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JAK/STAT Pathway in Psoriasis and Psoriatic Arthritis: Insights into Inflammation and Tissue Remodeling

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ABSTRACT

The Janus Kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) pathway plays an important role in mediating inflammatory immune responses and is central to the development of psoriasis and psoriatic arthritis (PsA). Both of these conditions are caused by unregulated immune responses, with overlapping mechanisms specifically in its cytokine-mediated JAK/STAT activation. In psoriasis, the JAK/STAT signaling pathway has been linked to increased keratinocyte proliferation, the release of inflammatory cytokines, and the formation of characteristic skin plaques. In PsA, this same pathway has been demonstrated to drive joint damage, hyperproliferation of synovial cells, and pannus formation. Cytokines, such as interleukin (IL)-9 and IL-22, serve as common initiators of the JAK/STAT pathway in both psoriasis and PsA, leading to increased cellular proliferation in affected tissues. Recent studies show that blocking JAK signaling may not only lessen inflammation but also psoriasis-related keratinocyte proliferation and synovial tissue remodeling. These results highlight the dual modality of the JAK/STAT pathway in regulating pathogenic tissue alterations and inflammation in these linked disorders. By focusing on the common inflammatory pathways, JAK inhibitors have demonstrated promise in the clinical treatment of both psoriasis and PsA. However, the effectiveness of current medications on the market vary, therefore more research is necessary to look

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into particular JAK inhibitors that are best for both psoriasis and PsA. The purpose of this review is to organize the current understanding in both psoriasis and PsA pathophysiology as well as new developments regarding co-treatments of both psoriasis and PsA.

Keywords: Psoriasis, Arthritis, JAK/STAT, Orthopedic Surgery, Dermatology, Autoimmune, Degenerative Joint Disease

INTRODUCTION

Immune-mediated inflammatory diseases (IMIDs) include a broad spectrum of chronic disorders characterized by dysregulation of the immune system, leading to persistent inflammation and tissue damage. In dermatology and rheumatology, IMIDs can manifest in different ways, yet immunologically they seem to be interconnected, especially conditions like psoriasis and psoriatic arthritis (PsA). These diseases are driven by abnormal or inconsistent activation of both the innate and adaptive immune systems, with proinflammatory cytokines playing a key role in disease initiation and its progression [1,2].

Before discussing the interrelationship of psoriasis and PsA, it is important to understand that inflammatory skin diseases can be broadly classified into autoimmune diseases and autoinflammatory syndromes. Autoimmune inflammatory dermatoses, for example like vitiligo and lupus erythematosus, are mediated by autoreactive lymphocytes that target self-antigens in the presence of pathogenic autoantibodies. On the other hand, psoriasis is an example of an autoinflammatory condition that is predominantly driven by innate immune mechanisms, although adaptive immune cells may contribute to its effect in chronic inflammation.

Psoriasis is a complex inflammatory skin disease marked by its interplay between T lymphocytes, keratinocytes, dendritic cells, and neutrophils. In 2022, a research study found keratinocytes to be the main initiator and progressor of this condition through its different phases [3]. In the beginning phases, antimicrobial peptides and stress signals are released by the keratinocytes which then activate plasmacytoid dendritic cells. These cells in turn promote the maturation of myeloid dendritic cells, which produce key cytokines, including interleukin (IL)-12 and IL-23, that drive the differentiation of T helper (Th)1 and Th17 cells [3]. The resulting cytokines of this differentiation, particularly IL-17A, IL-22, and interferon-gamma (IFN-γ), further stimulate keratinocytes and produce even more inflammatory mediators and antimicrobial peptides, creating a self-amplifying loop of immune activation [4]. Similarly, neutrophils also contribute to inflammation by releasing IL-17 and forming extracellular traps that further activate keratinocytes and recruit immune cells to the skin to form plaques [5]. Together, these cellular interactions drive the hallmark features of psoriasis, including keratinocyte hyperproliferation and immune cell infiltration.

Recent research has turned to the intracellular signaling networks that coordinate these immune responses. Among them, the Janus Kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) pathway has emerged as a main mediator of cytokine signaling involved in both psoriasis and PsA [6]. Due to its central role in immune cell activation, inflammation, and tissue remodeling, the JAK/STAT pathway has now become a compelling target for current therapeutic intervention. This review aims to organize current knowledge regarding the role of the JAK/STAT signaling in the pathogenesis of psoriasis and PsA, while highlighting new therapeutic strategies that target this pathway to mitigate disease burden and improve patient outcomes.

