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ROLL STANLEY BEAUGE

**Assessment of JAK1, JAK2, IL6 and IL6 receptor pathway gene expression in peripheral mononuclear cells of patients with severe psoriasis and treatment failure.**

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Dissertation presented to the Postgraduate Program in Molecular Pathology, at the University of Brasilia as a partial requirement for obtaining the title of Master in Molecular Pathology. Area of concentration: Health Science

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RESUMO

**Titulo :** Avaliação da expressão gênica das vias dos receptores JAK1, JAK2, IL6 e IL6 em células mononucleares periféricas de pacientes com psoríase grave e falha no tratamento.

**Introdução:** A psoríase é uma doença crônica de pele que afeta aproximadamente 2% da população mundial. A causa exata da psoríase permanece desconhecida, mas acredita-se que resulte de uma combinação de fatores genéticos, imunológicos e ambientais. Uma das características principais da psoríase é a produção anormal de citocinas, tanto de forma sistêmica quanto nas lesões cutâneas. No entanto, o processo inflamatório subjacente ainda não é totalmente compreendido.

**Objetivos:** Nosso principal objetivo foi avaliar o papel da IL-6, IL-6R e da ativação de JAK1 e JAK2 na fisiopatologia da psoríase e no fracasso terapêutico.

**Métodos:** De 1º de julho de 2023 a 30 de junho de 2024, incluímos consecutivamente pacientes com psoríase que frequentavam a clínica especializada em psoríase da Universidade de Brasília, Brasil (Hospital Universitário de Brasília). Após a consulta clínica, coletamos sangue total e separamos células mononucleares do sangue periférico (PBMCs) usando o gradiente de Ficoll. A quantificação relativa (QR) da expressão gênica de interleucina (IL) 6, receptor de IL-6 (R), Janus quinase (JAK) 1 e JAK 2 foi medida. Utilizamos modelos de regressão linear multivariada e técnicas de clusterização com o objetivo de relacionar os níveis dos mediadores às características clínicas dos pacientes estudados.

**Resultados:** Não houve associação entre nenhuma característica clínica, incluindo valores de PASI, e a expressão gênica QR de JAK1, JAK2 e IL-6. Por outro lado, encontramos associações entre a expressão gênica de IL-6R e certas características clínicas. Nosso modelo de regressão linear mostrou que a QR de IL-6R estava negativamente relacionada ao envolvimento genital (coeficiente de regressão linear (RL) = -108,26; valor de p = 0,030) e positivamente relacionada ao PASI > 10 (coeficiente de RL = 137,15; valor de p = 0,029).

**Conclusões:** Considerando o objetivo geral do presente estudo, apesar da sinalização de JAK estar relacionada a várias doenças inflamatórias, nenhuma relação direta foi encontrada entre a expressão gênica de IL-6, JAK1 e JAK2 com o fracasso terapêutico na psoríase. No modelo ajustado, a expressão gênica de IL-6R foi aumentada em pacientes com Índice de Área e Gravidade da Psoríase mais alto.

**Palavras-chave:** Psoríase, Biologia Molecular, Biomarcadores, Inflamação.

## ABSTRACT

**Title :** Assessment of JAK1, JAK2, IL6 and IL6 receptor pathway gene expression in peripheral mononuclear cells of patients with severe psoriasis and treatment failure.

**Introduction**: Psoriasis is a chronic skin disease affecting approximately 2% of the world's population. The exact cause of psoriasis remains unknown, but it is believed to result from a combination of genetic, immune, and environmental factors. One of the primary features of psoriasis is the abnormal production of cytokines, both systematically and within skin lesions. However, the underlying inflammatory process is not yet fully understood.

**Objectives:** Our main objective was to evaluate the role IL-6, IL-6R and the activation of JAK1 and JAK2 in the physiopathology of psoriasis and therapeutic failure.

**Methods :** From July 1, 2023, to June 30, 2024, we consecutively included psoriasis patients attending the specialized psoriasis clinic at the University of Brasília, Brazil (University Hospital of Brasília). After clinical consultation, we collected total blood and separated peripheral blood mononuclear cells (PBMCs) using Ficoll gradient. The relative quantification (RQ) of the gene expression of interleukin (IL) 6, IL-6 receptor (R), Janus kinase (JAK) 1 and JAK 2 were measured. We used multivariate linear regression models and clusterization technics aiming to relate mediator levels to clinical characteristics of patients studied.

**Results:** There were no associations between any clinical characteristics including PASI values and JAK1, JAK2 and IL-6 gene expression RQ. On the other hand, we found associations between IL-6R gene expression and certain clinical characteristics. Our linear regression model showed that IL-6R RQ was negatively related to genital involvement (Linear regression (LR) coefficient = -108.26; p- value = 0.030) and positively related to PASI > 10 (LR coefficient = 137.15; p-value = 0.029).

**Conclusions:** Considering the overall objective of the present study, despite JAK signaling being related to various inflammatory diseases, no direct relationship was found between the gene expression of IL-6, JAK1, and JAK2 with therapeutic failure in psoriasis. In the adjusted model IL-6R gene expression was upregulated in patients with hither Psoriasis Area Severity Index.

**Keywords:** Psoriasis, Molecular Biology, Biomarkers, Inflamação.

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## Acronyms and abbreviations

**BSA -** body surface area

**DLQI -** Dermatological Quality of Life Index

**IL** - Interleukin

**IL6R -** Interleukin 6 Receptor

**JAK –** Janus kinase

**PASI -** Psoriasis Area and Severity Index

**TYK2** – Tyrosine kinase 2

**UV -** Ultraviolet

## SUMMARY

# INTRODUCTION

Psoriasis is a chronic skin disease affecting approximately 2% of the world's population.(PAPP et al., 2021) The exact cause of psoriasis remains unknown, but it is believed to result from a combination of genetic, immune, and environmental factors.(GUO et al., 2023; RENDON; SCHÄKEL, 2019) One of the primary features of psoriasis is the abnormal production of cytokines, both systematically and within skin lesions. However, the underlying inflammatory process is not yet fully understood.

Recent advancements in treatment have significantly improved dermatological care for psoriasis patients. Biological drugs, in particular, have played a crucial role by offering better disease control and remarkable clinical improvement, often leading to the complete elimination of skin lesions. Today, effective oral and parenteral medications are readily available in developed countries and are increasingly accessible in developing nations.

Despite these advancements, there remains a significant need for more precise diagnostic tools and methods to assess the severity of psoriasis. Molecular biomarkers offer a promising solution in this regard. These biomarkers are measurable indicators of the severity or presence of a disease, and in the case of psoriasis, they can provide critical insights into the underlying biological processes and inflammatory mechanisms at play. The development of molecular biomarkers for psoriasis would enable early detection and accurate diagnosis, which are essential for initiating timely and appropriate treatment. Furthermore, these biomarkers could help in monitoring disease progression and response to therapy, allowing for more personalized and effective patient management. By identifying specific molecules related to the pathogenesis of psoriasis, researchers and clinicians could better understand the disease's complexity and variability among patients, leading to targeted therapies that address individual patient needs.

