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REVIEW ARTICLE

JAK inhibitors in lichen planus: a review of pathogenesis and treatments

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ABSTRACT

Lichen planus (LP) is an auto-inflammatory skin disorder identified by a presence of T-cell lymphocytes at the dermal-epidermal junction. It is hypothesized that the INF–γ/CXCL10 axis fulfills a major role in the onset and persistence of chronic inflammation in LP. Since Janus kinases (JAKs) are involved in the transduction of INF–γ signals, they may be good targets for LP treatment. Several case reports and case series described the safety and efficacy of upadacitinib (2 articles), tofacitinib (6 articles), baricitinib (4 articles), and Ruxolitinib (1 Article) in the treatment of LP variants. The predominant variants that JAK inhibitors improved were lichen planopilaris, nail LP, and erosive LP. Considering the role of the JAK pathway in LP pathogenesis and the evidence provided by these reports, it seems JAK inhibitors would be effective therapeutic agents for LP treatment. Hence, these agents should be trialed and evaluated further.

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Introduction

Lichen planus (LP) is an auto-inflammatory skin disorder identified by a presence of T-cell lymphocytes at the dermal-epidermal junction and specific clinical and histopathological findings. Epidemiological evidence shows a prevalence of 0.5 to 1% (1). Several clinical variants of LP show specific histologic features. Case series and case reports have shown the safety and efficacy of Janus kinase (JAK) inhibitors such as tofacitinib, baricitinib, and upadacitinib in treating LP variants. This review aims to analyze the role of the JAKs pathway on LP pathogenesis and collect available data on the use of JAK inhibitor agents for treating LP variants.

Lichen planus variants

Cutaneous lichen planus (CLP) classically presents as purple flat papules and polygonal and pruritic plaques. There are several morphological and regional variations, including nail, oral, eruptive, inverse, atrophic, annular, linear, hypertrophic, bullous, ulcerative, vulvovaginal, actinic, lichen planopilaris, and LP pigmentosus (2). Oral LP is a common form of this disease that usually appears as white spots with reticulated pattern in the oral cavity. Erosive LP (ELP) is a severe form of LP that particularly affects mucosal areas such as the genitals or the oral cavity, resulting in painful lesions that harm the patient's daily life by impairing the ability to speak and eat (3). Lichen planopilaris (LPP) involves hair follicle and causes permanent hair loss that does not have a clear etiology; despite the variety of treatments available, a cure is yet to be available (4). Lichen planus affects individuals of all ages. Adults account for up to 95 percent of all instances, with the majority of cases developing in those aged between 30–60; however, children represent about 5 to 10% of occurrences (5).

Lichen planus pathogenesis and janus kinase pathway

Lichen planus (LP) is an auto-inflammatory disorder in which CD8+ cytotoxic T cells induce apoptosis in the basal layer of the epithelium. The first step in the pathogenesis of this condition is the expression or un-marking of an antigen (heat shock protein or peptide) on the surface of keratinocytes (6). Then, either as a result of a chance meeting with an antigen during regular surveillance or as a result of a chemokine-dependent migration into the lowest layer of epithelium, CD8+ T cells and some CD4+ lymphocytes move into the epithelium; CD4+ T cells and or major histocompatibility complex-1 (MHC-1) on keratinocytes trigger the activation of these CD8+ cells. Furthermore, following the increase in the expression of MHC-2 on the surface of keratinocytes, the number of Langerhans cells increases in the region, which, following the presentation of antigens to CD4+ cells and the release of interleukin 12 (IL-12), activate CD4+ T cells, further activating CD8+ T cells *via* interleukin 2 and interferon γ (INF–γ) signaling. Then, the apoptosis of basal keratinocytes of OLP lesions is triggered by CD8+ T lymphocytes *via* Fas-FasL, tumor necrosis factor (TNF), or granzyme B (7,8).