Overview of the JAK/STAT Pathway in Immune-Mediated Inflammation

The JAK/STAT pathway is an intracellular signaling cascade that facilitates communication between extracellular cytokine signals and gene expression in the nucleus. Composed of four JAK family members (JAK1, JAK2, JAK3, and TYK2) and seven STAT proteins (STAT1–6, including STAT5A and STAT5B), this pathway manages a vast arrangement of cellular processes including immune cell proliferation, differentiation, apoptosis, and migration [7]. Upon cytokine binding, a receptor-associated JAK becomes activated through transphosphorylation, leading to the phosphorylation of STAT. Once phosphorylated, the STAT dimers travel into the nucleus, where they bind to DNA and control the transcription of genes involved in immune homeostasis and inflammation [8]. Tight regulation of this cascade is essential for maintaining immunological balance, as abnormal activation or suppression can result in autoimmune diseases, chronic inflammation, or malignancy [9].

In psoriasis and PsA, dysregulated JAK/STAT signaling contributes not only to sustained cytokine production but also tissue-specific immune responses. STAT3 has been found to be a transcription factor that is heavily implicated in both psoriasis and PsA pathogenesis. It is activated by

many cytokines (IL-6, IL-12, IL-21, and IL-2), but mainly STAT3 is important because it promotes Th17 differentiation and IL-22 secretion, both of which contribute to keratinocyte hyperproliferation and impaired differentiation in psoriatic skin [7,10]. A research study found that keratinocyte-specific overexpression of STAT3 in murine models is sufficient enough to produce spontaneous psoriasis-like lesions [9]. Interestingly, keratinocytes themselves can produce cytokines, such as IL-23 and IL-17E, contributing to inflammation through autocrine and paracrine loops involving STAT3 and STAT5 [11,12]. These findings show that STAT3 activation in keratinocytes is the main factor that is perpetuating a feed-forward inflammatory loop, leading to the increased expression of antimicrobial peptides and pro-inflammatory mediators [13]. Notably, different members of the JAK family are selectively involved in a more specific cytokine signaling cascades. TYK2 and JAK2 mediate IL-12/IL-23 signaling and are vital for Th1 and Th17 responses [14]. TYK2, in particular, has gained attention for its role in IL-23–mediated STAT3 activation [7,15]. Thus, the JAK/STAT pathway operates not only at the level of immune cell communication but also within epithelial compartments, adding another layer of complexity to disease manifestation.

Due to its central role in immune activation, the JAK/STAT pathway has become a major therapeutic target. Several JAK inhibitors, including tofacitinib, baricitinib, and upadacitinib, have been investigated for psoriasis and PsA, showing promise in reducing skin lesions and joint inflammation [8]. These small molecules inhibit JAK-mediated phosphorylation events, thereby dampening downstream STAT activation and inflammatory gene transcription. First-generation inhibitors often block multiple JAK pathways simultaneously, which can be effective, but also raises safety concerns due to broad immunosuppression [16]. As a result, new therapies aim for selectivity, such as TYK2-specific inhibitors, to reduce adverse effects while maintaining efficacy [7]. The ongoing development of JAK/STAT-targeting therapies shows a shift towards intracellular signal modulation as a strategy for controlling complex immune diseases like psoriasis and PsA.

JAK/STAT Pathway in Psoriasis Pathogenesis

Dysregulated Cytokine Activation

To further understand the complexity in psoriasis' pathogenesis, the specific roles of cytokines dysregulation must be understood as they play an essential role in orchestrating the inflammatory response. IL-23 functions as a key upstream regulator, modulating the activity of IL-17 and IL-22, two cytokines implicated in keratinocyte hyperproliferation and psoriatic plaque formation. Beyond its known activation of IL-17, IL-23 has also been associated with epigenetic alterations, particularly H3K9 dimethylation, which may contribute to aberrant inflammatory signaling [3]. STAT3 further amplifies this response by enhancing the expression of IL-17E via its receptor IL-17RB, leading to increased production of pro-inflammatory cytokines and chemokines by keratinocytes [3]. Similarly, IL-17A promotes the expression of multiple inflammatory genes and recruits immune cells to the epidermis, perpetuating the psoriatic phenotype. IL-22, while traditionally recognized for its role in epithelial repair and wound healing, has also been shown to induce keratinocyte proliferation through the upregulation of matrix metalloproteinases and anti-apoptotic proteins [17]. IL-9 contributes to the inflammatory milieu by stimulating keratinocyte proliferation and enhancing the production of HPK cytokines and vascular endothelial growth factor (VEGF) [18]. Collectively, dysregulation within these cytokine networks underpins the dermatologic and musculoskeletal manifestations characteristic of psoriasis and PsA.

