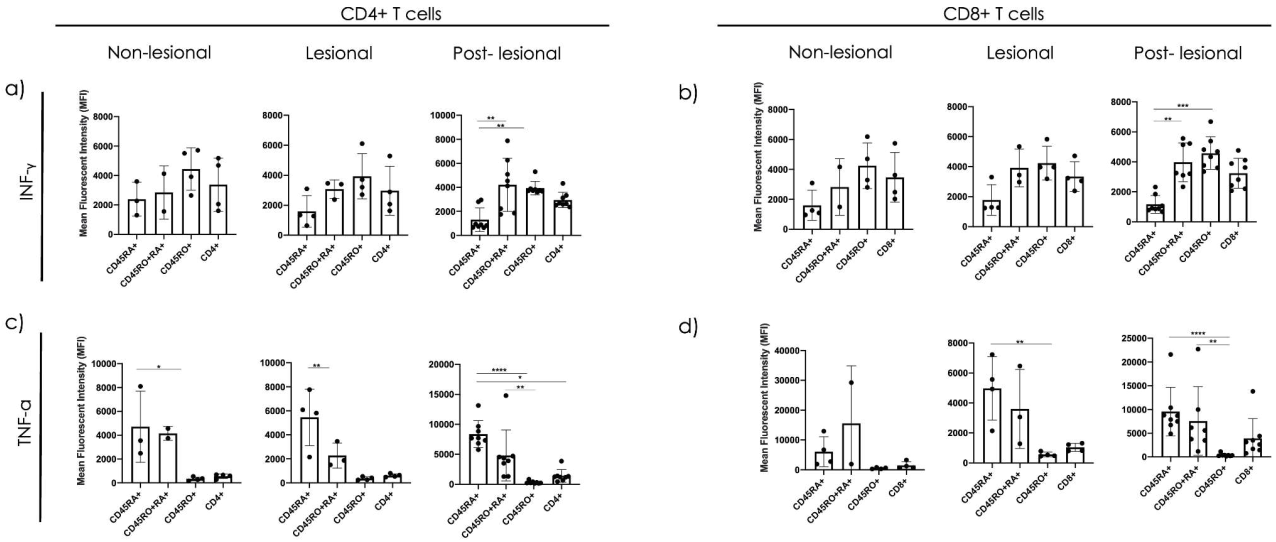

Figure 27. INF-γ and TNF-α expression by CD45RA+, CD45RO+ and double positive CD45RA+RO+ cells.
a) Mean fluorescent intensity (±SD) of INF-γ production by CD45RA+, CD45RO and double positive CD45RA+RO+ CD4+ and d) CD8+ T cells in non-lesional, lesional a and post-lesional skin.
a) Mean fluorescent intensity (±SD) of TNF-α production by CD45RA+, CD45RO and double positive CD45RA+RO+ CD4+ and d) CD8+ T cells in non-lesional, lesional a and post-lesional skin.
Kruskal-Wallis test for multiple comparisons with Dunn's post hoc. $p < 0,05$, ** $p<0.01$, ****$p <0.0001$

The simultaneous expression of INF-γ and TNF-α in cells carrying both CD45RA and CD45RO markers suggests that these cells are at an intermediate stage, transitioning from naive to memory T-cell forms. Established research supports this, indicating that antigen-specific T-cell differentiation involves a shift from CD45RA+ (naive) to CD45RO+ (memory). During this transitional phase, cells

commonly display both CD45RA and CD45RO markers -often termed "double-positive CD45RA+RO+"- and are usually found in active secondary lymphoid organs like tonsils (Hoy et al., 1993; Summers et al., 1994).

When integrated with our recent discovery of these dual-marked CD45RA+RO+ cells in skin tissue, it becomes highly suggestive that in psoriatic lesions, T cells might not only be infiltrating from the bloodstream post-activation in lymph nodes but could also be undergoing direct activation (or reactivation) within the skin itself. Therefore, we hypothesize that within the psoriatic skin could take place the formation of localized aggregates of lymphoid tissue, akin to conventional lymphoid follicles, known as tertiary lymphoid organs (TLOs), which are often observed in tissues experiencing chronic inflammation.