LP patients have higher levels of CD8+ T lymphocytes in their blood and skin. These lymphocytes are found near dyskeratotic keratinocytes and are involved in the pathogenesis of LP through cytotoxicity as a central mechanism. Epithelial-derived cytokines, chemokines, and stimulatory molecules, such as the

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Th1 chemokines like CXCL9/CXCL10, may play a significant role in LP (9). CD4+ T cells, including Th 17, Th2, Th1, and T-regulatory cells, are also involved (10). However, despite recent advances, some aspects of LP pathogenesis remain elusive.

It is becoming increasingly clear that lichen planus is most likely a Th1-driven disorder. However, Th17-associated cytokines have also been found in LP (11). Recent studies demonstrate a high number of Th1/Tbet + and IL-17A-positive cells in the T cell infiltrate under the basal layer of the epidermis, further supporting the theory that LP is an autoreactive pathology characterized by Th1/Th17 cells that respond to skin autoantigens (12). Inhibiting the function of IL-17 or IL-23 can be recognized as a new therapeutic approach to treating LP, and the presence of high levels of IFN-γ suggests that JAK inhibition might be a therapeutic target.

It is hypothesized that if the INF–γ/CXCL10 axis has a key role in the onset and persistence of chronic inflammation in lichen planus, it may be medically targeted to reduce inflammation. INF–γ particularly makes a signal *via* the JAK-signal transducer and activator of transcription (STAT) pathway. JAK members include JAK1, JAK2, JAK3, and TYK2, constituting one category of non-receptor protein tyrosine kinases that act as intracellular second messengers required for the cell to receive extracellular cytokine signals. Through interactions with cytokine receptors, JAKs regulate complex biological processes such as cell growth, differentiation, survival, development, and transformation, particularly in immune and hematopoietic cells (13).

Mutant cell lines lacking JAK1 are defective in IFN-1 and INF-2 signaling, while JAK2-deficient cell lines are defective in INF-γ signaling (14). Activation of the JAK-STAT pathway results in STATs being phosphorylated. Then, STAT1 homodimers reach the nucleus and are actively retained through a process that relies on JAK1 activity. Following the binding of STAT1 to the promoter region of the INF-γ gene, CXCL-10 is transcribed (Figure 1). Since JAKs (particularly JAK1 and JAK2) are involved in the transduction of INF–γ signals, they may be good targets for LP treatment. Tofacitinib, a pan-JAK inhibitor, can block INF–γ signaling and the production of CXCL10 downstream, making it an excellent alternative for treating LP patients. In light of recent research, it is possible to create new rational targeted treatments for debilitating illnesses like LP by interfering with the IFN-γ-CXCL10-CXCR3 axis (1).

Pietschke *et al.* showed that IL-6, IFN-ϰ, and IL-21 induce the inflammatory process in CLP, and STAT1 activation regulates the pro-inflammatory settings (15).

Shao *et al.* have revealed *in vitro* that INF–γ enhances T-cell-directed anti-keratinocyte responses by activating the JAK-STAT pathway in keratinocytes. Baricitinib, a JAK1/2 inhibitor, was demonstrated to reduce allogenic T-cell reactions against keratinocytes *in vitro* (16).

Use of janus kinase inhibitors for lichen planus

Tofacitinib is a novel pan-JAK inhibitor that acts through inhibition of the phosphorylation of STAT1, STAT3, and STAT5 by IL-6 and prevents the phosphorylation and activation of JAK1 and JAK3 (17). JAKs are not able to phosphorylate the cytokine receptors after tofacitinib treatment; as a result, the receptors cannot dock STATs and translocate to the nucleus. Lastly, the drug inhibits gene transcription and cytokine production. Dendritic cells, activated B cells, and CD4+ T cells such as Th1 and Th17 that result in multi-cytokine targeting are the main

