BRIEF ARTICLES

Apremilast for Lichen Planopilaris and Frontal Fibrosing Alopecia: A Case Series

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ABSTRACT

Importance: Lichen planopilaris and frontal fibrosing alopecia are characterized by scarring alopecia associated with pruritus, inflammation, and pain of affected areas. There is a paucity of data on treatment options for these disorders. The available management options are associated with significant adverse effects and poor efficacy.

Objective: To explore apremilast as a treatment option for refractory lichen planopilaris and frontal fibrosing alopecia

Design: This is a retrospective case series analyzing the outcomes of four patients with refractory lichen planopilaris or frontal fibrosing alopecia treated with apremilast.

Setting: The patients were seen in the faculty practice of an academic institution in New York City.

Participants: Four female patients with biopsy confirmed lichen planopilaris or frontal fibrosing alopecia refractory to currently used treatments

Observations: We report a case series of four patients with lichen planopilaris and frontal fibrosing alopecia who had failed multiple previous treatments, including intralesional steroids, anti-malarials, oral anti-inflammatory agents, minocycline, acitretin, mycophenolate mofetil, and laser treatment who responded to apremilast. While two of these patients discontinued the drug due to adverse effects such as gastrointestinal discomfort, clinical improvement was seen in every patient.

Conclusions: To date, this is the first report of the use of apremilast for lichen planopilaris or frontal fibrosing alopecia, indicating its possible use in patients refractory to other treatments.

INTRODUCTION

Lichen planopilaris (LPP) and frontal fibrosing alopecia (FFA) are inflammatory, follicular disorders, characterized by cicatricial alopecia with associated pain and pruritus of affected areas. The diagnosis is based on clinical history as well as histopathologic findings indicating inflammation of the infundibulum and isthmus of the hair follicle. It classically affects women more than men and can be challenging to treat. Currently used treatments include intralesional steroids, methotrexate, mycophenolate, hydroxychloroquine, finasteride, dutasteride, doxycycline, and minocycline. However, no randomized, double-blind trials have been conducted evaluating any treatments for LPP or FFA. We report a case series of four patients with biopsy proven LPP or FFA that was refractory to other treatments and responded to apremilast. To our knowledge, this is the first report of apremilast being used for LPP or FFA.

Case 1:
A 62 year-old white female presented with a 4-year history of a pruritic, scaly, erythematous eruption on her scalp with associated hair loss. Physical examination revealed irregular patches of decreased hair density over the anterior crown with perifollicular erythema and scaling. A scalp biopsy revealed perifollicular fibrosis and interface dermatitis involving the follicular infundibulum and isthmus, confirming the diagnosis of lichen planopilaris. The patient had previously attempted numerous treatments with minimal clinical response, including methotrexate at a dose of 15 mg weekly, hydroxychloroquine, finasteride, intralesional triamcinolone 10 mg/cc injections, acitretin 20 mg daily, cyclosporine 225 mg daily, mycophenolate mofetil 500 mg three times daily, and excimer laser. The decision was made to initiate treatment with apremilast at a dose of 30 mg twice daily and discontinue all other medications. Within 3 months, significant improvement was noted in the scalp inflammation and pruritus.

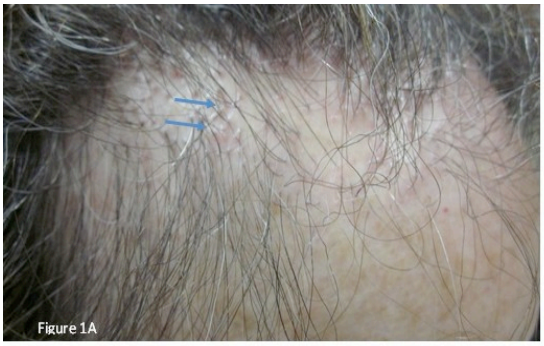
Case 2:
A 75 year-old white female with a history of hypothyroidism and depression presented with a one year history of hair loss and pruritus of the scalp. Physical examination revealed erythema and scaling of the right anterior scalp with patchy alopecia. A scalp biopsy was performed, which revealed rare diminutive hairs with condensation of elastic fibers around fibrous tracts, indicating a late stage scarring process. The patient had received intralesional triamcinolone injections and minocycline 100 mg twice daily for months with minimal effect. Apremilast was initiated at a dose of 30 mg daily and titrated up to 30 mg twice daily. There was some improvement in the patient's clinical symptoms; however, she began experiencing depressive symptoms, as well as gastrointestinal discomfort. The apremilast dose was decreased to 30 mg daily and eventually discontinued due to the aforementioned side effects.

