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Management of psoriasis in patients with inflammatory bowel disease

Inês Figueiredo Rodrigues dos Santos

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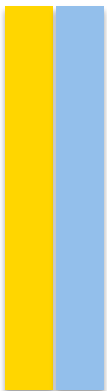

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Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto.

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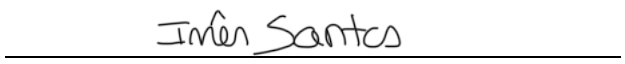

(Inês Figueiredo Rodrigues dos Santos)

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Resumo

A psoríase é uma dermatose inflamatória crónica, de natureza imunomediada, que se manifesta predominantemente ao nível cutâneo, exercendo um impacto substancial na qualidade de vida dos doentes. Encontra-se reconhecida pela Organização Mundial da Saúde como uma patologia grave e incapacitante, constituindo um desafio significativo para a saúde pública, não só pelos seus efeitos físicos, mas também pelo seu peso psicológico, social e económico. Estima-se que a sua prevalência atinja 2 a 3% da população mundial.

Esta condição encontra-se frequentemente associada a diversas comorbilidades, entre as quais se destaca a Doença Inflamatória Intestinal, um doença autoimune de caráter inflamatório que afeta o trato gastrointestinal. Esta divide-se em duas entidades clínicas principais, a Doença de Crohn e a Colite Ulcerosa e afeta aproximadamente 0,3 a 0,5% da população global.

Atualmente, diversos estudos comprovam a existência de uma associação entre a Psoríase e a Doença Inflamatória Intestinal, na medida em que partilham processos fisiopatológicos. A incidência da Doença Inflamatória Intestinal é mais elevada em indivíduos com diagnóstico de psoríase. Em contrapartida, indivíduos diagnosticados com Doença de Crohn ou Colite Ulcerosa apresentam um risco aumentado de desenvolver psoríase.

Face a esta interconexão, torna-se imperativo adotar uma abordagem terapêutica holística e multidisciplinar, centrada na gestão integrada de ambas as patologias quando coexistem num mesmo indivíduo.

Até à data, a Food and Drug Administration aprovou seis classes principais de agentes biológicos com um papel crescente no tratamento da psoríase moderada a grave: inibidores do TNF-α (etanercept, adalimumab, infliximab, certolizumab); inibidores da interleucina 17 (IL-17) (secukinumab, ixekizumab, brodalumab); os inibidores da interleucina 12/23 (ustekinumab); os inibidores da interleucina 23 (guselkumab, tildrakizumab, risankizumab), inibidores da PDE4 (apremilast) e os inibidores da TYK2 (deucravacitinib). .

Desta forma, o presente artigo tem como objetivo primordial apresentar e analisar o estado atual do conhecimento científico relativamente a estas terapêuticas, com especial enfoque no seu potencial de aplicação em doentes com diagnóstico concomitante de psoríase e doença inflamatória intestinal.

Palavras-Chave: Psoríase; Doença Inflamatória Intestinal; Doença de Crohn; Colite Ulcerosa; TNF-α ; IL -17; IL-12; IL-23; PDE4; TYK2; Infliximab; Adalimumab; Certolizumab; Etanercept; Ustekinumab; Secukinumab; Ixekizumab; Brodalumab; Guselkumab; Tildrakizumab; Risankizumab; Apremilast; Deucravacitinib.

Abstract

Psoriasis is a chronic, immune-mediated inflammatory disease that primarily affects the skin, significantly impacting patients' quality of life. The World Health Organization recognises it as a severe and disabling condition, posing a considerable challenge for public health not only because of its physical effects but also due to its psychological, social, and economic burdens. Its prevalence is estimated at 2% to 3% of the global population.

This condition is often associated with a range of comorbidities, including Inflammatory Bowel Disease, an autoimmune disorder that affects the gastrointestinal tract. It's divided into two main clinical entities, Crohn's Disease and Ulcerative Colitis, and affects approximately 0.3 to 0.5% of the global population.

Nowadays, several studies have proven the existence of an association between Psoriasis and Inflammatory Bowel Disease, as they share common pathophysiological processes. The incidence of Inflammatory Bowel Diseases is higher in individuals diagnosed with psoriasis. Simultaneously, individuals with Crohn's Disease or Ulcerative Colitis face a higher risk of developing Psoriasis.

Therefore, it is crucial to implement a holistic and multidisciplinary treatment strategy that emphasises the integrated management of both conditions when they coexist in a patient.

To this date, the Food and Drug Administration has approved six main classes of biological agents with an increasing role in the treatment of moderate to severe psoriasis: TNF-α inhibitors (etanercept, adalimumab, infliximab, certolizumab); interleukin 17 (IL-17) inhibitors (secukinumab, ixekizumab, brodalumab); interleukin 12/23 inhibitors (ustekinumab); interleukin 23 inhibitors (guselkumab, tildrakizumab, risankizumab), PDE4 inhibitors (apremilast) and TYK2 inhibitors (deucravacitinib).

In this way, the main aim of this article is to present and analyse the current state of scientific knowledge regarding these therapies, with a special focus on their potential application in the population with a concomitant diagnosis of Psoriasis and Inflammatory Bowel Disease.

Keywords: Psoriasis; Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; TNFa; IL -17; IL-12; IL-23; PDE4; TYK2; Infliximab; Adalimumab; Certolizumab; Etanercept; Ustekinumab; Secukinumab; Ixekizumab; Brodalumab; Guselkumab; Tildrakizumab; Risankizumab; Apremilast; Deucravacitinib.

List of Abbreviations

AS	Ankylosing Spondylitis
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CI	Confidence Interval
DLQI	Dermatology Life Quality Index
FAERS	FDA Adverse Event Reporting System
IBD	Inflammatory Bowel Disease
IFN-α	Interferon alfa
IFN-β	Interferon beta
IFN-γ	Interferon gamma
IL-1B	Interleukin 1 beta
IL-12	Interleukin 12
IL-12B	Interleukin 12 beta
IL-13	Interleukin 13
IL-17	Interleukin 17
IL-22	Interleukin 22
IL-23	Interleukin 23
IL-23R	Interleukin 23 Receptor
IL-5	Interleukin 5
IL-6	Interleukin 6
IL-8	Interleukin 8
IR	Incidence Rate
mDC	Myeloid dendritic cells
ORR	Objective Response Rate
PASI	Psoriasis Area and Severity Index
PDEs	Phosphodiesterases
PGA	Physician's Global Assessment
PsA	Psoriatic Arthritis
PsO	Psoriasis
sPGA	Static Physician's Global Assessment
T-reg cells	T Regulatory T Cells
TH1	T Helper 1 Cells
TH17	T Helper 17 Cells
TNF-α	Tumor Necrosis Factor-Alpha
Tyk2	Tyrosine Kinase 2
UC	Ulcerative Colitis

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Introduction

Psoriasis (PsO) is a chronic, immune-mediated inflammatory disease with predominantly cutaneous manifestations (characterised by persistent inflammation and excessive skin cell growth), which harms the patient's quality of life.[1,2]