Incorporating molecular biomarkers into clinical practice could revolutionize the approach to psoriasis care, offering a more nuanced understanding of the disease and improving patient outcomes. As research in this area continues to evolve, it is crucial to support and invest in the development of these biomarkers to enhance the precision and efficacy of psoriasis management.

# LITERATURE REVIEW

## Epidemiology of psoriasis

Psoriasis is a chronic skin disease affecting people of all ages and ethnicities across the globe. The reported prevalence of psoriasis varies widely among different countries, with estimates ranging from 0.09% to 11.43%.(PAPP et al., 2021) This makes psoriasis a significant global health issue, with at least 100 million individuals affected worldwide.(REICH et al., 2019a)

Several regions display varying prevalence rates influenced by genetic, environmental, and socio-economic factors. For instance, Scandinavian countries report some of the highest prevalence rates of psoriasis, exceeding 8%. In contrast, Asian and African populations generally report lower prevalence rates.(BENGTSSON et al., 2018; EGEBERG et al., 2017; MADLAND et al., 2005; THEIN et al., 2022) This variability underscores the importance of contextual factors in understanding and managing psoriasis.

In Brazil, the ethnic diversity, climatic conditions, and increased life expectancy contribute to unique epidemiological characteristics of psoriasis. Geographical disparities also exist within Brazil, with higher prevalence rates observed in the South and Southeast regions compared to the Midwest, North, and Northeast regions.(ANDRADE et al., 2024; ROMITI et al., 2023) These regional differences may be influenced by varying levels of healthcare access, environmental factors, and genetic predispositions.

Psoriasis significantly impacts patients' quality of life(LANGLEY; KRUEGER; GRIFFITHS, 2005; LEE et al., 2010). The chronic and visible nature of the disease, along with its systemic implications, contributes to the physical, emotional, and social burden experienced by patients.(BRUINS et al., 2020; KORMAN et al., 2016; KURIZKY et al., 2018; LYSEN et al., 2024) Understanding the epidemiology of psoriasis on both global and national levels is crucial for developing effective public health strategies and tailored interventions. This comprehensive approach can facilitate early diagnosis, improve patient management, and ultimately enhance the quality of life for individuals living with psoriasis.

## Psoriatic Disease

Psoriasis is associated with chronic inflammation of the skin and typically occurs in genetically predisposed individuals. There are various forms of psoriasis, each differing in severity and location. Psoriasis induces an abnormal reaction in skin cell renewal.(PUIG; JULIÀ; MARSAL, 2014; RENDON; SCHÄKEL, 2019) The immune system mistakenly identifies a substance as an invader and, even after neutralizing it, continues to respond. This leads to the creation of new skin cells that reach the surface too quickly, accumulating and forming the characteristic plaques of psoriasis.

While psoriasis is often recognized for its characteristic skin lesions, psoriasis is increasingly understood as a systemic condition with a wide array of comorbidities and systemic involvements.(DUARTE et al., 2016; NALDI; MERCURI, 2010; SCHMIEDER et al., 2012) This comprehensive review explores the various ways in which psoriasis extends beyond the skin, impacting overall health and quality of life.

## The Pathophysiology of Psoriasis

Psoriasis is primarily driven by an abnormal immune response that accelerates the life cycle of skin cells. This involves the overproduction of cytokines, leading to inflammation and rapid skin cell turnover. While the skin manifestations are the most visible aspect of the disease, the underlying inflammatory processes can have widespread effects throughout the body.

## Cardiovascular Involvement

One of the most significant systemic implications of psoriasis is its association with cardiovascular diseases. Patients with psoriasis have an increased risk of developing conditions such as hypertension, myocardial infarction, and stroke.(MASSON; LOBO; MOLINERO, 2020) The chronic inflammation observed in psoriasis is believed to contribute to endothelial dysfunction and atherogenesis, thereby elevating cardiovascular risk.(ORLANDO et al., 2022) Studies have shown that the risk of cardiovascular events is particularly high in patients with severe psoriasis, underscoring the need for comprehensive cardiovascular risk assessment and management in these individuals.

## Metabolic Syndrome

Metabolic syndrome, characterized by a cluster of conditions including hypertension, dyslipidemia, insulin resistance, and obesity, is more prevalent in psoriasis patients.(HAO et al., 2021; WU et al., 2022) The chronic inflammation associated with psoriasis can lead to insulin resistance and altered lipid metabolism, contributing to the development of metabolic syndrome.(FITZGERALD et al., 2021; GISONDI et al., 2018; OCAMPO; GLADMAN, 2019) This association highlights the importance of monitoring metabolic health and implementing lifestyle interventions to mitigate these risks in psoriasis patients.

## Psoriatic Arthritis

Psoriatic arthritis (PsA) is a common comorbidity in psoriasis patients, affecting approximately 30% of individuals with the skin disease. PsA is a chronic inflammatory arthritis that can lead to joint damage and disability if not appropriately managed. It typically presents with symptoms such as joint pain, stiffness, and swelling, and can affect any joint in the body.(OCAMPO; GLADMAN, 2019) Early diagnosis and treatment of PsA are crucial to prevent joint damage and improve patient outcomes.

## Gastrointestinal Involvement

Psoriasis has been linked to various gastrointestinal conditions, including inflammatory bowel disease (IBD), such as Crohn's disease and ulcerative colitis.(ROGLER et al., 2021) The shared inflammatory pathways and genetic predispositions between psoriasis and IBD suggest a common underlying mechanism.(FU; LEE; CHI, 2018) Patients with psoriasis should be monitored for gastrointestinal symptoms, and appropriate referrals to gastroenterologists should be made for further evaluation and management.

## Psychological and Psychiatric Implications

The psychological burden of psoriasis is substantial, with patients often experiencing significant distress, anxiety, and depression.(AMANAT; SALEHI; REZAEI, 2018; MAREK-JOZEFOWICZ et al., 2022) The visible nature of the skin lesions can lead to social stigma, low self-esteem, and impaired quality of life. Additionally, the chronic nature of the disease and the associated comorbidities can exacerbate psychological stress. It is essential to address the psychological aspects of psoriasis through supportive care, counseling, and, when necessary, pharmacological interventions.

### Renal and Hepatic Involvement

Emerging evidence suggests that psoriasis may be associated with an increased risk of renal and hepatic diseases.(KAFTAN et al., 1996; REN et al., 2017) Chronic inflammation and the use of certain systemic medications for psoriasis management can contribute to renal and hepatic dysfunction. Regular monitoring of renal and hepatic function is recommended for psoriasis patients, particularly those on long-term systemic therapy.