Impact on Skin Homeostasis

The epidermal barrier serves as a critical line of defense, safeguarding the skin from environmental insults, including physical trauma, chemical irritants, and microbial invasion, while also regulating transepidermal water loss [19]. Disruption of this barrier compromises its integrity and has been strongly associated with increased water permeability and the progression of psoriatic lesions [20]. Barrier dysfunction initiates a cascade of immune responses, including the release of pro-inflammatory mediators such as interleukins and TNF-α, further exacerbating cutaneous inflammation [21].

Central to this pathogenic cascade is the JAK/STAT signaling pathway, which is directly implicated in the upregulation of keratin 17 (K17), a key biomarker of psoriatic skin [22]. Overexpression of STAT1 and STAT3 has been shown to disrupt epidermal homeostasis by weakening barrier functionality and promoting inflammation [22]. Moreover, JAK-STAT signaling contributes to cutaneous pathology by perturbing lipid metabolism. Th2-associated cytokines activate this pathway, leading to alterations in fatty acid synthesis, decreased levels of triglycerides, and impaired production of palmitoleic acid, a key lipid involved in maintaining barrier integrity [23]. This metabolic dysregulation not only compromises structural

cohesion of the skin barrier but also amplifies the inflammatory response, perpetuating the cycle of disease in psoriasis.

The components of the JAK-STAT pathway involved in increased immune cell recruitment include STAT6, STAT3, STAT4, JAK3, and TYK2 [24]. STAT3 and STAT6 are key components that allow for recruitment of inflammatory cells. STAT3 is involved in the differentiation of keratinocytes, while STAT6 mediates keratinocytes to promote chemokine production [24]. Constitutive expression of STAT 6 is known to result in the production of dermatitis-related lesions along with high levels of B cell differentiation [25]. STAT4 impairment results in decreased production of Th1 cells which are a major regulator of keratinocyte proliferation [25]. JAK3 dysregulations result in discrepancies that involve absence or overproduction of T cells, B cells, and Natural Killer cells, thereby resulting in psoriasis pathogenesis [25]. TYK2 has a regulatory role in the signaling pathway, as low levels of it result in issues with Th1 and Th2 differentiation, contributing to skin lesions [25]. These molecular factors ultimately impact the development of pathologies like psoriasis and PsA.

Mechanistic Evidence

Recent advances in both clinical and preclinical research have elucidated the mechanistic underpinnings of the JAK/STAT pathway in psoriasis development. In a clinical study aimed at dissecting cytokine-specific contributions to psoriatic inflammation, a 3D human skin model was employed to map the activity of individual cytokines involved in disease progression [22]. This model provided compelling insight into how dysregulated cytokine signaling initiates and sustains cutaneous inflammation.

Preclinical investigations have further revealed that specific microRNAs may play a pivotal role in modulating this inflammatory axis. Notably, elevated expression of a particular microRNA was shown to suppress the expression of LCR-2, a lipoprotein implicated in pro-inflammatory signaling. This suppression led to the downstream inhibition of the JAK/STAT pathway, thereby attenuating inflammatory responses and halting psoriasis progression [26]. These findings suggest that microRNA-based interventions could offer a novel and targeted therapeutic strategy for psoriasis.

Pharmacologic inhibition of JAK signaling has also demonstrated clinical promise. The Janus kinase inhibitor JTE-052 was found to suppress excessive keratinocyte proliferation and preserve epidermal barrier function, two central components in the pathogenesis of psoriatic lesions [24]. In parallel, allosteric inhibition of TYK2, a member of the JAK family, has emerged as a particularly promising approach. TYK2 inhibitors have shown the ability to block key pro-inflammatory cytokines such as IL-23 and IL-17, both of which are instrumental in driving psoriatic inflammation and plaque formation [27].

Collectively, these mechanistic studies underscore the central role of the JAK/STAT pathway in psoriasis and support its viability as a therapeutic target. JAK and TYK2 inhibitors act by dampening cytokine overproduction, reducing chronic inflammation, and ultimately improving clinical outcomes in patients with psoriasis.