This condition manifests itself heterogeneously and can be classified into subtypes based on morphological characteristics, including guttate psoriasis, erythrodermic psoriasis, pustular psoriasis, and plaque psoriasis. Plaque psoriasis is the most common subtype (accounting for 90% of cases). It's clinically characterised by erythematous, pruritic, and scaly plaques, mainly located on the extensor surfaces of the elbows, knees, scalp, and lower back. However, any area of the body can be affected.[1,3]

PsO is a significant public health challenge due to its psychological, social, and economic impact. It has been recognised by the World Health Organisation (WHO) as a serious, disabling, and non-communicable disease.[4] It is currently estimated to affect around 2-3% of the world's population.[5] The average onset of symptoms shows a bimodal distribution, with peaks in men between the ages of 30–39 and 60–69, occurring about 10 years earlier in women.[6]

At the same time, PsO is a systemic disease. It is associated with multiple comorbidities such as psoriatic arthritis (PsA), cardiovascular disease, metabolic syndrome, diabetes mellitus, obesity, non-alcoholic fatty liver disease, psychological disorders, and inflammatory bowel disease.[7] For this reason, it's essential to adopt a holistic and multidisciplinary approach to their treatment.

Inflammatory bowel disease (IBD) is an autoimmune inflammatory gastrointestinal disorder that affects 0.3 to 0.5% of the world's population. It is divided into Crohn's disease (CD) and ulcerative colitis (UC). Despite sharing common characteristics, there are some differences in how they manifest themselves and in the areas they affect.[8]

IBD is a chronic disease with periods of exacerbation and remission. It is characterised by a progressive and unpredictable course marked by the development of symptoms such as abdominal pain, diarrhea, blood in the stool, and weight loss.[6]

UC is a diffuse and continuous inflammation of the colon that extends from the rectum to the most proximal region of the colon, unlike CD, which can occur anywhere from the mouth to the anus, with the terminal ileum and cecum being the most commonly affected areas.[6] Epidemiologically, although they can occur at any age, there are two peaks of incidence: the first between the ages of 15 and 30, and the second between the ages of 50 and 80.[9]

Its aetiology is not fully understood; however, research indicates that it results from an uncontrolled immune response to alterations in the gut microbiome among individuals with a genetic predisposition.[10,11]

Recent studies have demonstrated a correlation between PsO and IBD, suggesting that they may share underlying pathophysiological processes, including immune system dysfunction, microbiome dysbiosis, and common inflammatory pathways that lead to accelerated epithelial cell turnover and impaired barrier function.[6,12] The incidence of IBD is higher in individuals diagnosed with PsO, with PsO patients 2.2 times more likely to develop CD and 1.6 times more likely to develop UC. At the same time, those with CD and UC are more likely to develop PsO, with a 2.0- and 1.5-times greater risk, respectively.[11]

The literature suggests that these associations may be proven by the concomitant existence of an inflammatory pathogenesis mediated by T helper cells 1 and 17 in both pathologies. The activation of T cells induces the proliferation of cytokines (tumor necrosis factor-α [TNF-α], interleukin 23[IL-23], and interleukin 17[IL-17]) on the surface of the skin or intestinal mucosal barrier.[13]

Therefore, many immunosuppressive therapies currently used to treat PsO are also used to control IBD, with promising results in reducing inflammation and managing symptoms. There are, however, some medications that have the potential to induce or exacerbate IBD.[6,12]

Objectives

The primary purpose of this article is to summarise the current knowledge of the association between PsO and IBD, with particular emphasis on the analysis of therapies that can be used to manage the treatment of PsO in patients with a concomitant IBD diagnosis, without exacerbating the disease.

Methods

A comprehensive search was conducted for articles published in PubMed, Google Scholar, ScienceDirect, and clinicaltrials.gov databases between 2013 and 2024, with a preference for the most recent articles. The following search terms were used, either alone or in combination: “Psoriasis”; “Inflammatory Bowel Disease”; “Crohn’s disease”; “Ulcerative Colitis”; “Treatment”; “Inhibitors”; “TNF”; “IL-17”; “IL-23”; “PDE4”; “TYK2”; “Infliximab”; “Adalimumab”; “Golimumab”; Certolizumab”; “Etanercept”; “Ustekinumab”; “Secukinumab”; Ixekizumab”; “Brodalumab”; “Guselkumab”; “Tildrakizumab”; “Risankizumab” “Apremilast” e “Deucravacitinib”. Additional articles were found through the references of the articles identified in the initial search.

The selection of relevant studies was conducted through a rigorous process of analysis, based on titles, abstracts, and bodies. Only original articles or reviews published in English were included.

Pathophysiology of Psoriasis

Understanding pathophysiology is crucial for identifying the most effective molecular targets to develop treatments with fewer adverse effects. There are currently complex interactions between immunity, genetics, and multiple environmental factors, which play a crucial role in their development.[2]

The genetic component is a central factor in the aetiology of PsO. Approximately more than 40 loci have been identified in association with this pathology, including the genes encoding interleukin 12 (IL-12) and the interleukin 23 receptor (IL-23R). These findings highlight the fundamental role of the IL-23/Th17 axis in the pathogenesis of PsO.[6,14]

The HLA-Cw6 susceptibility allele has a significant impact on PsO and is strongly associated with disease susceptibility within the PSOR1 region on chromosome 6p21. It is linked to early disease onset and influences symptom severity. HLA-Cw6 affects the skin's immune response by promoting the activation and pro-inflammatory behaviour of T cells. As the primary genetic determinant of PsO, it accounts for approximately 50% of the disease's heritability.[6,15]

In addition to genetic and immunological elements, PsO can be triggered by various environmental factors, such as infections (mainly *β-hemolytic streptococci*), skin lesions (Koebner's phenomenon), stress, and certain medications (such as B-blockers and lithium), which activate the proliferation of keratinocytes. When there is a failure to regulate both adaptive and innate immunity, inflammation persists, causing the disease to progress to a chronic condition.[2]

Together with the activation of keratinocytes, there is an overexpression of antimicrobial peptides (AMPs) produced by them, including cathelicidin (LL37), β-defensins, and S100 proteins. The role of LL37 in the pathogenesis of PsO is significant, as it has been demonstrated to stimulate toll-like receptor 9 (TLR9) in plasmacytoid dendritic cells (pDC). This step is crucial for the development of the psoriatic plaque. The pDC then produces type I interferons (interferon alfa [IFN-α] and interferon beta [IFN- β]), which, in turn, lead to the phenotypic maturation of myeloid dendritic cells (mDC), thereby promoting the differentiation of T helper 1 (TH1) and T helper 17 (TH17) cells.[16]

The activation of Th1 cells leads to the production of inflammatory cytokines such as TNF-α, interferon gamma (IFN-γ), and IL-12, which trigger and drive local inflammation, recruiting more immune cells to the site of injury. Th17 cells produce IL-17 and interleukin 22 (IL-22), which promote activation and proliferation of keratinocytes, establishing a positive feedback loop.[15,16]