## Respiratory System Involvement

Patients with psoriasis have been found to have a higher prevalence of chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD).(ISHIKAWA et al., 2019; TAKESHITA et al., 2017) The systemic inflammation observed in psoriasis may contribute to the pathogenesis of these respiratory conditions. Screening for respiratory symptoms and appropriate referrals to pulmonologists are recommended for patients with psoriasis.

Psoriasis is a complex, multi-faceted disease with significant systemic involvement. The impact of psoriasis extends far beyond the skin, affecting cardiovascular health, metabolic function, joints, gastrointestinal tract, psychological well-being, and other organ systems. A comprehensive approach to psoriasis management is essential, incorporating regular screening for comorbidities, interdisciplinary care, and individualized treatment plans. By understanding and addressing the systemic aspects of psoriasis, healthcare providers can improve patient outcomes and enhance the quality of life for individuals living with this chronic disease.

## Skin manifestations

There are several types of psoriasis according to skin manifestations

## Psoriasis vulgaris

Psoriasis vulgaris, also known as plaque psoriasis, is the most common form of psoriasis.(REICH et al., 2019b) It typically presents as raised, red patches covered with a silvery white buildup of dead skin cells or scale. These plaques often develop on the scalp, elbows, knees, and lower back, but can appear on any part of the body. The severity of psoriasis vulgaris can vary significantly from one person to another, with some experiencing only minor symptoms and others suffering from extensive skin involvement that impacts their daily lives (Figure 1).

**Figure 1.** A typical case of plaque psoriasis (Source : The author).

The plaques associated with psoriasis vulgaris may be itchy and painful, and they can crack and bleed, leading to further discomfort and potential infection. The condition is characterized by periods of flare-ups and remission, with symptoms sometimes triggered by factors such as stress, infections, medications, and environmental changes. Psoriasis vulgaris is also associated with several comorbid conditions, including psoriatic arthritis, cardiovascular disease, and metabolic syndrome.

Diagnosis of psoriasis vulgaris is primarily clinical, based on the characteristic appearance of the skin lesions. In some cases, a skin biopsy may be performed to rule out other conditions with similar presentations.

### Multiple or Drop Psoriasis

This form presents as well-defined red plaques covered with whitish scaling skin. The size of the lesions varies, with smaller, rounded spots referred to as drop psoriasis, which can progress to larger plaques. Commonly affected areas include the elbows, knees, lower back, scalp, and nails.

### Scalp Psoriasis

In some cases, psoriasis affects only the scalp, with plaques forming in various parts of the skull or covering the entire scalp, also known as seborrheic helmets.

### Nail Psoriasis

Known as unguental psoriasis, this type causes slight punctiform deformities or thickening under the nail, leading to loss of transparency and potential thickening of the underlying skin

### Reverse Psoriasis

This form affects folded areas such as the interstitial folds, inguinal folds, axillary holes, under the breasts, and the navel. The lesions are inflammatory but typically do not scale much.

## Palmoplantar Psoriasis

Affects the palms of the hands and soles of the feet, causing very thick skin that may crack, referred to as keratoderma.

**Figure 2.** A case of plantar psoriasis (Source : The author).

## Pustular Psoriasis

Yellowish pustules localized on the palms and soles or generalized throughout the body, potentially affecting walking and manual work. In severe cases, it can alter the patient's general condition and risk life's prognosis.(HOEGLER et al., 2018; SAGGINI; CHIMENTI; CHIRICOZZI, 2014)

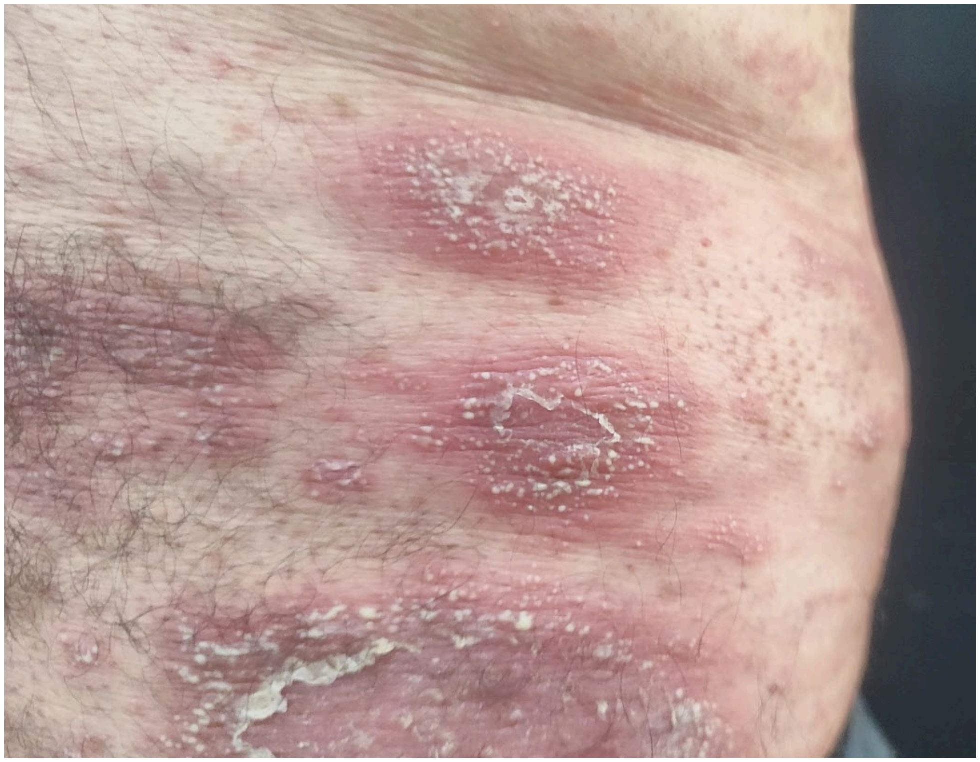

**Figure 3.** A case of pustular psoriasis (Source : The author).

## Diagnosis

The diagnosis of psoriasis is primarily clinical based on the appearance of lesions. In rare forms, a skin biopsy may be performed. Associated pathologies, such as type 2 diabetes, lipid abnormalities, or liver function anomalies, may also be investigated. Confusion with other conditions is possible, including: seborrheic dermatitis, secondary syphilis, eczema. A biopsy can help confirm the diagnosis but it is not mandatory in all cases.