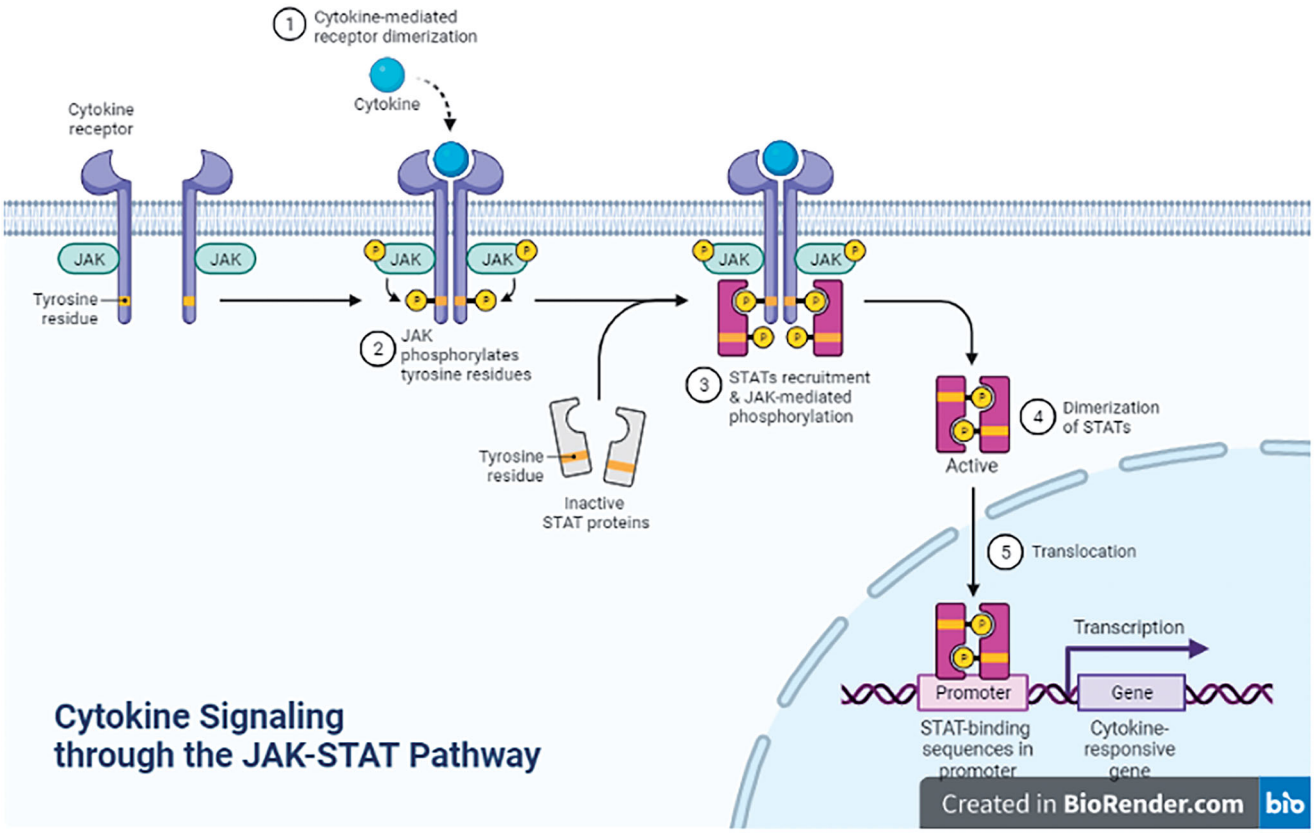

Figure 1. Janus kinase (JAK)/activator of transcription (STAT) pathway and associated cytokine signaling (Figure was created with the help of Biorender.com).

targets of tofacitinib. By preventing IFN-1-mediated signaling, tofacitinib can prevent dendritic cells from presenting antigens and stimulating T lymphocytes. After using tofacitinib, CD8+ T cell counts decline (18).

Several patients with nail LP, lichen planopilaris, and ELP have showed favorable improvement with tofacitinib (16,19,20). Studies showed that baricitinib selectively inhibits JAK1 and JAK2 with modest efficacy against tyrosine kinase 2 and significantly less against JAK3. Some case reports showed the safety and efficacy of baricitinib in treating LP variants (21–24).