Keratinocytes are responsible for the production and release of vascular endothelial growth factor (VEGF), which leads to enhanced angiogenesis and, consequently, the erythematous manifestation of psoriasis plaques.[15]

In summary, these cytokines play a crucial role in the pathogenesis of PsO by inducing keratinocyte proliferation, angiogenesis, and epidermal hyperplasia, ultimately leading to the formation of the disease's characteristic plaques.[6]

Pathophysiology of Inflammatory Bowel Disease

IBD is a complex condition with a pathophysiology that remains incompletely understood. However, it is well established that environmental factors, genetic predisposition, and alterations in the intestinal microbiome contribute to its development. These elements play a key role in disrupting intestinal immune regulation, ultimately leading to chronic gastrointestinal lesions.[6,17]

Genetic factors are key determinants in the pathogenesis of IBD, with more than 240 susceptibility loci identified. Among these are mutations in the *Nucleotide-binding oligomerisation domain-containing protein 2* (NOD2) gene, which modulates the inflammatory response through activation of the NF-κB pathway, and in the IL-23R gene, which is essential for the differentiation of Th17 cells. These genetic alterations compromise the integrity of the epithelial barrier and disrupt the regulation of both innate and adaptive immunity, thereby promoting the chronic inflammatory state that characterises IBD.[18]

Although gaps remain in understanding the mechanisms underlying IBD development, the scientific literature provides detailed insights into the immune response patterns associated with the disease. Innate immunity in these patients is compromised due to epithelial barrier dysfunction, increased infiltration of macrophages and dendritic cells, and excessive production of pro-inflammatory cytokines such as TNF-α and interleukin 1beta (IL-1β).[18]

Concerning adaptive immunity, the CD is characterised by a predominant Th1 and Th17 cell response, leading to high production of IL-12, IFN-γ, and IL-17. UC involves an atypical Th2 cell response, resulting in elevated levels of interleukin-5 (IL-5) and interleukin-13 (IL-13). However, this distinction is somewhat artificial, as all these cytokines are present simultaneously in the inflamed mucosa, differing only in quantity rather than quality. For this reason, intestinal inflammation is a highly complex and multifactorial process in which the dynamic interaction of cytokines plays a central role.[19]

The intestinal microbiota is also a trigger for inflammation. Dysbiosis compromises immune tolerance and contributes to immune activation. At the same time, environmental factors significantly influence the progression of IBD, including diets rich in fats and sugars, smoking (which aggravates CD but has a protective effect on UC), and psychological stress.[18]

In this context, IBD is the result of a complex interaction between genetic predisposition, alterations in the intestinal microbiota, immunological dysfunctions, and environmental factors, which generates a cycle of uncontrolled inflammation and impaired intestinal homeostasis.[18]

Mechanisms in common

PsO and IBD are both chronic diseases that are characterised by relapses and periods of clinical inactivity. They share common pathophysiological processes, including genetic alterations, immune system dysfunction, microbiome dysbiosis, and inflammatory pathways.[6,15]

From a genetic perspective, Genome-Wide Association Studies (GWAS) have identified 11 genes that predispose individuals to the development of both PsO and IBD.[20] The most important susceptibility locus for psoriasis (PSOR1) is located on chromosome 6p21, near IBD-3 (p23), which is implicated in the pathogenesis of IBD and, at the same time, near the gene encoding TNF-α.[21] Additionally, genes not directly related to the main compatibility complex, such as IL-23R and interleukin-12 Beta (IL-12B), have been concurrently identified in both PsO and IBD. The *IL23R* gene encodes a subunit of the IL-23 receptor, which influences the binding capacity of IL-23, essential for the differentiation and activation of Th17 lymphocytes that produce IL-17. In turn, IL-17 binding to its receptor promotes keratinocyte hyperproliferation and differentiation, as well as the maturation of mDC and the recruitment of neutrophils and macrophages in psoriatic lesions. In the gastrointestinal system, increased IL-17 expression is also observed in the intestinal mucosa of patients with IBD. The *IL12B* gene encodes the p40 subunit, which is involved in both IL-12 and IL-23 signalling pathways.[22]

The intestinal microbiota plays an essential role in the pathogenesis of PsO. At the intestinal level, patients with PsO exhibited a decrease in *Faecalibacterium prausnitzii* compared to healthy populations.[6] Similar to psoriasis, patients with IBD are characterised by notable dysbiosis. Studies have shown that they display an altered intestinal microbiome, highlighted by a decrease in *Faecalibacterium prausnitzii* and an increase in *Escherichia coli.*[20]

Faecalibacterium prausnitzii operates as a producer of anti-inflammatory molecules that modulate the host's immune system. It constitutes one of the most abundant sources of butyrate and functions as an inducer of regulatory T cells (T-regs). These cells are responsible for suppressing the abnormal activation of the immune system across various organs, including the gastrointestinal tract and skin.[6,20] Consequently, in PsO, these regulatory T cells exhibit a reduced ability to suppress immune responses, leading to an imbalance between T-regs and Th17 cells, which in turn exacerbates psoriatic disease. A similar phenomenon occurs in IBD, where there is often a decline

in the number of T-reg cells in the peripheral blood and inflamed intestinal mucosa, contributing to uncontrolled inflammation.[6]

These results support the presence of a gut-microbiome-skin axis.[20]

Treatment

PsO treatment ranges from topical to systemic therapies, depending on the severity of the disease. In less severe cases, topical therapies remain the mainstay of the therapeutic approach, including corticosteroids, vitamin D analogues, calcineurin inhibitors, keratolytics, or phototherapy.[6] In cases of moderate to high severity, conventional systemic therapies such as methotrexate, ciclosporin, and acitretin are used.[6] Regarding biological treatments, the U.S. Food and Drug Administration (FDA) has approved five classes of agents, which are playing an increasingly important role in the treatment of moderate to severe PsO:

A) TNF-α inhibitors (etanercept, adalimumab, infliximab, certolizumab);

B) IL-17 inhibitors (secukinumab, ixekizumab, brodalumab);

C) IL-12/23 inhibitors (ustekinumab);

D) IL-23 inhibitors (guselkumab, tildrakizumab, risankizumab);

E) PDE4 inhibitors (apremilast);

F) TYK2 inhibitor (deucravacitinib).[23]

These biological therapies have demonstrated significant efficacy in decreasing the severity of the disease and are frequently regarded as the preferred treatment for patients presenting with extensive plaque psoriasis.[6]

When making therapeutic decisions, it is essential to adopt a personalised approach, considering the patient's associated comorbidities and meticulously evaluating the potential impact of the selected agents on their overall health conditions.[15]

Modern biological treatments have some disadvantages, including side effects that manifest in the skin and gastrointestinal tract. This highlights the importance of the interconnection between the skin and the intestinal environment, commonly referred to as the gut-skin axis.[24] In this context, therapies used to treat PsO can potentially exacerbate or induce IBD, while drugs used to treat IBD may worsen psoriatic lesions.[24]

TNF Inhibitors

Drugs that target TNF-α, commonly known as first-generation biologics, mark a significant milestone in the treatment of immune-mediated inflammatory conditions. This group includes adalimumab, infliximab, certolizumab, and etanercept, whose mechanisms of action differ due to

their distinct molecular structures. These differences are reflected in their clinical efficacy as well as in the adverse reactions they may potentiate.[24]