To demonstrate the presence of TLOs, we developed a multiplex immunofluorescence staining technique applied to FFPE samples of non-lesional and lesional skin from three patients before and after therapy. This technique employed a panel of antibodies that specifically targeted T cell markers CD3, CD4, CD45RA, and CD45RO, as well as the B cell marker CD20. The technique's ability to simultaneously examine multiple cellular markers offers a distinct advantage, providing a comprehensive view of the cellular microenvironment that is particularly useful for identifying complex structures like TLOs where various cell types co-localize and interact.

We noticed elevated levels of B and T cells in the dermal papillae, specifically in lesional skin, where CD45RO+ and CD45RA+ T cells were also found in close contact; such observations were not present in non-lesional skin (Figure 28 a,b). These types of cellular interactions are often a hallmark of structured immune activity and could point to areas of cellular activation resembling TLOs.

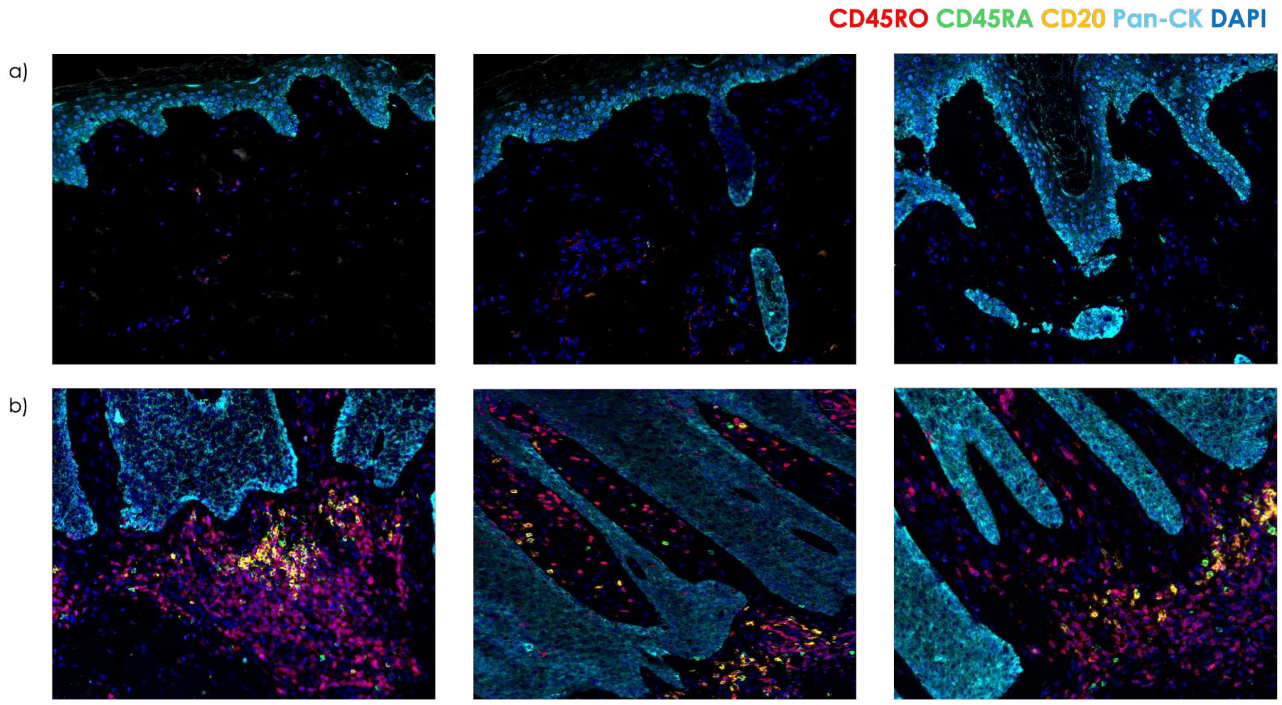

Figure 28. Multiplex immunofluorescence staining with Mantra.
a) Representative immunofluorescence image of non-lesional and b) lesional skin co-stained for CD45RA, CD45RO, CD20 markers, Pan-cytokeratin for epithelial structure and DAPI nuclear stain.