## Treatment

Psoriasis is a chronic condition with no definitive cure. Effective management involves addressing both the physical symptoms and the psychological impact of the disease. Depending on the type, extent, and severity of the lesions, various treatment options are available.(MINISTÉRIO DA SAÚDE DO BRASIL, 2020)

## Topical Treatments

For common, small-scale psoriasis, the primary treatment is the application of anti-inflammatory corticosteroids in the form of ointments, lotions, or creams. These are often combined with topical salicylic acid, which has keratolytic properties.(MINISTÉRIO DA SAÚDE DO BRASIL, 2020)

Other topical treatments include:

- Coal tar and dithranol - Known for their efficacy but can be very messy and stain clothing and skin.
- Vitamin D analogues - Calcipotriol and tacalcitol are kerato regulating agents used in topical applications.
- Retinoid derivatives - Tazarotene helps inhibit the excessive proliferation of skin cells. This medication is not available in Brazil.
- Topical calcineurin inhibitors - Tacrolimus and pimecrolimus can be used for sensitive areas like the face and flexures

## Phototherapy

In cases of extensive psoriasis, phototherapy is a common first-choice treatment. This involves exposure to ultraviolet (UV) light. Options include:

- PUVA Therapy - Combines oral or topical psoralen (a light-sensitizing medication) with UVA light exposure.

- UVB Therapy - Uses narrowband UVB light, which is less intense and doesn't require sensitizing agents.

Oral administration of retinoids, such as acitretin, during phototherapy can reduce the required UV dose for remission.

## Oral Treatments

For severe psoriasis, oral medications are considered. These include:

- Retinoids - Acitretin is effective for pustular psoriasis but has teratogenic risks.
- Antimetabolites - Methotrexate suppresses immune system activity and slows cell growth.
- Immunosuppressants - Cyclosporine can be used to reduce immune system activity and inflammation.
- Deucravacitinib - This is the first small-molecule approved for the treatment of psoriasis in Brazil.(CATLETT et al., 2022; STROBER et al., 2023)

## Biological Treatments

Biologicals are advanced medications targeted at specific mediators of psoriasis pathogenesis.

- TNF-alpha inhibitors - Etanercept, infliximab, and adalimumab reduce inflammation caused by psoriasis.(GOTTLIEB et al., 2021)

- Interleukin inhibitors - Ustekinumab targets IL-12 and IL-23, while secukinumab, brodalumab, bimekizumab and ixekizumab target IL-17.(GLATT et al., 2021; MÖSSNER; PINTER, 2020)
- IL-23 inhibitors – Guselkumab, risankizumab and tildrakizumab target the IL-23 pathway.(CROWLEY et al., 2022; REICH et al., 2019b)

Biological treatments often produce significant and rapid improvements in symptoms. However, they are expensive and require careful monitoring for infections and other adverse effects. With a comprehensive understanding of these treatments, healthcare providers can tailor therapies to individual needs, optimizing outcomes for those living with psoriasis.(MENG et al., 2014; NO et al., 2018)

## The JAK-STAT Pathway in Human Inflammation

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway is a critical signaling mechanism in the human body, playing a fundamental role in various physiological and pathological processes, including immune response and inflammation. The JAK-STAT pathway comprises three main components: cytokines, Janus kinases (JAKs), and signal transducers and activators of transcription (STATs).(CIOBANU et al., 2020; HU et al., 2023) Cytokines are signaling molecules that facilitate communication between cells, particularly in immune responses. Key cytokines involved in the JAK-STAT pathway include interleukins, interferons, and growth factors. JAKs are a family of intracellular, non-receptor tyrosine kinases that include JAK1, JAK2, JAK3, and TYK2.(BANERJEE et al., 2017;

LENSING; JABBARI, 2022; MIOT et al., 2023a) These kinases are activated by cytokines binding to their respective receptors on the cell surface. STATs are a family of transcription factors activated by JAKs. There are seven STAT proteins: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6, each with distinct roles in mediating cellular responses to cytokines.(HU et al., 2021; HUANG et al., 2022)

The JAK-STAT pathway is initiated when a cytokine binds to its cell surface receptor, causing receptor dimerization. This dimerization brings JAKs into proximity, leading to their mutual phosphorylation and activation. Activated JAKs then phosphorylate specific tyrosine residues on the receptor, creating docking sites for STAT proteins. STATs bind to these phosphorylated residues, are subsequently phosphorylated by JAKs, and form dimers. These activated STAT dimers translocate to the nucleus, where they bind to specific DNA sequences to regulate gene transcription.(HU et al., 2021; XIN et al., 2020)

The JAK-STAT pathway plays a pivotal role in modulating the immune response and inflammation. Here are key aspects of its involvement: The JAK-STAT pathway influences the differentiation and function of various immune cells, including T-helper (Th) cells. For example, IL-12 activates STAT4 to promote Th1 cell differentiation, while IL-4 activates STAT6 to promote Th2 cell differentiation. Activated STATs regulate the transcription of genes involved in inflammation, such as those encoding cytokines, chemokines, and acute-phase proteins. This regulation is crucial for mounting an effective immune response.(CIOBANU et al., 2020)

Aberrant activation of the JAK-STAT pathway is implicated in various inflammatory diseases, including rheumatoid arthritis, psoriasis, and inflammatory bowel disease. For instance, excessive STAT3 activation is associated with chronic inflammation and autoimmunity.(CIOBANU et al., 2020; HU et al., 2023)

## Therapeutic Targeting of the JAK-STAT Pathway

Given its central role in inflammation, the JAK-STAT pathway is a promising target for therapeutic intervention. JAK inhibitors, such as tofacitinib and baricitinib, have shown efficacy in treating various inflammatory diseases by modulating this pathway.(BANERJEE et al., 2017)

## JAK Inhibitors

JAK inhibitors are small molecules that inhibit the activity of one or more JAKs, thereby blocking the downstream signaling of pro-inflammatory cytokines. These inhibitors have been approved for the treatment of conditions such as rheumatoid arthritis and psoriasis. The use of JAK inhibitors has revolutionized the management of inflammatory diseases.(MIOT et al., 2023a) However, careful monitoring is required due to potential side effects, including increased risk of infections and malignancies. The JAK-STAT pathway is a crucial mediator of immune response and inflammation. Understanding its components, mechanisms, and role in disease has paved the way for targeted therapies that offer significant benefits for patients with inflammatory conditions. Ongoing research continues to unravel the complexities of this pathway, promising new insights and therapeutic opportunities for managing inflammation.

