

A Review on the Use and Effectiveness of JAK Inhibitor in the Management of Lichen Planopilaris

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Abstract:- Lichen planopilaris (LPP) is an inflammatory variant of primary cicatricial alopecia. It causes severe hair loss and can lead to complete baldness. It is an autoimmune disease and can affect patients' physical and mental lives greatly. JAK Inhibitors have been proven the most effective treatment option to treat LPP. This literature review aimed to analyze the effectiveness of JAK inhibitors in the management of LPP. In this review, we analyzed the ten most recent and comprehensive studies. The review has summarized existing case reports from clinical studies that have supported JAK inhibitors. The findings of the review show that JAK inhibitors are effective options for the treatment of LPP, however, there are still some concerns regarding the long-term safety of these drugs in the treatment of LPP. This review also highlights potential gaps in the literature and further need for research. Currently, there is a need for further research on the effectiveness of JAK inhibitors in the treatment of LPP.

Keywords:- Lichen Planopilaris, Scarring Alopecia, Janus Kinase Inhibitors, Tofacitinib, Ruxolitinib, Baricitinib.

I. INTRODUCTION

Lichen planopilaris (LPP) is an autoimmune condition that is responsible for a variety of hair loss patterns[1]. North American Hair Research Society (NAHRS) [2] recognizes it as the classic lymphocytic cicatricial alopecia and acknowledges it as a follicular variant of lichen planus [3,4]. The etiology of this condition is believed to be activated by T-lymphocytes targeting follicular antigens [5]. However, the exact reason for LPP is still not fully understood, with immune system reactions, immune privilege loss in the bulge of the hair follicle, bulge stem cell death, and changes in signaling pathways like reduced peroxisome proliferator-activated receptor- γ signaling being implicated in the progression of the disease [6]. Alopecic patches, perifollicular erythema, and scaling are common signs of LPP, however other symptoms such as itching, burning, or soreness may also be present.

LPP is the most frequent type of primary cicatricial alopecia (PCA) that involves inflammatory pathways for permanent hair loss [7]. Hair loss profoundly impacts patients' perceptions of themselves and their ability to go about their everyday lives [8]. Individuals suffer more distress, affecting their social lives and general health, due to the irreversible character of hair loss in LPP [9,10]. Despite the availability of several therapies for the management of LPP, their efficacy is often inadequate. In recent research, Janus kinase (JAK) inhibitors have shown encouraging outcomes in treating alopecia areata and other non-cicatricial inflammatory alopecia [11,12].

JAK inhibitors influence the immune system by focusing on the lymphocytes' JAK-STAT signaling pathway. They are often used to treat inflammatory disorders like rheumatoid arthritis and alopecia areata [10]. The JAK-STAT pathway, which involves JAKs, plays a crucial role in transmitting signals for inflammatory responses, making it a potential target for treating LPP [13]. Studies have shown promise in using JAK inhibitors to treat LPP by blocking this pathway, as cytokines activated by JAK-STAT are believed to contribute significantly to LPP's pathogenesis [14,15]. Inhibiting this pathway could be particularly beneficial for patients with persistent LPP [16]. Yang et al., in their study, reported that tofacitinib, a JAK inhibitor drug showed clinically significant improvements in 80% of LPP patients treated alone or combined with other treatment choices[17].

There is significant evidence that LPP affects the quality of life of affected patients, with one study demonstrating 70.7% of LPP patients had moderate or extreme effects on their quality of life [18]. Despite existing treatment modalities for LPP, management remains a clinical challenge. Therefore, it is important to assess the efficacy of JAK inhibitors as a new therapy option for LPP and to provide a thorough review of the present treatment options. This review has several goals: first, to give a synopsis of LPP's pathophysiology; second, to examine the current treatment modalities and their limitations; third, to investigate how JAK inhibitors work in LPP; fourth, to assess the safety and effectiveness of JAK inhibitors using

data from current clinical trials and case studies; and finally, to suggest avenues for future research in this area.

II. PATHOPHYSIOLOGY AND EPIDEMIOLOGY OF LICHEN PLANOPILARIS

➤ *Epidemiology of Lichen Planopilaris*

The estimated prevalence of LPP in the general population is 1.25% [19]. The onset of LPP often occurs between the ages of 40 and 70, with higher incidence reported in females. Females are twice more likely to be affected with LPP compared to the males [20].