The observations we've made in psoriatic skin could serve as initial evidence for the development of TLOs, and as such, they necessitate further in-depth exploration using multiplex immunofluorescence techniques. Moreover, single-cell multiomics could delve into the complex nature of dual-positive

CD45RO+RA+ cells, thereby enriching our understanding of their contribution to the onset and progression of psoriasis.

5. DISCUSSION

Plaque psoriasis is a chronic skin disease characterized by well-demarcated, scaly and erythematous, infiltrated plaques that can significantly impact a patient's physical, emotional, and social well-being (Parisi et al., 2013).

To date, the treatment of psoriasis in the first months after the disease onset is highly conservative and frequently based on topical agents or phototherapy. Treatment with systemic agents, in particular biologic drugs, generally begins only when topicals have proved unsuitable or ineffective (Nast et al., 2020; Sbidian et al., 2022, 2021).

Nonetheless, the use of targeted therapies from the very early stages of treatment has been shown to improve long-term patient outcomes in other IMIDs. Indeed, experience from rheumatoid arthritis, Crohn's disease and multiple sclerosis has shown that early intensive treatment can significantly improve long-term outcomes in disease activity by hindering immune pathways that eventually lead to the establishment of a chronic inflammation (Girolomoni et al., 2015).

In this context, some Authors (Iversen et al., 2018; X Liu, 2019; Schäkel et al., 2023) have hypothesized that an early targeted systemic treatment approach -*early intervention*- can improve the control of skin symptoms, modify the course of the disease at a skin and systemic level and reduce the risk of recurrence, as compared to a *late intervention*.

In our study, we assessed the potential superiority of *early intervention* with biologic drugs over *late intervention* in treating psoriasis, comparing patients with moderate to severe psoriasis (PASI>10) who began biologic treatment with anti TNF-α or anti IL-23 within 5 years (EP patients) or after 5 years (LP patients) from the disease's onset.

Early intervention in psoriatic patients yields better treatment outcomes

Our initial focus was to examine whether significant differences existed in disease severity and clinical improvement after 24 weeks of treatment between the two groups.

Our findings further support the hypothesis of a distinct difference between EP and LP psoriatic patients in terms of treatment outcomes. Indeed, despite both groups having similar baseline PASI values, EP patients consistently exhibited greater clinical improvement compared to LP patients. Remarkably, a greater fraction of EP patients achieved a PASI 90, a crucial benchmark in treatment, as compared to the LP patients (71.4% vs 18.2%, $p<0.05$). The results are in line with the outcomes seen in rheumatoid arthritis and Crohn's disease, as well as with the sub-analysis of the ERASURE and FIXTURE studies and the VOYAGE and GUIDE studies, which demonstrated that patients with shorter disease duration tended to have a better and faster clinical response and prolonged periods without relapse (Iversen et al., 2018; X Liu, 2019; Schäkel et al., 2023). Furthermore, the correlation analyses indicating a positive relationship between disease duration and PASI after 24 weeks of treatment and a negative association with the improvement percentage, reiterated that early intervention can potentially facilitate better clinical clearance and possibly modify the disease course at a clinical level.

The importance of an early intervention in addressing the systemic inflammation in psoriasis

The impact of psoriasis goes far beyond its visible skin symptoms. Indeed, current understanding suggests that the inflammation associated with psoriasis might extend beyond the skin, leading to the concepts of the "psoriatic march" or "inflammatory skin march" (Boehncke et al., 2011). This indicates that the effects of psoriasis can have systemic implications, underscoring the need for treatment strategies that address more than just the skin manifestations. In this context, as the analysis of the serum cytokine/chemokine profile provides valuable insights into the broader inflammatory state experienced by individuals with psoriasis (Girolomoni et al., 2015), we conducted an assessment of our patients' cytokine/chemokine signature.