JAK/STAT Pathway in Psoriatic Arthritis Pathogenesis

JAK/STAT Involvement in Synovial Hyperplasia and Joint Damage

In the disease process for psoriasis and PsA, an environmental trigger in patients genetically predisposed to either condition leads to a cytokine-mediated chronic inflammatory process involving the joints and skin [28]. In the case of PsA, this inflammation affects the joint synovium, leading to synovial hyperplasia and joint damage [29]. Synovial fibroblasts are the primary stromal cells of the joint synovium. In a healthy joint, synovial fibroblasts are found in layers one to two cells thick, and interspersed with resident macrophages [30]. The synovial fibroblasts produce extracellular matrix, and they are responsible for maintaining the cartilage integrity and lubrication of the joint [30]. However, inflammatory processes in the joint cause synovial lining thickening and immune cell infiltration. The synovial fibroblasts become activated and proliferate, invading, and destroying the adjacent cartilage [30]. The synovial fibroblasts also express innate immune receptors [30], yielding the inflammatory cascades seen in PsA.

Key cytokines, such as IL-23, TNF, IL-17, and IL-22, further drive inflammation in the joint and activate resident cells in the joint and enthesis, such as the synovial fibroblast-like synoviocytes, chondrocytes, osteoblasts, and osteoclasts [29]. These cells then secrete matrix-degrading enzymes and RANKL, resulting in cartilage degradation, osseous erosion, and joint damage [29]. These activated resident cells then perpetuate the immune response by recruiting more immune cells to the joint

[29]. The cycle of cytokine-driven inflammation perpetuates chronic joint and osseous degeneration.

The JAK/STAT pathway is a crucial contributor to the inflammation caused by PsA, as JAK molecules interact with signal transducers and transcription activators, which modulate gene transcription of several cell surface cytokines and growth factor receptors [31]. For example, IL-22 has been shown to induce osteoclastogenesis through RANKL activation of the JAK2-STAT3 signaling pathway [29]. Thus, the JAK/STAT pathway has been highlighted as a target for pharmacological treatment, where JAK/STAT inhibition can reduce or inhibit the signaling effects of multiple cytokines and growth factors on targeted cells [31]. For example, RANKL-induced osteoclastogenesis has been shown to be suppressed in vitro by inhibition of the JAK2/STAT3 pathway using a JAK2 inhibitor [32]. This highlights the importance of understanding the JAK/STAT pathway in mediating PsA joint and osseous pathology.

Shared and Distinct Cytokine Profiles with Psoriasis and Psoriatic Arthritis

Psoriasis and PsA feature chronic inflammation that leads to the production of cytokines, such as IL-23 by macrophages and dendritic cells [28]. IL-23 is a cytokine that is a major contributor to the pathogenesis of both psoriasis and psoriatic arthritis [28,33]. In animal models, it stimulates resident T-cells that are CD3+, CD4- CD8-, IL-23R+, and ROR γδ+ [28,33]. Subsequent activation of IL-17, IL-22, and TNF-α lead to inflammation and osseous destruction [28]. Thus, IL-23 is a key mediator not only of the inflammation present in both psoriasis and PsA, but of the pannus formation and synovial/bone remodeling seen in severe, chronic PsA.

Following IL-23-mediated activation, IL-22 release promotes the pathophysiology of both psoriasis and PsA [34]. In skin lesions, IL-22 drives keratinocyte hyperproliferation via STAT3 signaling [34]. In PsA, IL-22 promotes entheseal and periosteal osseous formation through STAT3 activation [34]. IL-23 also induces increased activity of IL-17, so IL-23-induced Th17 cytokines (IL-17 and IL-22) are large contributors to the psoriatic plaque, joint pannus formation, joint erosion, and new bone formation seen in PsA [35].

IL-9 has also been implicated in the initiation and maintenance of inflammation in psoriasis and PsA, with PsA featuring an over-expression of IL-9, produced primarily by Th9 cells in the peripheral blood and synovial fluid of PsA patients [36]. T cell receptor (TCR) activation also appears to work in a reciprocal manner with IL-9 and IL-23 [37]. TCR induces cytokine production and increases IL-9 and IL-23 receptor expression levels [37] The IL-9/IL-9 receptor system has specifically been shown to regulate proliferation of fibroblast-like synoviocytes, upregulate metalloproteinase 3 (MMP 3), and promote pro-inflammatory cytokine release, which are all key components of pannus formation in PsA [38].