## The JAK-STAT Pathway in Psoriasis

Psoriasis is driven by a complex interplay of immune cells and cytokines, with the JAK-STAT pathway playing a central role in mediating inflammatory signals.(DRAGOTTO et al., 2024; FORTUNES CU et al., 2024; MEGNA et al., 2023; MIOT et al., 2023b) Key pro-inflammatory cytokines involved in psoriasis pathogenesis include:

- Interleukin-6 (IL-6): IL-6 is a multifunctional cytokine that modulates immune responses and promotes inflammation. It activates the JAK-STAT pathway, particularly through JAK1 and JAK2, driving the expression of inflammatory genes.
- Interferon-gamma (IFN-γ): IFN-γ is produced by Th1 cells and activates JAK1 and JAK2, leading to STAT1 activation. It plays a crucial role in amplifying the inflammatory response in psoriasis.
- Interleukin-23 (IL-23): IL-23 is essential for the differentiation and maintenance of Th17 cells, which produce IL-17, a key cytokine in psoriasis. IL-23 signals through JAK2 and TYK2, activating STAT3 and contributing to inflammation and keratinocyte proliferation.

The interaction of these cytokines with their receptors and subsequent activation of the JAK-STAT pathway leads to the production of inflammatory mediators, recruitment of immune cells, and hyperproliferation of keratinocytes, all hallmark features of psoriasis.(MEGNA et al., 2023)

## Interleukin 6 in psoriasis

IL-6 is a multifunctional cytokine that plays critical roles in immune response modulation, inflammation, and tissue homeostasis. Produced by various cell types, including T cells, B cells, macrophages, fibroblasts, and keratinocytes, IL-6 is involved in both acute and chronic inflammatory responses.(ALVES et al., 2023; MORAIS JUNIOR et al., 2021)

IL-6 is a pro-inflammatory cytokine produced by immune cells in response to infection, tissue damage, or inflammation. It helps initiate and regulate the immune response by promoting the production of other cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-alpha), which play roles in inflammation and immune cell activation. In psoriasis, elevated levels of IL-6 contribute to the inflammatory environment and the activation of Th17 cells, which are crucial in the pathogenesis of the disease.

IL-6 influences keratinocyte behavior, promoting their proliferation and inhibiting their differentiation. This abnormal keratinocyte activity contributes to the characteristic thick, scaly plaques seen in psoriasis. By affecting keratinocyte function, IL-6 plays a direct role in the hyperproliferative aspect of the disease. IL-6 promotes angiogenesis, the formation of new blood vessels, which is a feature of psoriatic lesions. This angiogenesis supports the increased metabolic demands of the proliferating keratinocytes and contributes to the redness and swelling of the plaques.(BLAUVELT, 2017; TANAKA et al., 2020)

IL-6 binding to its receptor (IL-6R) leads to the activation of JAK1 and JAK2. These are kinases that phosphorylate STAT3, which dimerizes and translocates to the nucleus. In the nucleus, STAT3 regulates the expression of genes involved in inflammation, cell survival, and proliferation, contributing to the pathogenesis of psoriasis.

The interaction between IL-6 and the JAK-STAT pathway creates a feedback loop that perpetuates the inflammatory environment in psoriasis. Elevated levels of IL-6 activate the JAK-STAT pathway, leading to increased expression of inflammatory genes and further production of IL-6. This cycle contributes to the chronicity and severity of the disease. IL-6 interacts with other cytokines, such as IL-23 and TNF-alpha, to amplify the inflammatory response in psoriasis. The combined action of these cytokines through the JAK-STAT pathway leads to the activation of various immune cells, including Th17 cells, which are central to the disease's pathology.(GOODMAN et al., 2009; NIE et al., 2016; XU et al., 2021)

# OBJECTIVES

## General Objective

Our main objective was to evaluate the role IL-6, IL-6R and the activation of JAK1 and JAK2 in the physiopathology of psoriasis and therapeutic failure.

## Specific objectives

- Conduct a demographic assessment of patients with psoriasis treated at the University Hospital of Brasília, University of Brasília, Brazil.
- Validate the study of IL-6 and IL-6R gene expression in the Dermatomycology Laboratory, Faculty of Medicine at the University of Brasília.
- Relate JAK1 gene expression with the clinical characteristics of psoriasis.
- Relate JAK2 gene expression with the clinical characteristics of psoriasis.
- Relate IL-6 gene expression with the clinical characteristics of psoriasis.
- Relate IL-6R gene expression with the clinical characteristics of psoriasis.
- Evaluate whether the quantification of gene expression of JAK1, JAK2, IL-6, and IL-6R can be used as markers of psoriasis severity.

# JUSTIFICATION

Understanding the role of IL-6, IL-6R, and the JAK1 and JAK2 pathways in psoriasis is crucial for several reasons. IL-6 is a cytokine involved in the inflammatory response and has been found to be elevated in psoriatic lesions. By studying the expression levels of IL-6 and its receptor, IL-6R, we can better understand the mechanisms that drive inflammation in psoriasis and identify potential therapeutic targets.

Similarly, the JAK1 and JAK2 pathways are critical in transmitting signals from cytokine receptors to the nucleus of cells, leading to the activation of genes involved in inflammation. Dysregulation of these pathways can contribute to the pathogenesis of psoriasis. By examining the gene expression of JAK1 and JAK2, we can identify how these pathways are altered in psoriasis patients and explore new avenues for targeted therapy.

Studying the gene expression of IL-6, IL-6R, JAK1, and JAK2 in psoriasis patients is important for several reasons:

- Improved Understanding of Disease Mechanisms: By analyzing the expression levels of these genes, we can gain insights into the molecular mechanisms that drive the chronic inflammation seen in psoriasis.
- Identification of Biomarkers: The quantification of IL-6, IL-6R, JAK1, and JAK2 gene expression may help identify biomarkers that can predict disease severity and therapeutic responses, leading to more personalized treatment approaches.
- Development of Targeted Therapies: Understanding the role of these genes in psoriasis can facilitate the development of targeted therapies that specifically inhibit these pathways, potentially leading to more effective and less toxic treatments.

In summary, the study of IL-6 and JAK gene expression in psoriasis is essential for advancing our knowledge of the disease's pathogenesis, improving patient outcomes, and developing novel therapeutic strategies.

# METHODS

## Population

From July 1, 2023, to June 30, 2024, we consecutively included psoriasis patients attending the specialized psoriasis clinic at the University of Brasília, Brazil (University Hospital of Brasília). We included patients diagnosed with psoriasis who have been regularly followed up at the service for more than one year.

After signing an informed consent form, all patients underwent a specialized consultation for data collection. The collected data included demographic and clinical information related to psoriasis, as well as measurements of psoriasis characteristics and severity. The Psoriasis Area Severity Index (PASI) was considered the main method for evaluating psoriasis severity. We also used the Dermatology Life Quality Index (DLQI) to measure the impact of psoriasis in the quality of life of each included patient.

## Clinical samples

After clinical consultation, we collected 20 ml of total blood collected by cubital puncture and was inserted into 2 heparin tubes. Immediately after collection, the human peripheral blood mononuclear cells PBMC was isolated using a Ficoll gradient. The samples were stored in RNA later at -80 degrees until the RNA extraction took place up to 1 month after sampling.