In our study, we found that patients with psoriasis had significantly elevated levels of various inflammatory cytokines and chemokines compared to healthy individuals. Notably, eotaxin, G-CSF, IL-17A, IL-23p40, MCP-1, MDC, IL-6, and TNF-α were elevated, while levels of the anti-inflammatory cytokine IL-10 were reduced. These results align with prior research that underscores the ongoing inflammation related to psoriasis (Camela et al., 2022; Bieniek-Kobuszewskaet al., 2022; Arican et al., 2005; Mehta NN et al.; 2017), further emphasizing the disease's link to imbalances in the immune system.

In contrast to prior research (Wang et al. 2022) linking serum levels of IL-6, and TNF-alpha to the severity of psoriasis, our study found that these cytokines, as well as the levels of eotaxin, were more closely related to the age of the patients. This aligns with the concept of 'inflammaging,' a state of ongoing, low-level inflammation that tends to increase with age (Franceschi et al., 2014), suggesting that these molecules are poorly specific markers for psoriasis.

Notably, the IL-23p40 subunit—which is integral to both IL-23 and IL-12—was intimately correlated with disease severity and responsiveness to treatment. Coupled with the positive correlation between IL-17A, baseline PASI scores, and IL-23p40 levels, these findings, that aligns with previous results (Camela et al., 2022; Arican et al., 2005), emphasize the critical role of the IL-23/Th17 axis in not only the initiation but also the perpetuation of psoriatic symptoms, strengthening the argument for targeting this particular axis in therapeutic strategies.

Interestingly, the association between cytokine concentrations and PASI scores held consistent irrespective of whether the patients were in the early phase or late phase of the disease. This suggests that it is the severity of the disease, rather than its duration, that predominantly influences systemic inflammation.

However, when we evaluated the impact of biologic treatments on this inflammatory landscape, it became evident that the timing of intervention could play a significant role in treatment outcomes. EP patients experienced a significant drop in IL-17A levels when treated, even though their initial cytokine levels mirrored those of late-phase patients. This indicates a greater efficacy in early intervention, especially in suppressing key inflammatory markers like IL-17A. Considering the enhanced clinical results and significant reduction in IL-17A levels achieved with early intervention, and correlating these observations with the VOYAGE 2 study's conclusion that low levels of IL-17A are associated with improved long-term outcomes (Gordon et al; 2019), one might hypothesize that initiating treatment early could offer benefits that extend beyond immediate symptom management, potentially leading to a more effective long-term control of the disease.

Moreover, our study also highlighted the positive effects of treatment in reducing the overall inflammatory state. Indeed, we observed a general decline in proinflammatory cytokines alongside an increase in the anti-inflammatory cytokine IL-10.

The widespread systemic inflammation observed in individuals with psoriasis, which is believed to spread from the skin to the entire system, has been demonstrated to impact on multiple comorbidities, such as hypertension, diabetes, and dyslipidemia. Furthermore, psoriasis is currently considered an independent risk factor in the development of cardiovascular disease, including, myocardial infarction (MI), chronic heart failure (CHF), and cardiac arrhythmia. Interestingly, psoriasis has been shown to impact early on the vascular compartment, leading to endothelial dysfunction and subclinical atherosclerosis that might predispose to cardiovascular events (Orlando et al., 2022). Indeed, exploring the microvascular compartment by Coronary Flow Reserve (CFR), a diagnostic parameter which evaluate the capacity of the coronary arteries to increase blood flow in response to demand, such as during physical exercise, it has been shown that people with psoriasis have reduced CFR, even if they don't show any other signs of heart disease (Osto et al., 2012; Piaserico et al., 2019). Interestingly, alterations in CFR correlate directly with the severity of psoriasis, as measured by the PASI score (Tona et al. 2021).