Upadacitinib is classified as a specific JAK1 inhibitor (25) which is used to improve psoriatic arthritis, LP, ankylosing spondylitis, moderate to severe rheumatoid arthritis, and severe atopic dermatitis in patients who have not responded well to conventional therapy (26). In clinical trials, upadacitinib reduced the function of pro-inflammatory interleukins, momentarily boosted lymphocyte counts, and slightly lowered immunoglobulin levels (27). Also, this JAK inhibitor agent provided good results in two patients with erosive LP (28,29).

Tofacitinib

Seiringer *et al.* reported a 51-year-old man with a 30-year history of erythematous papules, hypertrophic plaques, and crusts located primarily on his extremities, diagnosed as hypertrophic LP based on histological features. Previous treatments including corticosteroids (topical, intralesional, and systemic), systemic retinoids, methotrexate, cyclosporine, mycophenolate mofetil, azathioprine, apremilast, ixekizumab, guselkumab, and photo (chemo) therapy did not adequately control the disease. Tofacitinib, a JAK1 and JAK3 inhibitor, was started at 5 mg twice daily. After 20 weeks, significant improvements were observed in all clinical parameters (30).

Another patient who suffered from several autoimmune diseases received tofacitinib. She was a 57-year-old woman had been diagnosed with hypothyroidism and rheumatoid arthritis who complained of alopecia areata. The patient developed severe trachyonychia of all fingernails when she was treated with methotrexate which microscopic examination confirmed nail LP. Methotrexate was interrupted, and intralesional triamcinolone acetonide was initiated without any improvement. The rheumatologist prescribed tofacitinib 5 mg twice daily; after six months, the hair and nail symptoms resolved completely (20).

In a case series, three patients presented with erosive LP on oral, genital, and ocular mucosa. Previous treatments including methotrexate, acitretin, mycophenolate mofetil, prednisone, and cyclosporine failed to improve these lesions. Hence, tofacitinib 5 mg twice a day was started. In one patient, adding tofacitinib to methotrexate and low-dose prednisolone caused a dramatic response. The two other patients, treated solely with tofacitinib 5 mg twice daily, improved completely (3).

Yang *et al.* described their experience prescribing tofacitinib 5 mg twice a day for ten patients with LPP. Five patients received combination therapy with hydroxychloroquine, topical tacrolimus, and intradermal triamcinolone acetonide. Eight showed good improvement. Two patients responded sufficiently after increasing the dose to 15 mg a day. The LPP Activity Index (LPPAI) showed 30 to 94% improvement which was not statically significant between subjects who received tofacitinib as monotherapy and those who were on combination therapy. Total blood cell count, liver function panel, metabolic panel, and lipid panel were evaluated before and after tofacitinib administration; no significant changes were observed. One patient who received 15 mg daily of tofacitinib noted weight gain after 12 months. No other side effects were observed (4).

In a retrospective study, nine patients with LPP received tofacitinib concurrent with other medications such as finasteride, dutasteride, mycophenolic acid, naltrexone, intralesional triamcinolone acetonide, topical pimecrolimus, topical tacrolimus, and topical minoxidil. Four patients were administered oral tofacitinib, and four other patients received topical tofacitinib 2%. One patient first received the topical form but was switched to the oral form due to a lack of response. The initiated systemic dose was 10 mg daily, which, in 2 patients, was increased to 15 mg daily. Topical tofacitinib 2% was administered twice a day. All patients were on systemic therapy showed a favorable initial response. Three of the patients who received the topical form improved sufficiently. One patient experienced mild, transient hemoglobin and creatinine abnormalities. Also, two patients experienced a mild elevation in triglyceride and cholesterol levels (19).

Rahbar Kooybaran *et al.* reported a 77-year-old woman with a 17-year history of LP and 40 years of suffering from pain attributed to oral mucosal lesions, diagnosed as esophagus lichen planus (ELP) based on the biopsy. The use of first-line therapies such as systemic corticosteroids, fluticasone, and endoscopic balloon dilation was unsuccessful, and the exacerbation of the disease led to combination therapy with swallowed fluticasone (880 μg twice a day) and tofacitinib (5 mg twice a day) for 14 weeks followed by maintenance therapy with tofacitinib 5 mg daily. This treatment protocol caused a significant improvement in the patient's dysphagia after 24 weeks, with a relative effect on the fibrotic esophageal stricture. The symptoms recurred after discontinuing tofacitinib, which led to the restart of combination therapy (fluticasone and tofacitinib 5 mg daily for six weeks), followed by maintenance with tofacitinib monotherapy. Since the discontinuation of tofacitinib led to recurrence and monotherapy with it prevented recurrence, while monotherapy with fluticasone did not resolve the symptoms of recurrence, it can be concluded that tofacitinib played a significant role in controlling the disease (31). The studies on use of tofacitinib in patients with LP presents at the Table 1.