IL-17A has also been heavily referenced in the literature as having an important role in the disease processes that psoriasis and PsA inflict at the skin, joints, and entheses, especially due to the high effectiveness IL-17A inhibitors have shown in treating PsA [39]. In psoriasis, IL-17 is found in elevated levels in the blood and skin lesions [39]. IL-17 producing T cells have been shown to have a potential role in recurrence of psoriasis at sites of prior resolution [39]. IL-17 has been shown to target keratinocytes, endothelial cells, and innate immune cells, yielding the tissue inflammation and the cardiovascular comorbidities seen in psoriasis [40]. In PsA, IL-17A has been shown to stimulate RANKL expression and inhibition of Wnt signaling, thereby inhibiting osteoblast activity and promoting bone erosion in PsA [39]. As discussed previously, the interplay between IL-23 and IL-17 is also a key piece in the pathophysiology of PsA, with IL-23 augmenting IL-17A production [39]. The sequelae of the activation of cytokines, such as IL-22 and IL-17, involve extensive inflammatory cascades leading to the release of pro-inflammatory cytokines such as IL-6, IL-8, IL-1, and TNF [41]. These pro-inflammatory cytokines then greatly contribute to the joint destruction and cartilage degradation seen in PsA.

Similarities between Psoriatic Arthritis and Rheumatoid Arthritis

PsA has been likened to similar autoimmune arthritic diseases, such as rheumatoid arthritis (RA), due to their shared involvement of inflammatory cascades leading to synovial inflammation [42]. A study on the effects of JAK inhibitor tofacitinib on synovial fibroblast function in PsA showed that they are activated similarly to synovial fibroblasts in RA, furthering the evident similarities between the pathophysiology of PsA and RA [43]. Thus, the success of using JAK inhibitors to interfere with the JAK/STAT pathway that produces the proinflammatory cytokines responsible for driving rheumatoid arthritis lends credence to the

effectiveness seen in using JAK inhibitors to treat PsA [42]. These studies demonstrate the interplay of autoimmune diseases and similar molecular pathways as shown in Figure 1, which can help with identifying similar treatment options.

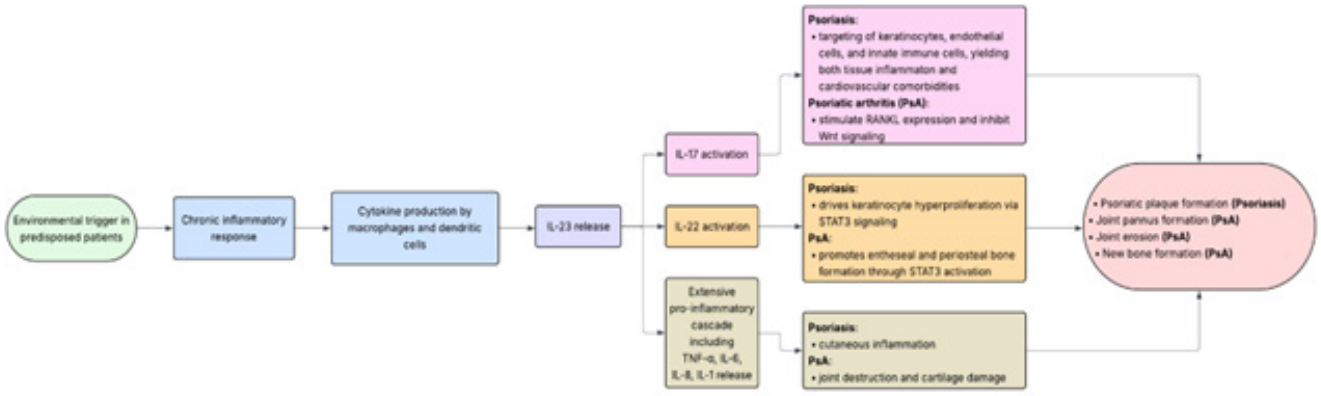

Figure 1. Pathway describing the similarities between psoriasis and psoriatic arthritis (PsA).