In our research, we also explored the significance of a molecule known as fractalkine, which exhibited altered levels in patients affected by both psoriasis (Congjun et al., 2015) and cardiovascular disease (Umehara et al., 2004). Our findings revealed that individuals with psoriasis had higher fractalkine levels, especially those with a history of MI, HF, or impaired CFR, indicating its possible involvement in the connection between psoriasis and CVD. Furthermore, there was a significant correlation between fractalkine levels and CFR values, which not only assess microvascular function but also correlate with the severity of the disease (Tona et al. 2021). The direct relationship between psoriasis severity (as indicated by PASI scores) and fractalkine levels pointed to the possibility that exacerbated psoriasis could boost the production of this chemokine, amplifying the cardiovascular risks.
This marked elevation in fractalkine levels, when associated with the severity of the disease and compromised microvascular functionality, underscores its probable role in bridging psoriasis and CVD.

In this context, it can be speculated that fractalkine, which is markedly produced by keratinocytes and dermal endothelial cells in individuals with psoriasis (Congjun et al., 2015), could extend its influence beyond the skin. Indeed, leaking from the psoriatic plaque, it might act in distant sites, contributing to the leukocyte adhesion and migration (Umehara et al., 2004), thereby potentially playing a role in the formation of atherosclerotic damage.

Additionally, our exploration into the therapeutic implications showed that both anti TNF-α and anti IL-23 treatments effectively normalized fractalkine levels, especially when introduced early in the disease's progression. Therefore, the pronounced impact of early therapeutic interventions on fractalkine concentrations emphasizes the necessity for prompt and focused treatments to counteract the systemic implications of psoriasis.

Overall, our investigation into the cytokine/chemokine compartment suggests that timely administration of biological medications has the potential to mitigate systemic inflammation in patients, and possibly address their accompanying comorbidities.

Early treatment can modulate 'disease memory' by reducing skin TRM cell numbers

After studying systemic inflammation, we focused on the effect of the treatment on both peripheral blood and skin cells in individuals with psoriasis.
Recognizing psoriasis as organ-specific T cell-driven inflammatory disease where T cells play a pivotal role in disease initiation, maintenance, and recurrence upon discontinuation of therapy (Benezeder et al. 2019), we focused our attention on the lymphoid cell subset.
In particular, we profiled the circulating and skin T cell landscape in psoriatic patients pre and post-treatment, placing an emphasis on understanding the memory compartment, with the aim to unravel the mechanisms regulating disease recurrence.

Our study concurs with prior findings (Langewouters et al., 2008) in indicating an elevated count of CD45RO+ cells within the CD4+ compartment in the blood of psoriasis patients, indicative of a skewing towards a memory phenotype, particularly Tcm. The prevalence of Tcm cells, which are critical for eliciting a quick and potent immune response upon re-exposure to an antigen, could signal a continued state of immune activation that might influence disease progression.

The contrasting prevalence of CD45RA+ cells in the CD8+ T cell compartment, which aligns with observations that naïve cells are the primary subtype within both compartments in healthy individuals (Sathaliyawala et al., 2013), underlines a divergence in the immune status of CD4+ and CD8+ T cells in our patients. This may suggest different roles or stages of activation for these two important immune cell types or reflect the different migratory behaviors of CD4+ and CD8+ T cells during and after activation. Indeed, CD4+ T cells are commonly described as "helper" cells and tend to be more abundant in the circulating blood, where they may perform their immunoregulatory functions. On the other hand, CD8+ T cells are often involved in tissue-mediated immunity and, upon activation, many of these CD8+ cells are likely to localize in peripheral tissues, thereby reducing their presence as memory cells in the bloodstream.

In line with previous findings (Langewouters et al., 2008), the result that treatment did not significantly alter the overall proportions of naïve and memory cells within the CD4+ and CD8+ T-cell compartments suggests that treatment was not strongly immunomodulatory in this respect. The observed decline in Tem in the CD4+ compartment post-treatment, especially when other T cell proportions remained unchanged, suggests that the treatment had a specific impact on this subset of cells. Given that Tem cells typically act as "first responders" during an immune challenge, their reduction could indicate that the treatment has effectively mitigated an ongoing immune response.