➤ *Pathophysiology of Lichen Planopilaris*

Although the exact mechanism of LPP remains poorly understood, there is consensus on the involvement of the immune system in LPP [21]. This autoimmune response is thought to be triggered by various factors, including genetic predisposition, environmental factors, and possibly viral infections. One of the key features of LPP is the infiltration of inflammatory cells, particularly T lymphocytes, into the hair follicles [22]. These activated T lymphocytes target the hair follicles, leading to their destruction and eventual scarring.

The activation of fibroblasts might be caused by inflammatory mediators such as TGF- β and b-FGF [23]. According to recent data, the demise of the pilosebaceous unit associated with LPP may be affected by PPAR- γ [24]. According to another research, cytokines, like interleukins (IL), tumor necrosis factor-alpha (TNF- α), and interferon-gamma (IFN- γ) are thought to have a role in mediating the inflammatory process in LPP and intensify tissue damage [25].

The role of immune dysregulation in the pathophysiology of LPP is further supported by the presence of autoantibodies targeting hair follicle antigens in some patients [26]. These autoantibodies may contribute to the destruction of hair follicles and the development of scarring alopecia in LPP.

➤ *Current Treatment Modalities*

LPP poses a significant therapeutic challenge due to its chronic and progressive nature, often resulting in permanent hair loss. Treatment aims to halt disease progression, relieve symptoms, and potentially promote hair regrowth. Various treatment modalities have been explored, including topical and systemic therapies, with varying degrees of success. However, there is no universally effective treatment for LPP, and management is often individualized based on disease severity and patient response.

➤ *Topical Therapies*

Topical corticosteroids are commonly used as first-line therapy for mild to moderate LPP. They help reduce inflammation and itching, but their efficacy in halting disease progression and promoting hair regrowth is limited [27].

Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, have also been used with some success, particularly in patients with facial involvement or those who cannot tolerate corticosteroids [7]. However, their long-term safety and efficacy in LPP remain uncertain.

➤ *Systemic Therapies*

Systemic corticosteroids are often used in moderate to severe cases of LPP, especially when there is rapid disease progression or significant symptoms. However, their long-term use is limited by the risk of adverse effects, including weight gain, diabetes, and osteoporosis [28]. Other systemic therapies, such as hydroxychloroquine, methotrexate, and mycophenolate mofetil, have been used in LPP with varying degrees of success [29]. These drugs work by suppressing the immune response, but their efficacy is often limited, and they may not prevent disease progression or promote hair regrowth.

➤ *Limitations and Challenges*

A significant challenge in treating LPP is the lack of reliable data supporting the effectiveness of current therapies. There have to be more strong clinical trials since most therapy recommendations are based on retrospective research, small case series, and expert opinion [30]. Additionally, the chronic nature of LPP requires long-term treatment, which can be challenging for patients due to the potential for side effects and the need for regular monitoring.

Another challenge is the variability in treatment response among patients [31]. While some individuals may experience significant improvement with a particular therapy, others may not respond at all. This highlights the need for personalized treatment approaches based on individual patient characteristics and disease severity. Further research is needed to identify more effective treatment strategies for LPP and to address the limitations and challenges associated with current therapies.

➤ *Role of Jak Inhibitors in Lichen Planopilaris*

LPP often requires long-term management to prevent further hair loss and scarring. Traditional therapies, including topical and systemic corticosteroids, immunomodulatory agents, and antibiotics, have shown varying degrees of efficacy but are often associated with limited success and potential side effects [32,33]. Newly developed Janus kinase (JAK) inhibitors show great promise as a reliable treatment for LPP. JAK inhibitors target to block the JAK-STAT signaling system. A possible method to stop the development of LPP is to reduce inflammation, which may be achieved by modulating the immune response using JAK inhibitors [34].

Several JAK inhibitors have been studied for their efficacy in treating LPP, including tofacitinib, ruxolitinib, baricitinib, and upadacitinib. These drugs have shown promise in both clinical trials and case studies, with many patients experiencing significant improvements in their condition [35].