Therapeutic Targeting of JAK/STAT in Psoriasis and PsA

Treatment modalities that target the JAK/STAT pathway have shown evidence-based efficacy. Facitinib, ruxolitinib, and baricitinib are three of the most studied JAK inhibitors in the context of psoriasis, each demonstrating potential in modulating the inflammatory processes central to disease pathogenesis. Tofacitinib, an oral JAK1/JAK3 inhibitor, has been evaluated extensively in clinical trials, including a Phase IIb dose-ranging study where doses of 2 mg, 5 mg, and 15 mg twice daily significantly improved Psoriasis Area and Severity Index (PASI) scores compared to placebo, with PASI75 response rates highest in the 5 mg and 15 mg groups [44]. However, the 15 mg dose showed an increased incidence of adverse events, making 5 mg BID a favorable balance between efficacy and safety. Ruxolitinib, a selective JAK1/JAK2 inhibitor, has been primarily studied in its topical formulation. In a randomized, double-blind Phase II trial, ruxolitinib cream applied twice daily significantly improved psoriatic lesions in patients with mild to moderate disease and demonstrated a safety profile comparable to vehicle cream, indicating a promising option for localized treatment with minimal systemic exposure [45]. Additionally, baricitinib has been investigated in a Phase IIb trial for moderate to severe psoriasis, leading to significant PASI75 responses, with generally mild side effects, such as nasopharyngitis and headache, supporting its candidacy as a viable oral therapy [46]. These investigations demonstrate the promising therapeutic benefits of localized treatment that target PASI75 for psoriatic diseases.

The clinical efficacy of JAK inhibitors in psoriasis is largely attributed to their ability to interrupt the JAK/STAT signaling cascade, which is critical for the transduction of signals from pro-inflammatory cytokines that drive keratinocyte hyperproliferation and chronic inflammation [3]. Psoriasis is characterized by the aberrant activation of cytokines, such as IL-23, IL-17, and IL-22, which not only amplify immune responses, but also promote excessive growth and impaired differentiation of keratinocytes [47-49]. By targeting JAK pathways, particularly JAK1, JAK2, and JAK3, these inhibitors diminish the downstream STAT activation responsible for transcription of genes involved in inflammation and cell cycle regulation in keratinocytes [3]. As shown in both clinical and preclinical models, JAK inhibition reduces cytokine-mediated signaling, thereby suppressing the inflammatory milieu within psoriatic plaques and normalizing epidermal turnover. This dual anti-inflammatory and antiproliferative action makes JAK inhibitors a unique class of therapeutics capable of addressing both immune and structural components of psoriatic diseases. While their oral and topical formulations offer flexibility in treatment approaches, further research is needed to optimize long-term safety, efficacy, and patient stratification for these agents.

These medications have also emerged as a therapeutic option for PsA. However, treatment responses exhibit notable variability, largely due to joint tissue-specific mechanisms. PsA is characterized by inflammation across multiple domains, including peripheral joints, entheses, and axial skeleton, each potentially responding differently to JAK inhibition [42,50,51]. For instance, while some patients experience

significant relief in peripheral arthritis symptoms, others may not achieve comparable improvements in axial disease or enthesitis [31]. This variability underscores the complexity of PsA pathophysiology and suggests that JAK inhibitors may not uniformly modulate all inflammatory pathways involved in the disease. Additionally, individual differences in drug metabolism, presence of comorbidities, and prior treatment history further contribute to the heterogeneous responses observed with JAK inhibitor therapy.

Given these challenges, there is a pressing need for optimized small-molecule inhibitors capable of effectively targeting both skin and joint manifestations of PsA. Current JAK inhibitors, while effective in certain aspects, may not comprehensively address the diverse clinical presentations of PsA. The development of more selective inhibitors, such as those targeting TYK2, offers a promising avenue [52]. For example, upadacitinib, a selective JAK1 inhibitor, has demonstrated efficacy in treating PsA, leading to its FDA approval for this indication [16]. Moreover, the advent of dual inhibitors that can simultaneously modulate multiple signaling pathways implicated in both skin and joint pathology holds potential for more comprehensive disease control. Advancements in precision medicine, including the identification of biomarkers predictive of treatment response, are also crucial to tailor therapies effectively, minimize adverse effects, and enhance overall patient outcomes in PsA management.

When comparing JAK inhibitors to biologic therapies, such as TNF-α inhibitors and IL-17/IL-23 blockers in the treatment of PsA, several distinctions in efficacy and application emerge. JAK inhibitors have demonstrated effectiveness in addressing musculoskeletal manifestations of PsA, offering therapeutic benefits comparable to those of TNF-α inhibitors [53,54]. However, IL-17 and IL-23 inhibitors have shown superior efficacy in managing cutaneous symptoms associated with PsA. This differential response underscores the importance of tailoring treatment strategies to individual patient profiles, considering the specific clinical manifestations present. The potential for combination therapies or personalized treatment approaches is an area of active investigation. Emerging evidence suggests that combining JAK inhibitors with biologics targeting IL-17 or IL-23 pathways may offer enhanced efficacy for patients with recalcitrant PsA [55]. Combination therapy may be beneficial in achieving comprehensive disease control. Nonetheless, further research is necessary to establish the safety, optimal dosing, and long-term benefits of such regimens, paving the way for more personalized and effective treatment paradigms in PsA management.