In examining the skin, our findings highlighted the potent ability of biologic drugs to reshape the T cell profile, bringing the levels of inflammatory cells in post-lesional skin to even lower levels than in non-lesional skin. Interestingly, while non-lesional skin had fewer inflammatory signs than active psoriatic skin, it displayed more inflammation than skin that had fully healed. This validate the possibility that non-lesional skin, despite appearing clinically unaffected, might be on the cusp of an inflammatory response, leaning towards what might be termed a "pre-lesional" phase (Gallais Sérézal et al., 2019; Körver JE et al., 2006). This suggests that changes in the immune system might occur even before the disease shows clinical symptoms, potentially accounting for the Köbner phenomenon in psoriasis, characterized by the formation of psoriatic skin lesions following physical injuries to the skin.

Although the entire T cell compartment underwent extensive remodeling after the therapy, it was the memory subset that exhibited the most pronounced changes. In fact, while memory T cells were the dominant group in non-lesional, lesional and post-lesional skin, and their numbers rise with the severity of the disease, highlighting their potential role in both maintaining and worsening psoriatic symptoms (Kurihara K, et al. 2019), they significantly decrease following treatment.
Specifically, Tem cells, that dominated in both non-lesional and lesional skin -further supporting a 'primed' immune state even before clinical symptoms-, underwent a notable decline after the treatment, whereas, Tcm and naive T cells increased in number. This suggests that therapeutic interventions have a profound and specific impact on the Tem population: treatments led to a more balanced distribution of Tem and Tcm cells in post-lesional skin, possibly indicating a more regulated, yet vigilant, immune state at this site. The predominance of Tems over naive cells could suggest that the skin environment, even post-lesion, is geared for quick responsiveness to potential triggers, although it might be in a more controlled status than in active lesions.

This aligns well with the intrinsic nature of psoriasis, a disease marked by its tendency to relapse in areas that were previously affected, even after apparent clinical healing. The specific immune activities that keep a sort of “disease memory” in psoriasis have been attributed to TRMs, a unique cell subtype that persist in healed skin and can reignite inflammation upon certain triggers (Benezeder et al. 2019; Puig et al. 2022)

Therefore, our investigation, focused on mapping out the population of TRM cells present in the skin layers of the dermis and epidermis, found that a noteworthy percentage of T cells in the skin of psoriatic patients can be categorized as TRMs.

Consistent with prior research (Vo et al., 2019), we observed a rise in TRM cell frequency as the disease progressed. Indeed, even if not significant, EP patients had a lower presence of TRMs compared to those in the later stages of the disease. Moreover, an intriguing subtlety becomes evident upon closer examination of the post-treatment landscape. In detail, EP patients had a more pronounced contraction of TRMs post-treatment and achieved lower TRMs frequencies in post-lesional skin compared to LP patients, suggesting that early interventions might alter the inflammatory milieu differently than in later phases, thus leading to a modulation of the “disease memory” and eventually to longer disease-free periods. Furthermore, as TRMs appear to increase in number over time, one might speculate that starting treatment in the early stages of the disease might offer a "window of opportunities" in psoriasis, preventing the establishment and consolidation of pathogenic memory and therefore allow the modification of the disease with curative intent.

Nonetheless, the earlier finding that individuals with a greater abundance of TRM cells in their lesions often suffer from more severe forms of psoriasis and thicker skin plaques (Kurihara K, et al. 2019) may elucidate why, in our study, patients who received an early treatment showed greater clinical results compared to those treated later in the disease progression.