Therefore, selecting the most appropriate agent for each patient requires a careful analysis of their characteristics, taking into account the specific benefits and risks associated with each medication.[24]

Adalimumab

Adalimumab is a human IgG1 monoclonal antibody that binds to TNF with high affinity and specificity, thereby inhibiting its activity. It is used in the treatment of more than 15 conditions worldwide and has been approved by the FDA since 2002 for both PsO and IBD.[25]

Elewaut et al. conducted a retrospective cohort study involving 24,114 patients from 75 clinical trials using adalimumab, accounting for a total of 36,508 patient-years of drug exposure. The objective was to evaluate the incidence of IBD-related adverse events in individuals undergoing treatment with adalimumab. Within this study, a cohort of 3,703 adult patients with an initial diagnosis of PsO (5,409 patient-years) were administered adalimumab. The incidence of IBD-related adverse events was found to be extremely low, with only one event reported in 3,703 patients, equating to <0.0 [95% confidence interval (CI) 0.0-0.02]/100 patient-years. During the placebo control periods, the incidence of IBD was comparable between patients treated with adalimumab (0.1/100 patient-years) and those in the placebo group (0.1/100 patient-years). These findings suggest that adalimumab does not significantly increase the risk of IBD.[26]

Infliximab

Infliximab is a biologic monoclonal antibody that inhibits TNF-α. The FDA approved infliximab for CD in 1998, PsO in 2006, and UC in 2006. It was also approved for paediatric CD in 2006 and paediatric UC in 2011.[12]

Phase III clinical trials have demonstrated its efficacy in the treatment of PsO, CD, and UC.[12,27-29]

Paradoxical psoriasis is defined as the development of new psoriatic lesions or the exacerbation of pre-existing ones during biological therapy.[30] It is a common adverse reaction to TNF-α inhibitors, especially in paediatric patients.[31]

Coubertte et al. analysed the prevalence of paradoxical psoriasis among 147 children between the ages of 2 and 18 diagnosed with IBD and treated with infliximab. A total of twenty patients (13.6%) developed infliximab-induced psoriasis. Furthermore, all cases of paradoxical psoriasis identified in this study were associated with patients suffering from CD and exhibiting perianal involvement, leading the authors to propose a common underlying immunological

mechanism. The psoriatic lesions were effectively managed through the application of topical corticosteroids, with no patient requiring discontinuation of infliximab treatment.[31]

Certolizumab pegol

Certolizumab pegol is a PEGylated monoclonal antibody fragment that inhibits TNF-α. In contrast to adalimumab and infliximab, certolizumab does not incorporate an Fc region. Consequently, it does not fix complement or induce antibody-dependent cell-mediated toxicity in vitro.[32] It is currently approved by the FDA for CD (since 2008) and for moderate to severe PsO (since 2018). Although it is approved for several other conditions, UC is not included among them.[12] At the time of writing, there are no published clinical trials specifically evaluating the efficacy or safety of certolizumab pegol in the treatment of ulcerative colitis.

CIMPACT (NCT02346240) is a phase III study that evaluated the safety and efficacy of certolizumab in adults suffering from moderate to severe chronic PsO. Patients were randomly assigned in a 3:3:1:3 ratio to receive either certolizumab at a dosage of 400 mg, certolizumab at 200 mg, or placebo every two weeks for 16 weeks, or etanercept 50 mg twice a week for 12 weeks. Individuals who achieved a Psoriasis Area and Severity Index (PASI) response of greater than 75% were continued on treatment for an additional 32 weeks.[33]

Patients who received certolizumab 400 mg demonstrated a response rate of 74.7% after 16 weeks, achieving a PASI 75. The group receiving certolizumab at 200 mg exhibited a response rate of 68.2 % at 16 weeks. In contrast, the placebo group presented a response rate of only 3.8% at 16 weeks. Furthermore, certolizumab at 400 mg was determined to be more efficacious than etanercept, with a response rate of 66.7% at 12 weeks, relative to etanercept's 53.3%. Analyses of Physician's Global Assessment (PGA) 0/1 and PASI 90 yielded analogous conclusions. Consequently, treatment with certolizumab pegol has been established as an effective strategy for managing PsO, particularly at the highest dose of 400 mg.[33]

PRECISE 1 (NCT00152490) is a phase III clinical trial that aims to investigate the efficacy of induction and maintenance treatment with certolizumab pegol in 662 patients diagnosed with moderate to severe CD. Patients were randomly assigned to receive either 400 mg of certolizumab pegol or placebo at weeks 0, 2, and 4, with subsequent treatment administered every four weeks. At week 6, 35% of patients in the certolizumab group exhibited a positive response to treatment, compared to 27% in the placebo group ($P = 0.02$). Furthermore, a lower incidence of serious adverse events was observed in the certolizumab group, with only 10% of patients experiencing such events, compared to a mere 7% in the placebo group.[34,35]

Xie et al. conducted a retrospective analysis of 30 studies, which reported 913 cases of PsO or psoriasiform lesions among 24,547 patients diagnosed with IBD who had been exposed to anti-

TNF agents. This corresponds to an incidence rate of 3.7%. The overall pooled incidence of PsO and/or psoriasiform lesions after anti-TNF therapy was documented at 6.0% (95% CI: 5.0-7.0%; I^2 = 93.9%), with the incidence for psoriasiform lesions at 6.9% (95% CI: 5.1-8.7%; I^2 = 92.4%) and for psoriasis at 4.6% (95% CI: 3.6-5.6%; I^2 = 93.9%), respectively. The present study demonstrates that the incidence of PsO or psoriasiform lesions in patients with IBD undergoing treatment with adalimumab (Odds Ratio [OR]: 1.48, 95% CI: 1.03-2.13, I^2 = 52.8%, n = 6 studies) and certolizumab (OR: 2.87, 95% CI: 1.04-7.91, I^2 = 62.6%, n = 2 studies) is significantly higher than that observed in patients receiving infliximab.[36]

Etanercept

Etanercept is a recombinant anti-TNF fusion protein approved by the FDA for the treatment of PsO (since 2004).[12] In contrast to other anti-TNF agents, etanercept has been observed to increase the risk of developing IBD in patients with PsO. In comparison to other drugs in this class, etanercept only binds to two of the three TNF-α binding sites, in addition to binding to TNF-β. This may modify the inflammatory immune response and contribute to the paradoxical effect observed in some patients.[24]