Baricitinib

Moussa *et al.* reported a 63-year-old woman who suffered from chronic alopecia areata (AA) and concomitant acute oral LP. She had been received long-term prednisolone (12.5 mg daily) and intermittent intralesional corticosteroid for AA. To control her AA, she began taking 3.4 mg twice daily of barcitinib. The patient's improvement in her OLP was observed after her 1 month of treatment with baricitinib and was maintained for 4 months. A near complete improvement of the oral lesions was observed. Baricitinib was well tolerated, except for a modest increase in cholesterol (6.2 mmol/l) (21).

A retrospective study collected data was related to the LPP patients who had received baricitinib at least for 3 months. The LPP Activity Index (LPPAI) was applied to asses Disease activity which described a value of 0 indicating no disease activity and a value of 10 indicating maximum disease activity. The median LPP Activity Index score was 5.8 at the baseline. From a total of 12 patients with recalcitrant LPP; 7 patients with classical LPP, and 5 patients with frontal fibrosing alopecia (FFA) were identified. the mean dose of barcitinib was 3.4 mg and titrated based on response and acceptability. The reduction in the median LPP Activity Index score was 1.2 and 1.3 at the initial and latest reviews, respectively. Two patients with frontal fibrosing alopecia and 2 with classical lichen planopilaris had no improvement

Table 1. Case reports and case series on the use of tofacitinib in patients with lichen planus (LP).

Article	Year	No. of patients	Disease type	Gender	Dose	Outcome
Seiringer et al.	2020	1	Hypertrophic LP	Male	5 mg BD	Improvements in all clinical parameters after 20 weeks
Iorizzo et al.	2021	1	Nail LP associated with alopecia universalis	Female	5 mg BD	Hair and nails improved consistently after 6 months
Damsky et al.	2020	3	Erosive LP; LP	2 Females 1 Male		Improvement in all patients
Yang et al.	2018	10	LPP	6 Females 4 Males		Improvement in 80% of patients; no adverse effects
Plante et al.	2020	9	LPP	8 Females 1 Male		Both topical and oral formulations were effective; minor laboratory abnormalities
Rahbar Kooybaran et al.	2022	1	Esophageal lichen planus	Female	5 mg BD that reduced to 5 mg daily	Significant improvement in the patient's dysphagia; Relative effect on fibrotic esophageal stricture; Neutral effect on vaginal involvement.

LP: lichen planus; LPP: lichen planopilaris.

Table 2. Case reports and case series on the use of baricitinib in patients with lichen planus (LP).

Article	Year	No. of patients	Disease type	Gender	Dose	Outcome
Moussa et al.	2022	1	Oral LP	Female	3.4 mg twice daily	Improvement of the patient's OLP after 1 month; sustained after 4 months
Moussa et al.	2022	12 (7 classic LPP and 5 FFA)	LPP	3 Males 9 Females	3.4 mg daily	5 of 7 with classic LPP demonstrated an initial reduction in the median LPPAI score, as did 3 of 5 patients with FFA. 2 patients with classic LPP and 2 with FFA failed to improve despite dose escalation, 2 of whom experienced disease progression
Pünchera et al.	2021	1	Nail LP	Female	4 mg daily	Substantial improvement after 2 months; complete resolution after 6 months
Kreuter et al.	2022	1	FFA	Female	4 mg daily for 2 months	Complete clearance of SCLE; stopped further progression of FFA

LP: lichen planus; LPP: lichen planopilaris; FFA: frontal fibrosing alopecia, LPPAI: Lichen Planopilaris Activity Index; SCLE: subacute cutaneous lupus erythematosus.