## Peripheral blood mononuclear cells (PBMC) separation

1. Collection tubes were centrifuged at 1,9 g, 22ºC for 10 minutes.
2. After centrifugation, the heparinized plasma was separated with the aid of a 10mL serological pipette.
3. Remaining blood was diluted and homogenized in 1:1 in Gibco® incomplete RPMI.
4. The content was applied using a 10mL serological pipette, using half (2:1 ratio) of the volume of a Ficoll-Hypaque (1077) solution at room temperature, already distributed in 50mL (polypropylene conical tubes.
5. Tubes were centrifuged at 680g for 40 minutes at 22ºC, with low acceleration and deceleration
6. RPMI supernatant was removed and discarded. The ring of mononuclear cells were then removed with the help of a glass Pasteur pipette and transferred to a 15mL polypropylene conical tube.
7. Up to 14mL of incomplete RPMI were added and gently homogenized by inversion and centrifuged at 400g for 7 minutes at 4ºC (1st wash). This procedure was repeated 2 times.
8. Cell pellets, were resuspended in 1mL of incomplete RPMI and stored in RNA*later* Stabilization Solution (Thermo Fisher Scientific, Waltham, United States) and stored at -80 until RNA extraction.

## Analysis of the quantification of gene expression

The total PBMC RNA was extracted using the native protein purification kit mirVanaTM PARIS RNA (Thermo Fisher Scientific, Waltham, United States). Immediately after extraction, complementary DNA (cDNA) was formed using the high-capacity reverse cDNA transcription kit (Thermo Fisher Scientific, Waltham, United States). A reverse transcription reaction was performed in a T100 Thermal Cycler (BIO RAD, Hercules, United States).

Messenger RNA (mRNA) expression analysis was performed using Taqman-based probes (Thermo Fisher Scientific, Waltham, USA) labelled with 5' (MGB) minor cave liaison probes and a 3' non-fluorescent burner. (MGB). According to the decision of a specialist, we have selected a pool of cytokines described as involved in the pathogenesis of psoriasis and, also, mediators that can regulate inflammation. We have measured the genetic expression of JAK1 (Catalog Number (CN): Hs01026983_m1), JAK2 (CN : Hs 01078136_ m1), IL-6 (CN : Hs00174131_m1) and IL-6R (CB : Hs01075664_m1). As endogenous controls, we tested 3 target candidates: glyceraldehyde-3-phosphate dehydrogenase (GAPDH; CN: Hs99999905_m1), eukaryotic RNAr 18S (18s; CN : Hs 99999901_s1) and actin beta (ACTB; CN:: Hs9999903_m1). After comparing the performance of qPCR, GAPDH was chosen as endogenous reaction control.

The reactions were carried out in a Thermocycler Quantstudio 5 (Thermo Fisher Scientific, Waltham, United States). The reaction was initiated at 50 °C for 2 minutes (UNG incubation), followed by 95°C for 10 minutes (polymerase activation) followed with 40 95 °C PCR cycles for 15 seconds (denature) and 60 °C cicles for 60 seconds (anneal/extend). The reactions were carried out in a final volume of 15 µl including 1x TaqMan TM Gene Expression Master Mix (Thermo Fisher Scientific, Waltham, USA), 0.75 µl of manufactured Taqman probes, 2 µl cDNA sample of each patient and ultra-pure water. All samples were tested in triplicates. For normalization, we used a reference sample (calibrator) formed from a pool of total RNA extracted from PBMCs of 20 healthy controls. All samples were also evaluated for false positive amplifications.

For the comparison of the quantification of gene expression, we used the comparative method Ct (ΔΔCt). Calculations were performed in the Applied BiosystemsTM analysis software (Thermo Fisher Scientific, Waltham, United States). We only looked at reactions with Cq values of at least 35 and satisfactory proximity between the replicates to be included in the quantification analysis.

## Statistical analysis

Demographic, clinical and laboratory data were compiled. Frequencies were analyzed using the Chi-square test or its exact version. Numerical variables were compared to clinical characteristics using the Student t test or the Wilcoxon signed test. RQ gene expression values were expressed using mean values and an interquartile range (IQR). An attempt was made to detect clinical groups using clustering models (Dendrograms). An exploratory linear regression model was carried out where the RQ value of all gene expressions evaluated was adjusted for sex, age, scalp involvement, genital involvement and PASI > 10.

The statistical significance was considered to be $p < 0.05$ and a 95% confidence interval. The clinical relevance of gene expression was taken into account when the groups had a minimum difference in RQ of 2x. The R program version 4.1.2 (R Core Team 2021) was used for the analysis.

## Ethics

All patients were included after signing the informed consent form. This study is in line with the Helsinki Declaration and has been approved by the Ethics Committee of the Faculty of Medicine of the University of Brasilia (CAAE: 68068323.3.1001.5558).

# RESULTS

We included 58 psoriasis patients 33 (56.90%) of patients were women. Twelve patients presented a PASI >10 and were considered as presenting therapeutic failure. Higher PASI scores were significantly linked to poor quality of life (higher DLQI); scalp involvement and genital involvement (Table 1).

**Table 1:** Demographic characteristics of patients with psoriasis included according to the classification of the Psoriasis Area Severity Index (PASI).

| | PASI>10<br>n = 22 | PASI≤10<br>n = 46 | p value |
|---|---|---|---|
| Sex | | | 0.101 |
| Male | 8 | 17 | |
| Female | 4 | 29 | |
| Age median (IQR) | 42.50(21.50) | 50.5(19.75) | 0.047 |
| DLQI median (IQR) | 12.50(14.50) | 1.0(8.00) | 0.002 |
| IMC | 27.42(92.64) | 28.61(73.89) | 0.796 |
| Nail involvement | 6 | 11 | 0.158 |
| Scalp involvement | 9 | 8 | <0.001 |

| | | | |
|---|---|---|---|
| Genital involvement | 7 | 6 | 0.003 |
| Smoking | 1 | 5 | 1.000 |
| Alcohol abuse | 2 | 6 | 0.665 |

**Table 2.** Relative quantification of gene expression (RQ) expressed in median values (interquartile range) in subgroups of patients with psoriasis area severity index (PASI) greater than 10.

| | PASI>10 | PASI≤10 | p value |
|---|---|---|---|
| JAK1 | 4.84(2.13) | 3.41(3.14) | 0.278 |
| JAK2 | 2.67(4.11) | 3.16(2.35) | 0.712 |
| IL-6 | 5.35(4.12) | 6.02(3.74) | 0.602 |
| IL-6R | 1.39(4.01) | 0.44(3.02) | 0.109 |

## Dendrogram

To construct the dendrogram, adjusted clustering techniques were used for all expressions analyzed. The dendrogram has not clearly separated patients by PASI classification or other clinical characteristics measured in this study, but we can identify two endotypic response patterns at the left and right end of the heatmap. (Figure 1). On the left side of the heatmap, we can observe a group of patients with relatively higher expressions of JAK1, JAK2 and IL-6 gene expression RQ.