Korzenik et al. conducted a cohort study involving 17,018 patients with autoimmune diseases, including rheumatoid arthritis, PsA, PsO, and ankylosing spondylitis (AS), who were treated with anti-TNF-α agents, as well as a control group of 63,308 patients not exposed to these drugs. They concluded that treatment with etanercept was associated with a twofold higher risk of developing IBD compared to the control group, with an adjusted risk index of 2.0 (95% CI: 1.4-2.8) for CD and 2.0 (95% CI: 1.5-2.8) for UC. The hazard ratios for infliximab were 1.3 (95% CI: 0.8-2.2) and 1.0 (95% CI: 0.6-1.6) for adalimumab 1.2 (95% CI: 0.8-1.8) and 0.6 (95% CI: 0.3-1.0), for certolizumab pegol 2.1 (95% CI: 1.0-4.8) and 1.3 (95% CI: 0.5-3.5) and for golimumab 2.1 (95% CI: 1.1-4.0) and 1.0 (95% CI: 0.4-2.6), respectively for CD and UC. No significant risks were observed with the use of infliximab, adalimumab, certolizumab, and golimumab.[37]

IL-17 inhibitors

IL-17 inhibitors have revolutionised the treatment of PsO and are considered an excellent therapeutic option due to their ability to provide significant and sustained improvements in skin symptoms. This effectiveness is attributed to the key role of the IL-17 cytokine in regulating the immune response. [38,39]

IL-17 is a cytokine produced by a subset of CD4+ T cells known as Th17 cells. There are six isoforms of IL-17, designated IL-17A through IL-17F, and five corresponding receptors (IL-17RA to IL-17RE).[39]

IL-17A acts on different cell types, including neutrophils, lymphocytes, macrophages, dendritic cells, epithelial cells, endothelial cells, and keratinocytes.[15] At a cutaneous level, it plays a vital role by stimulating the release of pro-inflammatory mediators by keratinocytes, which consequently allows the influx of neutrophils, lymphoid cells, dendritic cells, and more Th17 cells.[39] The use of these inhibitors in patients with CD or UC can play a significant role in aggravating IBD or even inducing its onset in undiagnosed patients.[15] Within the intestinal tract, IL-17 is produced by Th17 cells following its activation by IL-23, which is released when lipopolysaccharides and peptidoglycans bind to Toll-like receptors on antigen-presenting cells. IL-17 stimulates the secretion of interleukin 6 (IL-6) and interleukin 8 (IL-8) by epithelial cells and myofibroblasts. IL-8 is a chemotactic factor that attracts neutrophils to the site of inflammation, where they release inflammatory mediators that contribute to the epithelial cell damage observed in IBD.[39]

Deng et al. conducted a retrospective study on IBD induced by IL-17 inhibitors based on FDA Adverse Event Reporting System (FAERS) data from 2015 to 2022. They reported 388 cases of gastrointestinal inflammatory events (268 IBD and 120 colitis) associated with IL-17 inhibitors, of which 348 cases (89.7%) were related to the use of secukinumab, 36 cases (9.3%) to ixekizumab and 4 cases (1%) to brodalumab. It was concluded that the risk of developing IBD was statistically significant for secukinumab (ORR=2.13, 95% CI 1.96-2.30) and ixekizumab (ORR = 2.79, 95% CI 2.39-3.27), but not for brodalumab. The primary symptoms identified were diarrhea (90.9% of cases), abdominal pain (57.6%), bloody diarrhea (51.5%), and fever (36.4%).[40]

Patients must undergo continuous monitoring during treatment with IL-17 inhibitors, as the manifestation of gastrointestinal symptoms constitutes an imminent warning sign for the onset of IBD.[41]

Although there are no specific therapeutic guidelines, it is recommended to avoid the use of IL-17 inhibitors in patients with active IBD or a previous history of the condition, as exacerbation of this comorbidity may occur. In addition, special care should be taken when prescribing these drugs to patients with a family history of IBD, even in the absence of a previous diagnosis of the condition.[24]

Secukinumab

Secukinumab is a fully humanised immunoglobulin G1 (IgG1) κ monoclonal antibody that inhibits IL-17A and has been approved by the FDA for PsO (since 2015).[12]

In 2019, Schreiber et al. conducted a comprehensive analysis of 21 clinical trials to investigate the emergence of IBD in patients undergoing treatment with secukinumab for PsO, PsA or AS. The study included a total of 7,355 patients, of whom 5,181 were diagnosed with psoriasis. Among these patients, 14 cases of UC, 5 cases of CD, and 1 case of unclassified IBD (IBDU) were

identified. Of these 20 cases, 14 were considered to be recurrences during treatment. The exposure-adjusted incidence rates (EAIRs) for PsO were calculated as 0.05 per 100 patient-years for CD, 0.13 per 100 patient-years for UC, and 0.01 per 100 patient-years for IBDU. The authors concluded that the occurrence of IBD associated with the use of secukinumab was rare.[42]

Eshwar et al. carried out a retrospective analysis to describe the adverse effects associated with the use of secukinumab between 2015 and 2021, utilising the FAERS database. Of a total of 256,337 adverse event reports related to FDA approved drugs indicated for the treatment of PsO, 44,761 (17.45%) were attributed to the use of secukinumab. Although many of the adverse events were common to biological agents in general, secukinumab showed a particular disproportionality in specific conditions, such as ocular infections (ORR = 2.31; 95% CI, 1.96-2.74) and IBD (ORR = 2.16; 95% CI, 2.08-2.24). This study reinforces the safety profile of secukinumab, but emphasises the need for ongoing clinical surveillance to identify and manage specific adverse events, particularly infections and gastrointestinal complications.[43]

Ixekizumab

Ixekizumab is a humanised monoclonal antibody of the immunoglobulin G subclass 4 (IgG4) that selectively binds to IL-17 and prevents its interaction with its receptor.[44]

Reich et al. analysed the adverse effects observed in 4,209 patients diagnosed with moderate to severe plaque PsO treated with Ixekizumab, totalling 6,480 patient-years of exposure. This analysis was based on the adverse impact data derived from seven distinct clinical studies: UNCOVER-1, UNCOVER-2, UNCOVER-3, UNCOVER-A, UNCOVER-J, a Phase I study, and a Phase II study. The analysis revealed 19 cases of IBD, including 7 cases of CD with an incidence rate of 1.1/1,000 patient-years of exposure, and 12 cases of UC with an incidence rate of 1.9/1,000 patient-years of exposure. Among these cases, four patients exhibited signs of pre-existing disease prior to the initiation of therapy. Despite concluding that cases of IBD were infrequent (less than 1%), the researchers recommended careful monitoring of patients with a history of IBD when prescribing ixekizumab.[45]

In 2022, Armstrong et al. reported similar findings. From a population-based sample of 5,898 diagnosed PsO patients treated with Ixekizumab (18,000 patients per exposure year) gathered from 12 clinical studies, 24 cases of IBD were identified, corresponding to an incidence rate (IR) of 0.2 per 100 patient-years. Of these, 16 were cases of UC (IR 0.1/100 person-years) and 8 were cases of CD (IR < 0.05/100 person-years). In concordance with the conclusions drawn in the preceding study, the authors also determined that UC and CD were uncommon occurrences.[46]

Brodalumab

Brodalumab is a human IgG2 monoclonal antibody that binds to the IL-17A receptor.[12] It was recently introduced to the market (in 2017) and is recommended for the treatment of moderate to severe plaque PsO by the FDA.[12,41]