Tofacitinib had particularly shown promise in the treatment of LPP. According to a case report, Tofacitinib reduced scalp inflammation and promoted hair regrowth in thirteen patients with refractory LPP [36]. Similarly, a retrospective analysis of 9 tofacitinib-treated LPP patients revealed encouraging results, with most patients attaining a partial or complete response to therapy [37]. Another JAK1/2 inhibitor that has shown potential in treating LPP is ruxolitinib. Significant hair regrowth and reduction in scalp inflammation were seen in all seven patients treated with ruxolitinib for LPP in a case study [13]. Similarly, after 6 months of therapy with ruxolitinib, a patient with refractory LPP had full clearance of hair regrowth and scalp lesions [38].

The effectiveness of the JAK1/2 inhibitors baricitinib and upadacitinib in LPP has also been investigated on six patients

in a case series. All six patients treated with baricitinib improved, and in some cases, the scalp lesions disappeared entirely [39]. Similarly, following 12 weeks of therapy with upadacitinib, a patient with LPP had a significant improvement in inflammation of the scalp and hair regrowth [40]. In general, there is sufficient evidence in literature that JAK inhibitors are effective in treating LPP, with several patients reporting substantial improvement in their symptoms. Nevertheless, more studies are required to determine the medications' safety and effectiveness in long-term treatment of LPP. However, for individuals with LPP who have not responded to conventional treatments, JAK inhibitors provide a new and successful alternative.

Table 1 highlights various studies that discuss the role of JAK inhibitors in the management of LPP.

Table 1. Literature Review about Jak Inhibitor in the Management of Lichen Planopilaris

Sr.	Study and Year	Design	Effectiveness of Jak Inhibitor in Management of Lichen Planopilaris
1.	Damsky et al. (2020) [41]	Case Study	JAK inhibitor 'tofacitinib' was effective in managing severe lichen planus.
2.	Yang et al. (2018) [17]	Case Study	Oral tofacitinib, used alone or with other treatments, can result in significant improvement in cases of lichen planopilaris.
3.	Abduelmula et al. (2023) [16,42]	Systematic Literature Review	JaK inhibitors, tofacitinib, baricitinib, ruxolitinib, and upadacitinib, were effective in treating lichen planus. Tofacitinib showed partial resolution in 60% of patients and complete resolution in 10% of patients.
4.	Nasimi & Ansari (2024) [10]	Literature Review	JAK inhibitors show promise for treating LPP and FFA, especially in refractory cases, but further research is needed to confirm their efficacy.
5.	Montilla et al. (2019) [43]	Systematic Literature Review & PRISMA Analysis	JAK/STAT pathway drugs, tofacitinib and ruxolitinib, were effective in atopic dermatitis (AD). Responses varied in vitiligo and alopecia areata (AA), with some cases being unresponsive.
6.	Hosking et al. (2018) [44]	Literature Review	Topical JAK inhibitors improve psoriasis and atopic dermatitis scores, but results for vitiligo and alopecia areata are inconclusive.
7.	Dunn et al. (2023) [38]	Case Series & Literature Review	JAK inhibitors have the therapeutic potential in recalcitrant FFA/LPP, but further research is needed for safety and efficacy.
8.	Huang & Shi (2023) [45]	Case Study	Successful treatment of nail lichen planus with tofacitinib, highlighting JAK inhibitors as a potential therapy for inflammatory skin diseases.
9.	Plante et al. (2020) [46]	Stepwise Approach, Clinical Study	Tofacitinib, both topical and systemic, as viable adjunctive treatment options in refractory LPP cases.
10.	Bazargan et al. (2023) [47]	Case Report & Literature Review	Successful treatment of resistant plantar ulcerative lichen planus with tofacitinib tablets, suggest a new therapeutic application for tofacitinib in treating skin diseases.

➤ Safety and Adverse Effects of Jak Inhibitors

Research has proved JAK inhibitors' promising role in the treatment of LPP, however, there are some adverse effects as well. In general, JAK Inhibitors don't show any adverse effect at the initial stage of their administration, but their long-term use is associated with some side effects. One of the most important and serious effect of JAK inhibitors is that they can increase the potential risk of different infections. As LPP is an autoimmune disease, JAK inhibitors suppress the response of

immune system to remove the disease but as a result it can also make the patients more susceptible to certain fungal, bacterial and viral infectious diseases [10]. So, it is recommended that the patients should be monitored closely during their treatment with Jak inhibitors.