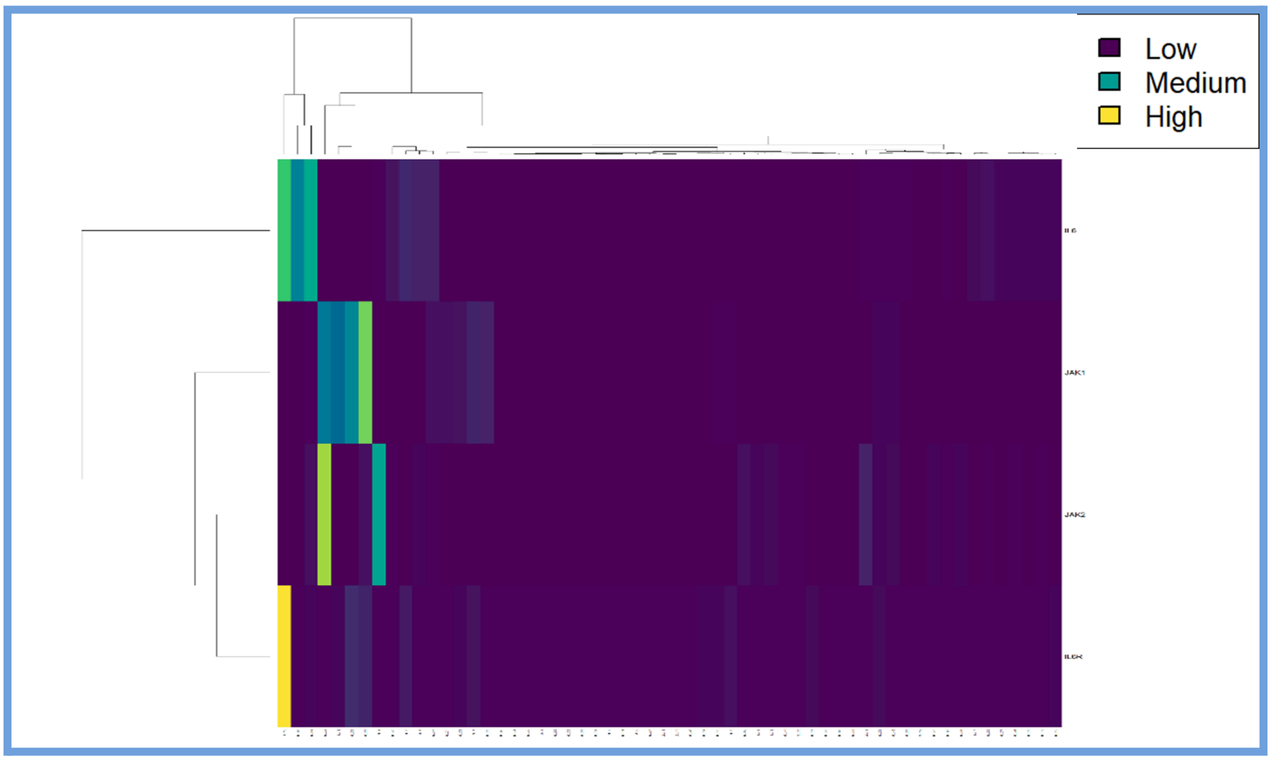


**Figure 4:** Heatmap of the level of gene expression expressed by the included patients.

## Linear regression model results

There were no associations between any clinical characteristics including PASI values and JAK1, JAK2 and IL-6 gene expression RQ. On the other hand, we found associations between IL-6R gene expression and certain clinical characteristics. Our linear regression model showed that IL-6R RQ was negatively related to genital involvement (Linear regression (LR) coefficient = -108.26; p- value = 0.030) and positively related to PASI > 10 (LR coefficient = 137.15; p-value = 0.029)(Table 3).

**Table 3:** Linear regression model on the interaction of relative quantification (RQ) of IL-6R gene expression adjusted for sex, age, scalp involvement, genital involvement and psoriasis area severity index (PASI) greater than 10.

| IL-6R | Coefficient | Adjusted p value |
| --- | --- | --- |
| Sex | 55.71 | 0.115 |
| Âge | 2.39 | 0.084 |
| Scalp involvement | 69.48 | 0.093 |
| Genital involvement | -108.26 | 0.030* |
| PASI>10 | 137.15 | 0.029* |

Subsequently, an attempt was made to use the median value of IL-6R dosage in the entire population as a cutoff point to identify patients with genital involvement (p = 1.000) or with PASI > 10 (p = 0.103), but the results were not significant (Table 4)

# DISCUSSION

Psoriasis is a multifactorial disease in which environmental stimuli affect genetically predisposed individuals. This association generates a complex inflammatory dysregulation that is still partially understood. Several signaling pathways are active in psoriasis, including a synergistic action of innate and adaptive immunity. However, the IL-6 activation pathway is a very important pathway for the inflammatory homeostasis of psoriasis and high levels of IL-6 have already been widely described in patients with psoriasis.(ALVES et al., 2023; GOODMAN et al., 2009; XU et al., 2021) Despite this, this cytokine appears to have a role parallel to the main inflammatory axis of psoriasis, which consists of inhibiting the Th17 response with the stimulation of keratinocytes by IL-17.(BLAUVELT, 2017; SAGGINI; CHIMENTI; CHIRICOZZI, 2014)

Even so, it is important to study all the inflammatory pathways of psoriasis as this study has several uses. In addition to researching new treatments and understanding the pathophysiology of the disease, these studies can play a role in recognizing inflammatory patterns and early recognition of serious cases. This recognition can help the clinical team to treat early or intercept complications of psoriasis.

The present study began with the clinical assessment of patients. Studies show that the main method of assessing the severity of psoriasis is the size of the affected body surface and the activity of the lesions. For this reason, PASI is always used in clinical trials. Other forms, such as psoriasis of special areas, are also considered serious forms, as they greatly affect patients' quality of life. In this study, as expected, severe forms of psoriasis with genital and scalp involvement were also associated with a PASI greater than 10.

Recently Alves et al. 2024 found that elevated baseline IL-6 levels measured by flow cytometry assay are a significant predictor of treatment interruption in patients with moderate to severe psoriasis. Specifically, patients with higher IL-6 levels at the start of the study had nearly double the risk of stopping their treatment prematurely (HR = 1.99; 95% CI 1.29–3.08; p = 0.002).(ALVES et al., 2023) Additionally, a poor quality of life was also identified as a predictor of treatment interruption.(ALVES et al., 2023) These findings suggest that monitoring IL-6 levels could be crucial for managing psoriasis treatment effectively.