Table 3. Case reports and case series on the use of upadacitinib in patients with lichen planus (LP).

Article	Year	No. of patients	Disease type	Gender	Dose	Outcome
Balestri et al.	2022	1	Erosive LP	Female	15 mg daily	Good improvement of erosive oral LP
Koohbaran et al.	2021	1	Erosive LP	Female	15 mg daily	Good improvement of erosive oral LP and esophageal LP

despite baricitinib dose escalation; among them, two experienced disease progression (22).

Pünchera *et al.* introduced a 60-year-old woman who complained of severe nail dystrophy of all fingernails of both hands, which had appeared one year prior. The diagnosis of LP was established. Her nail was substantially improved with baricitinib (4 mg daily) after two months; they were completely clear after six months (23).

A 62-year-old woman presented with a four-year history of subacute cutaneous lupus erythematosus (SCLE). The patient also suffered from hair loss on the temporal and frontal hairline. she also lost her eyebrows completely. The diagnosis of FFA was established. Barcitinib was started 4 mg daily for two months. The dose was maintained at 2 mg daily of barcitinib. SCLE was completely cleared and FFA stopped further progression (24). The studies on use of baricitinib in patients with LP presents at the Table 2.

Upadacitinib

Balestri *et al.* reported a 45-year-old woman with erosive LP on the tongue, gums, and oral mucosae, who suffered from peripheral psoriatic arthritis at the same time. She was administered monotherapy with the JAK1 inhibitor upadacitinib (15 mg once daily) for psoriatic arthritis. Drastic improvement of the oral lesions was associated with treating the psoriatic articular impairment on follow-up examination after seven days, sustained after 12 weeks of treatment (28).

Another patient was a woman in her 59 s with erosive oral LP that started five years prior with periodic exacerbation of mucosal lesions, causing pain and dysphagia. Esophagogastroscopy and histological examination showed severe exfoliative esophagitis. Preexisting medications included a topical corticosteroid and several pulses of dexamethasone, but her symptoms improved only partially and were resistant. Accordingly, therapy with the JAK1 inhibitor upadacitinib was initiated at 15 mg daily. Drastic improvements were observed in all clinical and paraclinical parameters after four weeks of treatment with upadacitinib. Esophagoscopy and histological exams showed improvement of the exfoliative esophagitis 24 weeks after treatment; the oral lesions were shown complete improvement (29). The studies on use of upadacitinib in patients with LP presents at the Table 3.

Ruxolitinib

In a prospective phase II clinical study, twelve patients with a median age of 63 years diagnosed with cutaneous LP by

histopathological assessments received the topical form of ruxolitinib, a JAK1 and JAK2 inhibitor, twice a day for eight weeks. The prevalent form in all cases was typical LP; however, five patients had hypertrophic LP, and half had a history of systemic treatment. Previous treatments including acitretin, hydroxychloroquine, methotrexate, metronidazole, or topical and oral corticosteroids had failed to control the disease. The side effects were mild and transient. Finally, Brumfiel *et al.* demonstrated in their trial how successful topical ruxolitinib was in treating cutaneous LP, marked by notable decreases in the number of lesions (by 50 lesions on average) and mCAILS (modified Composite Assessment of Index Lesion Severity) scores over four weeks of therapy. They also showed in their transcriptomic analysis that the interferon-stimulated gene (Interferon 1 and 2) down-regulation correlated with the response to treatment (32).

Conclusion

Because of the key role of the IFN/CXCL10 pathway in LP pathogenesis, inhibition of the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is a therapeutic target for LP. The available data evaluating the efficacy and safety of these agents are limited to case reports and case series. Most reports concerned the treatment of cases of erosive, nail, or follicular LP, which had responded poorly to other treatments. We conclude that JAK inhibitors could open a new therapeutic window for LP, with clinical trials warranted to evaluate their efficacy.

Limitations

The most current data on the role of the JAK inhibitors in LP are based on case reports and frequent coexisting with other inflammatory skin diseases.

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