Challenges, Discussion, and Future Directions

Current therapies in clinical practice for PsA and psoriasis include topical, systemic and phototherapy. Topical therapies, especially corticosteroids, remain a gold standard for managing Psoriasis and PsA [56]. Vitamin D3 analogs like calcipotriene, as well as anthralin, tar, tazarotene, and calcineurin inhibitors like tacrolimus are also options in the management of psoriasis [57]. These topical therapies have been effective in managing symptoms but are limited in their systemic effects. Long-term use of these therapies can cause greater irritation and lead to adverse side effects. Because of this combination therapy with biologics or systemic agents may be beneficial. Systemic therapies include methotrexate, NSAIDs, biologics, systemic retinoids, and calcineurin inhibitors like cyclosporine [57]. These therapies may offer more potent and greater efficacy in overall symptom relief and suppression. Biologics include TNF inhibitors; infliximab, etanercept, ADA, golimumab and certolizumab pegol [58]. However, use is often restricted due to cost, and adverse side effects that include risk of opportunistic infection, hepatotoxicity, and injection-site reactions [56]. Phototherapy has shown promise as another treatment option for systemic psoriatic disease. Available methods include natural sunlight, ultraviolet-A, narrow-band ultraviolet-B (NB-UVB), and psoralen plus UVA (PUVA) therapy [56]. This can be used in combination with topical therapy especially with extensive skin involvement. However, adverse effects such as non-melanoma skin cancer, irritation, and phototoxicity remain a challenge [56].

Given these challenges with current therapies, there is an opportunity for advances that are both cost efficient and associated with lesser side effects. JAK and tyrosine kinase inhibitors expand the therapeutic options for PsA and psoriasis. Additionally, several other options are undergoing clinical trials and include Retinoic acid-related orphan receptor (RORγT) inhibitors, oral IL-23 inhibitor, JNJ-2113, Rho-associated protein kinases (ROCK-2) inhibitors, Sphingosine-1-phosphate (S1P1R) antagonists and A3 adenosine receptor agonists [56]. However, these therapies are still being evaluated for their safety and efficacy and with further studies hold potential for incorporation into future practice.

JAK/STAT inhibitors have shown promise in modulating the inflammatory pathway in psoriasis and PsA. However, they

are not without adverse effects and limitations. Among the different JAK inhibitors, ruxolitinib, tofacitinib, and baricitinib have been associated with a significant risk of infection [59]. Because JAK inhibitors target the JAK/STAT pathway, which is essential for immune system function, their suppression can impair the body's ability to fight infections. The use of immunomodulators long-term causes an even greater immune suppression, thus increasing individuals' risk of infections. The most commonly observed infections in patients taking JAK inhibitors include upper respiratory infections and nasopharyngitis. Among opportunistic infections, herpes zoster presents the most significant concern [60]. This suggests that individuals who are unvaccinated or have no prior history of herpes zoster may be at an increased risk of infection while on JAK inhibitors. Furtunescu et al. reported that the increased infection risk was notable in patients taking tofacitinib and upadacitinib compared to placebo [6]. Additionally, studies have examined the dose-dependent effects on infection risk. Higher doses of immunomodulators, particularly JAK inhibitors, have been shown to further increase the risk of adverse effects and infections. More cases of herpes zoster were observed with upadacitinib at a 30 mg dose compared to other JAK inhibitors [6,60]. Thus, it is important to have close follow up and monitoring of patients on high doses of JAK-inhibitors for clinical improvement of psoriasis, and symptoms of PsA.

Risk of cardiovascular and venous thromboembolic events (VTE) increases in patients with immune mediated inflammatory diseases like psoriasis and PsA. Risk of these events are stratified by presence or absence of baseline risk factors of cardiovascular and VTE. Tofacitinib has been the main JAK inhibitor studied for safety. Concerns about tofacitinib's use were raised in 2019 when higher rates of pulmonary embolism and mortality were noted [61]. Prior studies have looked at incident rates of these events associated with tofacitinib usage. The rate of VTE was elevated in patients with versus without baseline cardiovascular or VTE risk factors [62,63]. This is to be expected as patients with risk factors are more susceptible to events due to pre-existing conditions. Majority of patients who experienced VTE had multiple risk factors. Future studies could further classify the type of risk factors to the association of adverse effects. Incidence of events was not significantly associated with dosage of medications. Incidence rates were similar in patients with PsA taking tofacitinib 5 mg versus 10 mg twice daily [62]. However, it is unclear how JAK inhibitors affect the inflammatory pathway and coagulation pathways specifically. Physicians should weigh the benefits and risks of JAK inhibitors and determine use based on a patients' overall clinical picture. Long-term follow up of JAK inhibitors can be further studied to obtain a greater understanding of risk for thromboembolic events. An observational, longitudinal study in France being conducted by Truchetet et al., is currently underway to investigate the effects of JAK inhibitors on patients with inflammatory rheumatoid disorder over a 5-year period [64]. This study can provide long-term real-world data on the safety and efficacy of JAK inhibitors, which has not been investigated previously. Future studies can continue to explore the long-term effects of JAK inhibitors.