Case 3:
A 70 year-old female presented with a few months history of hair loss and a painful sensation of the scalp. Examination revealed erythematous patches with scaling and decreased hair density of the frontal scalp. Scalp biopsy revealed perifollicular fibrosis and dermatitis involving the infundibulum. The patient was initiated on intralesional triamcinolone injections, minocycline 100 mg daily, and hydroxychloroquine 200 mg daily. The patient's condition was not significantly improving, and apremilast 30 mg twice daily was initiated. Four months later, the patient's dose was decreased to 30 mg daily and eventually discontinued due to gastrointestinal discomfort and diarrhea. However, her lichen planopilaris had shown improvement.

Case 4:

A 28 year-old female presented with a few months of burning sensation of the scalp and associated scattered hair loss. Examination revealed decreased hair density with hyperkeratosis and perifollicular erythematous papules of the anterior crown of the scalp and bilateral eyebrows. Scalp biopsy revealed concentric fibrosis of the hair follicles with a lymphocytic infiltrate of the infundibulum. She initiated monthly injections of intralesional triamcinolone for 10 months with concomitant topical clobetasol solution daily with minimal response. She also attempted oral finasteride for 10 months without effect. Apremilast was then initiated at a dose of 30 mg twice daily. The patient reported some mild gastrointestinal discomfort, but continued to take the medication and reports improvement in her symptoms.

FIGURES



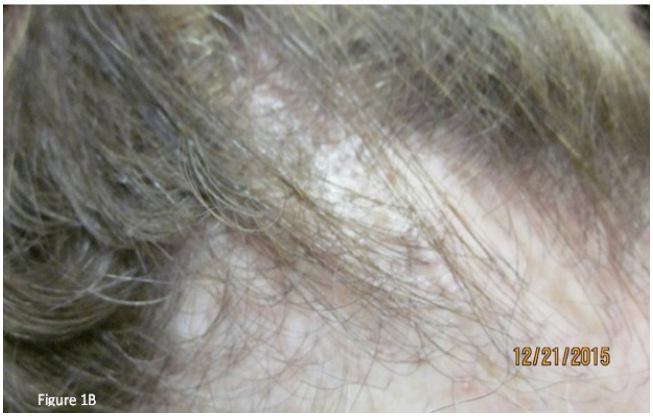
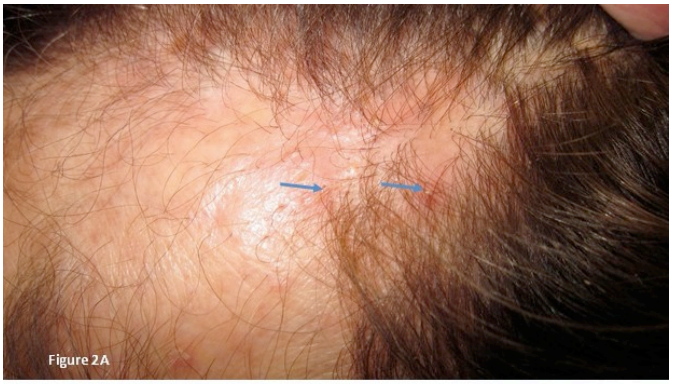


Figure 1A. A 62 year-old white female presented with a 4-year history of LPP prior to initiation of apremilast. Note the arrows indicating perifollicular erythema.

Figure 1B. 15 months into treatment with apremilast. Note the resolution of perifollicular erythema.



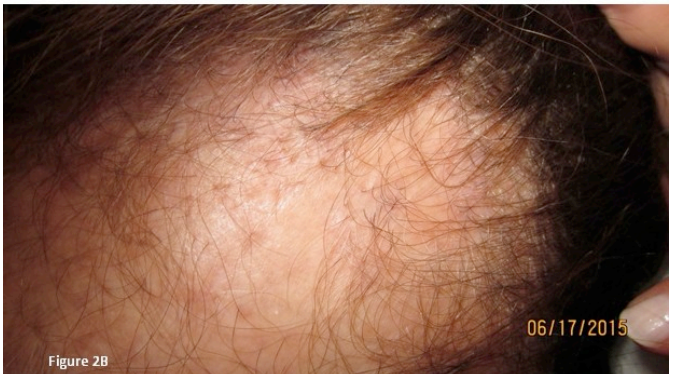


Figure 2A. A 75 year-old white female with a 1 year history of LPP prior to initiation of apremilast. Note the arrows illustrating perifollicular erythema.