Its mechanism of action is based on blocking multiple IL-17 isoforms that contribute to psoriatic disease, including IL-17A, IL-17C, and IL-17F. Additionally, it reduces the expression of the IL-23 and IL-12 subunit genes, thereby decreasing inflammatory markers associated with PsO that act upstream of the IL-17A receptor.[47]

A randomised phase II study was conducted in patients with moderate to severe CD to assess the safety of brodalumab in this population. The study enrolled 130 patients, with 98 receiving brodalumab and 32 receiving a placebo, over 12 weeks. The trial had to be discontinued due to a disproportionate increase in disease worsening among patients treated with brodalumab. The treated group showed a significantly marked odds ratio for worsening CD (OR = 6.64; 95% CI: 1.48–29.88) compared to the placebo group. The most common adverse effects reported were worsening of CD (25%), fever (12.5%), nausea (8.3%), and abdominal pain (7.3%).[48]

IL12/23 inhibitors

Interleukin-12 (IL-12) promotes the Th1 response, which is responsible for the production of IFN-γ and TNF. It also stimulates the production of group 1 innate lymphoid cells (ILC1), which secrete IFN-γ. As for IL-23, it is essential for the activation of the Th17 pathway and, consequently, the activation of group 3 innate lymphoid cells (ILC3s) and invariant NKT cells.[49]

Ustekinumab

Ustekinumab is a monoclonal antibody that inhibits the p40 subunit of IL-12 and IL-23, approved by the FDA for the treatment of PsO (since 2009), CD (since 2016), and UC (since 2019).[12,49]

Pugliese et al. conducted a multicenter retrospective study to evaluate the efficacy and safety of ustekinumab in patients with IBD and concomitant PsO or PsA. It included 64 patients with CD and 6 with UC who received treatment with ustekinumab due to PsO or PsA. Initially, only 56 patients (52 CD, 4 UC) had active disease, and among these, 34 (60.7%) were in clinical remission with ustekinumab treatment at the last follow-up visit. The cumulative probability of achieving remission was 84.7% at 6 months and 63.9% at 12 months. Only two patients who started ustekinumab in clinical remission of IBD experienced a clinical relapse of IBD during follow-up. At the same time, ustekinumab induced clinical remission in 37 (82.2%) of 45 patients with PsO and

15 (60%) of 25 patients with PsA. The study concluded that ustekinumab proved to be effective and safe in treating IBD patients who also have PsO or PsA conditions.[50]

Wu et al. carried out a retrospective analysis of 28 articles. Of the nine articles reviewed on patients with CD and severe psoriatic lesions, all concluded that there was a good response to treatment with ustekinumab.[51]

IL-23 inhibitors

Three drugs are currently available for the treatment of PsO that block the IL-23 receptor, in particular, its p19 subunit: guselkumab, tildrakizumab, and risankizumab. These drugs have a rapid onset of action and greater long-term efficacy than biological drugs. Furthermore, these medications have been observed to demonstrate an excellent safety profile, with only minor side effects reported, including nasopharyngitis, upper respiratory tract infections, and headaches.[15]

Guselkumab

Guselkumab is a human IgG1 monoclonal antibody that targets the p19 subunit of IL-23 and has been approved by the FDA for the treatment of moderate to severe PsO and mild to severe UC.[12,52]

QUASAR is a phase III clinical trial evaluating guselkumab as a therapeutic option for moderate to severe UC. The study included 701 participants divided into two groups: 421 patients received guselkumab, and 280 received a placebo at weeks 0, 4, and 8. Patients who showed a clinical response 12 weeks after induction with guselkumab were re-randomised into three groups to receive subcutaneous guselkumab every 4 weeks (200 mg), every 8 weeks (100 mg), or placebo. At week 12, 23% of patients treated with guselkumab achieved clinical remission (Crohn´s Disease Activity Index [CDAI] < 150), compared to 8% in the placebo group (induction phase). At week 44, 50% of patients receiving 200 mg every 4 weeks and 45% of those receiving 100 mg every 8 weeks achieved clinical remission, compared to 19% in the placebo group (maintenance phase). Guselkumab demonstrated both efficacy and safety in the induction and maintenance phases, promoting clinical, endoscopic, and histological remission in patients with moderate to severe UC.[53]

GALAXY-1 is a phase II clinical study designed to evaluate the efficacy and safety of Guselkumab in the treatment of moderate to severe CD. Three hundred nine participants diagnosed with CD were randomly assigned to five groups and given different doses of guselkumab IV (200 mg, 600 mg, and 1200 mg), ustekinumab, or placebo. After 12 weeks, there was a significant reduction in the CDAI in the groups treated with guselkumab. In addition, 53.0% of patients using guselkumab achieved clinical remission (CDAI < 150), compared to 16.4% in the placebo group. Furthermore, 35.7% of patients treated with guselkumab achieved a favourable endoscopic

response, compared to only 11.5% in the placebo group. Sandborn et al. concluded that guselkumab demonstrated superior clinical and endoscopic efficacy compared to placebo in patients with moderate to severe CD, which supports the continuation of phase III studies to evaluate its use as induction and maintenance therapy.[54] Currently, GALAXI 2 and GALAXI 3 are both ongoing Phase III confirmatory studies.[55]

In 2019, Grosseberg L. reported a case-report of a 66-year-old woman diagnosed with both CD and PsO treated with Guselkumab who achieved a high remission rate of CD (demonstrated by colonoscopies without changes and biopsies without signs of inflammation), as well as a significant improvement of PsO symptoms after previous treatment with infliximab and ixekizumab had failed.[56]

Risankizumab

Risankizumab is a humanised monoclonal antibody that selectively inhibits the p19 subunit of IL-23.[57] It has been approved by the FDA since 2019 for the treatment of moderate to severe plaque PsO, since 2022 for moderate to severe CD, and since June 2024 for moderate to severe UC.[55,58]

VALUE (NCT03982394) is a prospective post-marketing observational study to assess the effectiveness of risankizumab in treating patients with moderate to severe PsO, compared to other approved biologics. This included an analysis of 2,639 patients, 1,765 of whom were treated with risankizumab and 874 with other biologics. At 25 months, 70.9% of patients treated with risankizumab achieved PASI 90, compared to only 51.5% in the group treated with other biologics. PASI 100 was achieved by 56.6% in the risankizumab group versus 40.2% in the comparative group. The treatment maintenance rate was higher in the risankizumab group, with a lower likelihood of switching to another therapy (16% vs. 29% in the other biologics group). Dermatology Life Quality Index (DLQI) were better in the risankizumab group (70.0% vs. 52.9%). Risankizumab has demonstrated superior efficacy in reducing PsO severity, along with higher treatment persistence and improved quality of life and patient satisfaction compared to other biological therapies.[59]