Completing these findings and consistent with the expression of IL-23R on CD8+ TRM cells (Cheuk et al. 2014) and their inclination to differentiate and proliferate under IL-23 influence (Whitley et al., 2022), we noted that these cells showed a greater reduction after the treatment with anti IL-23 as compared to anti TNF-α and that this difference tended to be significant. This lends support to the idea that targeting the IL-23 pathway might offer a more robust strategy for preventing psoriasis recurrence at its root. This finding is also congruent with earlier studies showing that guselkumab, an IL-23 inhibitor, was effective in reducing TRM cell numbers in healed skin, potentially leading to a more enduring remission of the disease compared to treatments targeting TNF-α (Mehta et al., 2021; Gordon at al., 2019). Additionally, given that the long-term remission observed after stopping guselkumab treatment has been attributed to the reduction of TRM cells (Gordon et al., 2019), it is plausible to hypothesize that extending the time between individual doses of anti IL-23 medication could still maintain patients' clinical remission.

Psoriatic skin might act as a tertiary lymphoid organ

In a parallel setting, our research identified a "double positive CD45RA+RO+" cell population primarily localized within psoriatic lesions, which have not been previously been described in the skin. Existing literature posits these cells as an intermediate state during antigen-specific differentiation, wherein T-cells evolve from the CD45RA+ (naive) phenotype to CD45RO+ (memory) (Hoy et al., 1993). Our phenotypical analysis aligns with this understanding. Specifically, when examined alongside the cytokine expression of naive and memory cells, the double positive cells appear to reside in an intermediary position concurrently expressing TNF-α, primarily seen in naive cells, and INF-γ, mainly expressed by memory cells.

Intriguingly, while CD45RA+RO+ cells are typically linked to secondary lymphoid locations like tonsils (Summers et al., 1994), their presence in the skin, in particular lesional skin, rather than in the bloodstream, and their cytokine expression pattern, heavily skewed towards INF-γ and TNF-α, crucial cytokines in perpetuating the inflammatory cycle in psoriasis, allude to a more intricate immune reaction involving T-cell differentiation pathways.

The findings suggest that the accumulation of immune cells in the skin of psoriasis patients may be due not just to the migration of immune cells from the bloodstream, but also to an in-situ T cell activation or re-activation. This could lead to the creation of localized clusters of lymphoid tissue that resemble traditional lymphoid follicles, called tertiary lymphoid organs (TLOs), commonly seen in tissues affected by long-term inflammation. Indeed, these structures have been noted in the inflamed tissues of people with conditions like rheumatoid arthritis, Hashimoto's thyroiditis, and in those who have received organ transplants (Khairutdinov et al., 2017).

TLOs resemble the organized lymphoid follicles found in secondary lymphoid organs and are composed of various immune cells, including B cells, T cells, and dendritic cells; however, unlike conventional lymph nodes, TLOs are not surrounded by a protective capsule, allowing for direct interaction with nearby tissues.

In the skin samples we examined, our initial observations highlighted an increased presence of both B and T cells in the dermal papillae, in particular naive and memory T cells in close proximity, exclusively in areas affected by psoriasis. Indeed, the presence of B cells could indicate local presentation of antigens to T cells; in particular their interacting with both naive and memory T cells, could imply a broad adaptive immune response. Such cellular interactions, generally indicative of organized immune responses, could point to confirmation of the existence of localized zones of immune activity similar to TLOs within the psoriatic skin.

Conclusions and limitations

In conclusion, our preliminary findings have relevant translational aspects suggesting that early targeted systemic treatment, especially with biologics targeting the IL-23/Th17 axis, might not just lead to quicker symptom resolution but may alter the natural history of the disease, leading to longer remission periods and possibly reduced risks for comorbidities.

Moreover, our study provides valuable insights into the role of skin as a potential tertiary lymphoid organ in psoriasis and the unique lymphocyte subpopulation characterized by both naïve and memory markers.

However, the notable limitations, in particular, the relatively small sample size and the drop-out rate of patients at the T3, imply that future studies with larger sample sizes and longer follow-up periods are necessary to confirm our findings and further elucidate the potential benefits and mechanisms behind early targeted treatment in psoriasis. Furthermore, to strengthen the robustness and validity of our findings, further research employing a wider array of techniques is necessary: among them, we envision in the very next future to further profile patient skin specimens by single-cell multiomics and multiplexed imaging.

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