The interleukin-6 receptor (IL-6R) plays a critical role in the inflammatory response and has a complex structure and mechanism of action.(MIHARA et al., 2012; WOLF; ROSE-JOHN; GARBERS, 2014) IL-6R is composed of two distinct protein chains: an 80 kDa IL-6 binding protein (IL-6Rα) and a 130 kDa signal-transducing component known as glycoprotein 130 (gp130 or IL-6Rβ). The IL-6 cytokine first binds to IL-6Rα, forming a complex that subsequently associates with gp130.(CAO et al., 2024; HEINRICH et al., 2003; KANG et al., 2020; UCIECHOWSKI; DEMPKE, 2020) This tripartite complex initiates intracellular signaling cascades that involve the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways, as well as the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways.

Mechanistically, once IL-6 binds to the IL-6Rα, the receptor undergoes a conformational change that allows it to dimerize with gp130, leading to the activation of JAKs.(CAO et al., 2024; DRAGOTTO et al., 2024; WOLF; ROSE-JOHN; GARBERS, 2014) These kinases then phosphorylate specific tyrosine residues on gp130, creating docking sites for STAT proteins. STAT proteins are phosphorylated, dimerize, and translocate to the nucleus, where they modulate the expression of target genes involved in inflammation, immune responses, and cell survival. Additionally, the activation of the MAPK and PI3K pathways contributes to the regulation of cell proliferation, differentiation, and apoptosis, further amplifying the inflammatory response.

IL-6R signaling is tightly regulated by various mechanisms, including the soluble form of IL-6R (sIL-6R) and negative feedback loops involving the suppressor of cytokine signaling (SOCS) proteins.(DURHAM et al., 2019; HUANG et al., 2020; SANTOS et al., 2020) The sIL-6R can bind IL-6 and facilitate its interaction with gp130 on cells that do not express membrane-bound IL-6R, thus broadening the range of IL-6-responsive cells. This phenomenon, known as trans-signaling, is particularly important in chronic inflammatory diseases.

The significance of IL-6R in inflammation is underscored by its involvement in various pathological conditions, including rheumatoid arthritis, psoriasis, and inflammatory bowel disease. Targeting IL-6R with therapeutic agents, such as monoclonal antibodies, has shown efficacy in mitigating these diseases, highlighting the receptor's pivotal role in mediating inflammatory processes.(BURMESTER et al., 2016; HAYAKAWA et al., 2019; HUGHES; CHINOY, 2013; PAPO et al., 2014; STONE et al., 2020) However medications such as tocilizumab were not clinically effective for the use in psoriasis patients. It can be probably explained by the fact that psoriasis is a multifactorial disease that is more related to cytokines such as IL-23 and IL-17 than to the general effect of the proinflammatory IL-6 pathway. (HAYAKAWA et al., 2019)

In the adjusted model the results of this study indicate a significant association between genital involvement and PASI scores greater than 10 with a downregulated and upregulated gene expression of IL-6R respectively. Although this may seem a paradoxical result once we also found that genital involvement was related to higher PASI it seems that genital psoriasis can be less dependent on IL-6R activation than severe plaque psoriasis. This is reinforced by other studies that found that IL-6 elevation can be a marker for therapeutic failure in psoriasis.

However, when the researchers attempted to use the median value of IL-6R dosage as a cutoff point for identifying patients with genital involvement or high PASI scores, the results were not significant ($p = 1.000$ for genital involvement and $p = 0.103$ for PASI > 10). This indicates that IL-6R levels alone may not be sufficient for stratifying patients based on these clinical characteristics. IL-6R plays a role in the inflammatory response, and while it has been implicated in psoriasis, its utility as a biomarker in this context appears limited based on the study's findings. This was also true when using all markers measured in this study since cluster techniques could not differentiate clinical groups.

Recent studies state that psoriasis is much more dependent on the activation of TYK2 by IL-23 that will ultimately produce high amounts of IL-17 directed to the keratinocytes. IL-6 is more related to the activation of JAK1 and JAK2 pathways that may  not be as important to psoriasis in comparison to the TYK2 pathway activation. New medications targeting the TYK2 pathway (deucravacitinib) are already approved for psoriasis. On the other hand the blocking of IL-6R with tocilizumab is not effective for psoriasis.

# CONCLUSION

Considering the overall objective of the present study, despite JAK signaling being related to various inflammatory diseases, no direct relationship was found between the gene expression of IL-6, JAK1, and JAK2 with therapeutic failure in psoriasis. In the adjusted model IL-6R gene expression was upregulated in patients with hither Psoriasis Area Severity Index.

The demographic and clinical data demonstrated that quality of life, as measured by DLQI, scalp involvement, and genital involvement were associated with greater psoriasis severity, as measured by PASI, representing a greater surface area involvement.

The analysis of gene expression for IL-6 and IL-6R was successfully standardized at the Dermatomycology Laboratory, Faculty of Medicine at the University of Brasília.

IL-6R gene expression was negatively related to genital involvement of psoriasis but positively related to a higher PASI.

Unfortunately, the attempt to use gene expressions measured here as markers of psoriasis severity was not successful.

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# Annex 1

Proof of work presented at national congress

77º CONGRESSO DA SOCIEDADE BRASILEIRA DE DERMATOLOGIA

A DERMATOLOGIA NA CIDADE DO SOL

NATAL 2024

05 A 07 DE SETEMBRO DE 2024

# Certificado

Certificamos que os autores **PAOLA BORGES ECKSTEIN CANABRAVA; ANA PAULA AVILA PINZON; LOUISE HABKA CARIELLO; KALYNNE DUARTE VARELA DANTAS; ROLL STANLEY BEAUGE; PATRÍCIA SHU KURIZKY; CIRO MARTINS GOMES** participaram do **77º CONGRESSO DA SOCIEDADE BRASILEIRA DE DERMATOLOGIA**, realizado no período de 05 a 07 de setembro de 2024 no Centro de Convenções de Natal, em Natal - RN, na qualidade de **autores** do TRABALHO **AVALIAÇÃO DA EXPRESSÃO GÊNICA DA VIA DE SINALIZAÇÃO DA TYK2 NO SANGUE PERIFÉRICO DE PACIENTES COM PSORÍASE GRAVE E PERDA DE RESPOSTA AO TRATAMENTO SISTÊMICO** na forma de apresentação **INVESTIGAÇÃO**.

Natal, 07 de setembro 2024.

Para validar este certificado, acesse: https://icongresso.sbd.itarget.com.br//certificado/auth/validar
Código de validação: i84RWNb1n6

**Regina Jales**
Presidente do 77º Congresso da SBD

**Heitor de Sá Gonçalves**
Presidente da SBD

**Francisca Regina Oliveira Carneiro**
Presidente da Comissão Científica do 77º Congresso da SBD

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