ADVANCE and MOTIVATE are two Phase III clinical trials that evaluated the efficacy of risankizumab as an induction treatment in patients with moderate to severe CD. Both concluded this drug was effective in clinical and endoscopic remission at week 12 of treatment.[49] FORTIFY is a phase III clinical trial designed to investigate the efficacy of subcutaneous risankizumab in maintenance treatment for moderate to severe CD. A total of 462 patients diagnosed with CD (who had previously responded to treatment with IV risankizumab in the ADVANCE and MOTIVATE studies) were randomised into three groups to receive subcutaneous risankizumab at doses of 180 mg, 360 mg, or placebo every 8 weeks for 52 weeks. A significantly higher proportion of patients

treated with risankizumab 360 mg (68.6%) and 180 mg (70.8%) maintained clinical remission (CDAI < 150) compared to the placebo group (56.3%). Endoscopic response was maintained in 70.2% (360 mg) and 68.2% (180 mg) of patients, compared to 38.4% in the placebo group. Endoscopic remission was achieved in 74.4% (360 mg) and 45.5% (180 mg) of the patients, compared to 23.9% in the placebo group.[60]

INSPIRE Substudy 2 (NCT03398148) and COMMAND Substudy 1 (NCT03398135) are two phase III clinical trials conducted to evaluate the efficacy of risankizumab in the induction and maintenance treatment of ulcerative colitis (UC), respectively. In the induction study, a total of 975 patients were randomised in a 2:1 ratio to receive 1200 mg of risankizumab or placebo intravenously at weeks 0, 4, and 8. Clinical remission rates at week 12 were 20.3% for the risankizumab group and 6.2% for the placebo group, with an adjusted difference of 14.0% (95% CI, 10.0%–18.0%; P < 0.001). The maintenance study included 548 patients who had achieved a clinical response during the induction phase. These patients were re-randomised in a 1:1:1 ratio to receive 180 mg, 360 mg, or placebo of subcutaneous risankizumab. At week 52, clinical remission rates were 40.2% for the 180 mg group, 37.6% for the 360 mg group, and 25.1% for the placebo group. The adjusted difference was 16.3% (97.5% CI, 6.1%–26.6%; P < 0.001) for the 180 mg dose and 14.2% (97.5% CI, 4.0%–24.5%; P = 0.002) for the 360 mg dose. The studies concluded that risankizumab achieved statistically significant remission rates compared with placebo in both the induction and maintenance phases.[61]

Tildrakizumab

Tildrakizumab is a monoclonal antibody that targets the p19 subunit of IL-23. The FDA currently approves it for the treatment of moderate to severe plaque PsO.

Gooderham et al. analysed the incidence of IBD cases reported during a phase IIb clinical trial (NCT01225731) and two phase III trials (reSURFACE 1, NCT01722331; reSURFACE 2, NCT01729754). All studies included subjects diagnosed with moderate to severe plaque psoriasis, randomised into three groups to receive a subcutaneous placebo, tildrakizumab 100 mg, or tildrakizumab 200 mg at week 0, week 4, and every 12 weeks thereafter. Of the 1 911 patients in the three clinical trials, only 7 had a previous diagnosis of IBD, including three patients with ulcerative colitis, of which two were under treatment with tildrakizumab (one at 100mg and the other at 200mg) and 1 included in a placebo; 2 patients with CD, both in the tildrakizumab 200 mg group; and two patients with IBD unclassified, both in the tildrakizumab 100 mg group. None of them showed an exacerbation of the disease when treated with tildrakizumab. In addition, no new cases of IBD were observed.[62]

PDE4 inhibitors

Phosphodiesterases (PDEs) are a large, heterogeneous family of enzymes that catalyse the degradation of the intracellular second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which modulate intracellular signal transduction pathways. In this way, they play a crucial role in regulating various physiological processes related to inflammation and the immune response.[63]

Nowadays, there are eleven different families of PDE isoenzymes in mammals, which have a specific distribution by species and organ. There are four subtypes of PDE4 (PDE4A, PDE4B, PDE4C, and PDE4D). These enzymes are specific cAMP hydrolases and are expressed in various immune cells, including basophils, mast cells, eosinophils, B and T lymphocytes, monocytes, macrophages, neutrophils, and endothelial cells. When cAMP levels decrease, there is reduced activation of protein kinase A (PKA) and cAMP-regulated exchange proteins 1 and 2 (Epac1/2). This, in turn, enables the activation of nuclear factor kappa B (NF-κB), which promotes the production of pro-inflammatory mediators and leads to a pro-inflammatory state.[64]

Consequently, PDE4 inhibitors increase intracellular cAMP levels by preventing its degradation, leading to the activation of PKA and Epac1/2, and subsequently inhibiting the NF-κB pathway. Additionally, levels of phosphorylated CREB (pCREB) increase, promoting the production of anti-inflammatory mediators.[64]

Apremilast

Apremilast is a specific PDE4 inhibitor. Since September 2014, it has been approved by the FDA for the treatment of moderate to severe PsO.[65] However, there are still no published clinical trials on the use of apremilast in IBD.[63]

Schmidt et al. conducted a retrospective cohort study of patients with PsO who started treatment with apremilast between 2014 and 2020, to evaluate the discontinuation rates in patients with and without IBD, irritable bowel syndrome (IBS), and other gastrointestinal comorbidities (gastroenteritis, colitis, vascular bowel disorder, intestinal obstruction, diverticulitis, fissure/fistula, abscess, and haemorrhoids). Of a total of 11,618 patients included in the study, 57.2% had GI comorbidity, 3.2% had IBD, and 7.5% had IBS identified a priori. Among all the patients, 25.5% discontinued within 60 days, and 56.4% discontinued within 180 days. Concerning IBD, at 60 days, 30.3% of patients with IBD were discontinued from treatment compared to 24.4% without IBD (p=0.018). At 180 days, 63.6% of those with IBD had discontinued medication versus 57.2 % without IBD (p=0.026). Patients with IBS also exhibited numerically higher discontinuation rates compared to those without the condition. In contrast, a numerically reduced proportion of

patients with GI comorbidities had their treatment discontinued compared to a control group without such comorbidities, with discontinuation rates ranging from approximately 25% at 60 days to nearly 60% at 180 days. The premature discontinuation of apremilast is a common occurrence, with significantly higher rates noted in patients who have comorbid gastrointestinal conditions. Additional research is necessary to clarify the underlying causes of this.[66]

Danese et al. conducted an experimental Phase II clinical study to evaluate the efficacy and safety of apremilast in patients with UC who had never received treatment with biologics or had failed, were intolerant, or had contraindications to conventional therapies, such as mesalazine, corticosteroids, or immunosuppressants. A total of 170 patients were randomised into three groups to receive either apremilast 30 mg (57 patients), apremilast 40 mg (55 patients), or placebo (58 patients) twice a day for 12 weeks. After this phase, the patients continued active treatment for up to 52 weeks, with clinical, endoscopic, laboratory, and histological evaluations. At week 12, 31.6% of patients in the apremilast 30 mg group had achieved clinical remission, compared to 12.0% in the placebo group (P = 0.01). The 40 mg group of apremilast demonstrated a remission rate of 21.8%, exhibiting no statistically significant difference when compared to the placebo group (P = 0.27).[67]