Figure 2B. Two months into apremilast treatment, note the resolution of perifollicular erythema.

DISCUSSION

Lichen planopilaris is a form of lichen planus characterized by inflammation and scarring alopecia of the scalp. It is subdivided into three forms depending on the pattern of involvement, classic lichen planopilaris, frontal fibrosing alopecia, and Graham-Little-Piccardi-Lasseur syndrome.[1] Frontal fibrosing alopecia presents with alopecia involving the frontotemporal scalp, eventually progressing to the parietal scalp and eyebrows as well. It is most commonly seen in post-menopausal women of Caucasian descent.[2] Because of this, some have speculated that the pathophysiology is related to hormonal imbalances; however, no consistent patterns of hormonal abnormalities have been detected in affected patients.[3]

The pathogenesis of LPP is not well understood; however, the leading theory is an autoimmune destruction of the hair follicle focused on the infundibulum and the isthmus, leading to the death of follicular stem cells as they are located in this region.[1]

In addition to disfigurement, LPP is associated with significant pruritus, discomfort, and pain of affected areas. As a result, patients often seek treatment and symptomatic relief for this condition. Currently used treatments include topical and intralesional steroids, systemic steroids, oral minocycline, mycophenolate mofetil, hydroxychloroquine, methotrexate, excimer laser, and cyclosporine.[4] Unfortunately, these modalities often do not result in satisfactory outcomes and are associated with significant adverse effects, such as skin atrophy, Cushing's syndrome, hepatoxicity, renal toxicity, and neutropenia.[4] Furthermore, there are no randomized clinical trials assessing treatment agents for either LPP or FFA. Mesinkovska et al has illustrated oral pioglitazone, a peroxisome proliferator-activated gamma (PPAR-γ) agonist to be effective in treatment of LPP based on recent evidence implicating the dysfunction of PPAR- γ in cicatrical alopecias.[5,6] However, this has not been replicated elsewhere.

Apremilast, a phosphodiesterase type IV inhibitor, acts to reduce the production of cytokines such as TNF-α, interferon-γ, leukotriene B4, and interleukins 2, 5, 8, and 12.[7] It has been used successfully in psoriasis, psoriatic arthritis, rheumatoid arthritis, and sarcoidosis, and shows promise for other conditions.[7] Paul et al carried out a pilot study showing that apremilast may be an effective agent for the treatment of lichen planus.[8] The results showed that 8 of 10 patients with biopsy-proven lichen planus demonstrated a 2-grade or higher improvement in the Physician Global Assesment following 12 weeks of therapy. Given that LPP is a follicular variant of lichen planus, we used apremilast in our cohort of patients with LPP refractory to currently used treatment modalities. We found apremilast to be effective in treating these patients' symptoms, with all of them showing signs of improvement. However, two of our patients experienced significant gastrointestinal discomfort and one reported depression, leading to discontinuation of the drug. It is worth noting that one of these patients carried a previous diagnosis of irritable bowel syndrome and the patient who reported depression had a previous diagnosis of mood disorder. Furthermore, these events were noted to be less prominent once the dose was lowered to 30 mg daily. Two patients reported significant clinical improvement within three months of initiation of apremilast, with no significant adverse events noted.

Because LPP is a condition that causes significant morbidity and is often refractory to available treatments, patients are in dire need of novel agents that can provide symptomatic relief. To our knowledge, this is the first report of the use of apremilast for LPP. Our limitations include our small sample size and lack of use of a standardized measure of

clinical improvement. Furthermore, spontaneous clinical improvement is a possibility in our patients; however, a retrospective review of 46 patients with lichen planopilaris showed that over 80% of patients had active disease 3 months after starting treatment.[9] Our experience suggests that apremilast may be a useful agent in treating refractory LPP. Larger randomized trials are needed to fully assess its efficacy and tolerability.

Conflict of Interest Disclosures:
Mark Lebwohl is an employee of the Mount Sinai Medical Center, which receives research funds from AbGenomics, Amgen, Anacor, Boehringer Ingleheim, Celgene, Ferndale, Lilly, Janssen Biotech, Kadmon, LEO Pharmaceuticals, Medimmune, Novartis, Pfizer, Sun Pharmaceuticals, and Valeant.

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