Another most important and life-threatening risk is the development of malignancies, especially lymphomas. The research has shown that the risk is quite low but it has been

reported that the cases being treated with JAK inhibitors develop lymphomas in their life afterwards [43]. So, the patients should be monitored regularly during their treatment with JAK inhibitors for any signs of malignancy. Gastrointestinal disturbances are also among the adverse effects of JAK inhibitors like abdominal pain, nausea, and diarrhea; it can also increase hepatic enzymes [10]. In some cases, the Jak inhibitors have also caused potential changes in blood pressure levels and lipid profiles of the patients being treated. Additionally, research has also reported that some patients also had cardiovascular problems, like thromboembolic problems in the patients, so, the patients should be monitored through the treatment duration and after the treatment [10].

In short, JAK inhibitors have a promising role in the treatment of LPP but their usage needs careful monitoring and observation for the safety of the patients. Further research is needed to understand the long-term effects of JAK inhibitors to improve its benefits.

III. FUTURE DIRECTIONS & CHALLENGES

Despite significant research on the effect of JAK Inhibitors on LPP, there exists considerable gaps in the research and future research should focus on several key areas. Firstly, to validate the efficacy and safety of JAK Inhibitors in the treatment of LPP, more randomized controlled trials (RCTs) are needed. The trials should include larger sample sizes and longer follow-up periods to test the long-term effectiveness of Jak Inhibitors.

Secondly, there is a lack of evidence about the dosage and duration of JAK Inhibitors administration on the patients of LPP. Currently, there exists a wide gap in research about the exact effective dosages and treatment durations for LPP. Further research is required to establish standardized treatment plans to improve treatment outcomes and minimize adverse effects. Besides that, more research is needed to explore some other therapies combined with JAK inhibitors to enhance the therapeutic effectiveness of medicines. Different pathways involving different pathogenesis of LPP should be used in the future studies to compose better treatment plans. Another important area of study that should be focused on future research is the identification of biomarkers to predict the treatment responses to JAK inhibitors in LPP treatment. The biomarkers can help create personalized treatment plans, leading to more effective and targeted therapeutic interventions.

Research has proved that the role of JAK inhibitors in the treatment of LPP is very promising but there are also different challenges and limitations associated with them that should be addressed in the future studies. The most important challenge is the cost of JAK Inhibitors, which can make its access limited to only those patients who can afford it. This high cost

should be reduced and made affordable for its widespread usage in LPP treatment. The second challenge is about the adverse effects associated with JAK Inhibitors like liver enzyme abnormalities and risk of different infections. Further research is required to deal with these side effects and to ensure the safe usage of JAK inhibitors. Furthermore, there are not enough studies about the long-term effects of JAK inhibitors in LPP treatment. To determine the risks of long-term JAK inhibitor usage, such as the emergence of malignancies and severe infections, further studies are required.

In short, more RCTs, customized treatment plans, combination therapeutic interventions, predictive biomarkers, and solutions to cost and safety issues should all be the focus of future research to improve the clinical usage of JAK inhibitors for LPP.

IV. CONCLUSION

In conclusion, LPP is a chronic inflammatory disease that results in scarring alopecia, predominantly affecting adults, with a higher prevalence in women. It is believed to be an autoimmune disorder characterized by the infiltration of inflammatory cells, particularly T-lymphocytes, into the hair follicles. Current treatment modalities for LPP are often unsuccessful in achieving long-term remedies. JAK inhibitors have been proven as an effective treatment option for LPP, with studies showing significant improvement in patients. To completely understand the role of Jak inhibitors in the treatment of LPP, further studies are required. For the treatment of LPP, JAK inhibitors should be studied in more RCTs to determine their efficacy and safety, as well as to solve the cost and safety issues. Continued research and clinical trials are needed to understand JAK inhibitors' involvement in LPP therapy and enhance patient outcomes.

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