Treatment with apremilast resulted in improvements in inflammatory markers, including ultrasensitive C-reactive protein (hsCRP) and faecal calprotectin (FCP), as well as endoscopic and histological improvements. At week 52, clinical remission was maintained by 40.4% of the patients initially treated with 30 mg and by 32.7% of those receiving 40 mg, indicating a sustained long-term effect. Although the study did not formally meet its primary endpoint in statistical terms, the authors observed relevant clinical and laboratory improvements with the use of apremilast, particularly at the 30 mg dose, suggesting that the drug may be a promising alternative for patients with active UC who do not respond to or tolerate conventional treatments.[67]

TYK2 inhibitors

Tyrosine kinase 2 (Tyk2), a member of the Janus kinase (JAK) family, plays a key role in signal transduction and immune system regulation. Tyk2-mediated signalling is involved in both innate and adaptive immune responses, promoting the expansion and functionality of Th1 and Th17 cells.[68]

Deucravacitinib

Deucravacitinib received FDA approval in 2022 for the treatment of moderate to severe PsO, making it the first TYK2 inhibitor to be authorised for this condition.[69]

Deucravacitinib is an allosteric TYK2 inhibitor. POETYK PSO-1 (NCT03624127) and POETYK PSO-2 (NCT03611751) are randomised phase III clinical studies that evaluated the efficacy and safety of deucravacitinib in the treatment of moderate to severe plaque PsO In both studies, participants (individuals with a PASI of 12 or more, static Physician's Global Assessment [sPGA] score of at least 3, and impairment of at least 10% of the body surface area) were randomly assigned to receive one of the following forms of treatment: deucravacitinib (6 mg once a day), apremilast (30 mg twice a day) or placebo. At week 16, deucravacitinib demonstrated significantly superior efficacy compared to placebo and apremilast in achieving clear or almost clear skin (sPGA 0/1) and a reduction in PASI score of at least 75% (PASI 75). In the POETYK PSO-1 study, 53.6 % of patients achieved an sPGA of 0 or 1, in contrast to the 7.2% observed in the placebo group. At the same time, a higher number of patients treated with deucravacitinib (58.4%) achieved PASI 75 compared to the placebo group (12.7%). POETYK PSO-2 corroborated these results, with 53% of patients treated with deuravacitinib achieving a PASI 75 response, in contrast to 9.4% of the placebo group and 39.8% of the apremilast group. At the 52-week mark, the outcomes remained consistent, thereby reinforcing the efficacy of this therapeutic approach as a long-term treatment option. The most frequently reported adverse events included upper respiratory tract infections, elevated levels of creatine phosphokinase, herpes simplex, oral ulcers and acne.[68,69]

The LATTICE-UC phase II study evaluated the safety and efficacy of deucravacitinib in 131 patients with moderate to severe UC who were unresponsive or intolerant to conventional or biologic therapies. After 12 weeks, the study failed to meet its primary and secondary endpoints, showing no significant clinical remission.[68]

Discussion

PsO and IBD are classified as inflammatory diseases, with the two conditions sharing similarities in their pathophysiological mechanisms.[6,12,15,18] These include the presence of shared genes that predispose individuals to the development of both conditions, as well as the activation of the Th17/IL-23 pathways and the production of pro-inflammatory cytokines such as TNF-α, IL-23, and IL-17.[15,16,18-22] In addition to the high concomitant prevalence of these pathologies, their treatment often involves the use of the same immunosuppressive therapies.[5,6,8,11,12] Consequently, there is a considerable need for a comprehensive global study of therapies that benefit one or both diseases, as well as those that may exacerbate one of the conditions.[6,12]

Infliximab and adalimumab, both anti-TNFα agents, have demonstrated robust efficacy and are generally well tolerated in patients with concomitant PsO and IBD.[24-29] They are often considered first-line therapies in this clinical context. On the other hand, certolizumab pegol,

another anti-TNFα agent, is approved for the treatment of CD and moderate-to-severe PsO, but it is not approved for use in UC.[33-35] Several studies have reported cases of paradoxical PsO (either new onset or exacerbation of pre-existing lesions) in patients with IBD receiving infliximab, adalimumab, and certolizumab.[30,31,36] Consequently, careful monitoring is needed, particularly in paediatric populations where these reactions may be more pronounced.[31]

In the case of etanercept (anti-TNFα agent), its use in patients with PsO who also have concomitant IBD is contraindicated, as clinical studies have demonstrated an increased risk of IBD developing or exacerbating.[24,37]

IL-17 inhibitors (secukinumab, ixekizumab, and brodalumab), despite their high efficacy in the treatment of PsO, have been associated with the induction or exacerbation of IBD.[38-40,42-48] Therefore, continuous monitoring of patients undergoing IL-17 inhibitor therapy is essential to detect early signs of IBD.[41] These agents should be avoided in patients with active IBD or a personal history of the condition, to minimise the risk of disease flare or onset.[24] Alternative therapeutic classes with a more favourable safety profile should be prioritised in such cases.

Ustekinumab, an antibody that targets the p40 subunit common to IL-12 and IL-23, stands out for its efficacy and safety in treating IBD patients who also have PsO. [49,50] This drug is a promising option for treating CD patients who have developed PsO during previous treatment with anti-TNF drugs.[53]

Regarding IL-23 inhibitors, such as guselkumab, risankizumab, and tildrakizumab, recent clinical trials have demonstrated encouraging data on their efficacy in both diseases, with a low risk of gastrointestinal adverse effects and superior long-term efficacy compared to other biologics.[15,34,53,55,56,58-62] Ongoing studies aim to further assess their potential as safe and effective treatment options for patients with concomitant PsO and IBD.[55]

PDE4 inhibitors (apremilast) and TYK2 (deucravacitinib) represent recent therapeutic approaches, with still limited but promising data for the concomitant treatment of both pathologies.[25,63,66-69]

It is essential to acknowledge that, despite the efforts undertaken to assemble the most relevant and up-to-date scientific evidence regarding the management of PsO in patients with concomitant IBD, this literature review is not free from limitations.

A significant proportion of the data analysed is derived from observational or retrospective studies, along with clinical trials that are characterised by limited sample sizes and considerable heterogeneity in inclusion criteria and follow-up durations. This methodological variability compromises the comparability of results across studies and restricts the generalizability of the findings to clinical practice.

Regarding the safety and efficacy of biological agents in patients simultaneously affected by PsO and IBD, there is a limited number of prospective clinical trials specifically designed for this patient population. Accordingly, a considerable amount of the evidence is predicated on indirect data, which inherently possesses a diminished level of scientific rigour. In light of these constraints, there is a significant need for large-scale studies that focus exclusively on individuals with concomitant PsO and IBD. Such studies would facilitate a direct and controlled comparison of therapeutic options, thereby providing more substantial guidance for clinical decision-making.

Furthermore, considering the rapid and ongoing advancement of biological therapies, the findings and conclusions articulated in this review must be contextualised within the temporal framework of the available literature.

Conclusion

PsO and IBD are ongoing conditions that significantly impact patients' quality of life. Due to their common pathophysiological mechanisms and frequent overlap, a tailored treatment approach is crucial for managing both diseases effectively without compromising one for the other. Further research is needed to clarify the therapeutic efficacy of existing drugs and to identify new, more effective treatment options.

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