Current studies are underway that address some of the limitations discussed. A study in Italy is looking at the efficacy of Upadacitinib during the first 6 months of follow up and comparing its use between psoriatic arthritis and rheumatoid arthritis [65]. Additional clinical trials are underway that are investigating the use of JAK inhibitors for other inflammatory conditions. A randomized, placebo-controlled study is evaluating upadacitinib on spondyloarthritis outcomes in patients with active psoriatic arthritis [66]. A phase 3 randomized, placebo-controlled, double-blind study is looking at Upadacitinib as therapy in combination with corticosteroids in adolescents and adults with atopic dermatitis [67]. These trials are essential in addressing the gaps in knowledge of long-term use of JAK inhibitors and its efficacy in other rheumatological and dermatological diseases.

Future clinical studies can explore the development of isoform specific inhibitors to minimize the adverse effects from JAK inhibitors. By developing different isoforms, further clarification on the direct impact on cytokine release and inhibition of signaling pathways can be assessed. Differences in JAK isoforms have been studied in patients with rheumatoid arthritis, but future research can be directed at looking at the use in psoriasis and PsA [68]. Emerging research in novel JAK/STAT modulators are also on the rise. New therapies including tyrosine kinase 2 inhibitor, modulator of sphingosine 1-phosphate receptor 1, and Rho-associated kinase 2 inhibitors, are being investigated. Clinical trials for these therapies are currently underway [69]. Notably, these modulators hold promising effects in patients suffering from psoriasis and PsA and would give patients broader treatment options. Other possible options include combination therapies integrating JAK inhibitors with biologic therapies. Hren et al. reported success rates in treatment of PSO/PsA with combined

JAK or TYK2-inhibition plus biological therapy [55]. However, minimal studies have looked at the efficacy and safety profile with combination therapy. The rate of unexpected adverse effects, and especially the risk of infections could be increased due to a double immunosuppression mechanism derived from some combinations [70]. However, combination therapy should still be considered in patients who are refractory or fail to reach treatment goals with monotherapies.

CONCLUSION

The JAK/STAT pathway is a central mediator of inflammation and tissue remodeling in both psoriasis and PsA, integrating key cytokine signals, such as IL-23, IL-17, IL-22, and TNF-α, that drive immune dysregulation and structural damage. JAK inhibitors have demonstrated significant efficacy in psoriasis by reducing keratinocyte hyperproliferation and modulating immune cell recruitment, leading to notable improvements in skin lesions. In PsA, these agents have shown promise in alleviating peripheral joint inflammation, though their effectiveness in treating enthesitis and axial disease remains inconsistent. The heterogeneity of PsA pathophysiology suggests that JAK inhibitors may not uniformly modulate all inflammatory pathways, particularly those driven by IL-23 and IL-17, which play key roles in joint destruction. While newer agents, including TYK2 inhibitors, offer improved selectivity with potentially fewer adverse effects, challenges, such as infection risk, thromboembolic events, and long-term safety concerns require ongoing evaluation. Additionally, the lack of long-term real-world data limits our understanding of the durability of response and comparative effectiveness against biologic therapies targeting IL-17 and IL-23. The variability in patient populations and disease phenotypes further complicates the generalizability of current findings. Combination strategies targeting multiple inflammatory pathways, such as dual inhibition of JAK/STAT and IL-23/IL-17 signaling, may enhance therapeutic efficacy but require further investigation to establish safety and long-term benefits. Future research should prioritize the development of targeted, disease-specific interventions that optimize treatment outcomes while minimizing adverse effects. Refining precision medicine approaches will be key to advancing the therapeutic landscape for psoriasis and PsA, ultimately improving long-term patient care and quality of life.

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CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest.

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