

Response of Lichen Planopilaris to Pioglitazone Hydrochloride

Erik L. Peterson BS, Daniel Gutierrez MD, Nooshin K. Brinster MD,
Kristen I. Lo Sicco MD, Jerry Shapiro MD
The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, NY

ABSTRACT

Lichen planopilaris (LPP) is a cicatricial alopecia that often causes permanent hair loss. Pioglitazone, a peroxisome proliferator activated receptor-gamma (PPAR- γ) agonist, has demonstrated immunomodulatory properties that may offer an effective treatment modality. This retrospective analysis describes 23 patients with LPP treated with adjunctive pioglitazone. Most (18/25) demonstrated significant reduction in patient-reported symptoms and clinical signs of inflammation. No adverse effects were reported.

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INTRODUCTION

Lichen planopilaris (LPP) is a cicatricial alopecia characterized by perifollicular hyperkeratosis, erythema, permanent hair loss, and pruritus, pain or burning in affected areas. LPP demonstrates four clinical variants that share similar histologic findings: frontal fibrosing alopecia (FFA), Graham-Little-Picardi-Lasseur syndrome (GLPL) and fibrosing alopecia in a pattern distribution (FAPD).[1,2] Together, these represent the most common primary scarring alopecias.[1,2] Histopathology reveals lymphocytic infiltrates centered around the follicular infundibulum, interface dermatitis, and progressive perifollicular hyperkeratosis and fibrosis.[7] Treatment centers on reducing disease symptomatology and decreasing inflammation to prevent scarring. Most therapeutic regimens consist of high potency topical glucocorticoids and immunosuppressants, topical minoxidil, intralesional glucocorticoids, and systemic anti-inflammatory agents such as doxycycline and hydroxychloroquine.[3] While the pathogenesis of LPP is poorly understood, disease activity likely involves a combination of hormonal and androgenetic factors with autoinflammatory destruction of the hair follicle.[4]

The perioxisome proliferator-activated receptor gamma (PPAR- γ) pathway has been of interest as an additional tool in the treatment of LPP. One study demonstrated a reduction in PPAR- γ tissue expression in LPP,[5] although these results were not reproducible in another study.[6] Decreased PPAR- γ expression results in increased inflammatory lipids, local inflammation, and destruction of the pilosebaceous unit.[5] Thus, PPAR- γ agonists may be efficacious in addressing the underlying pathology of LPP. This study represents single-center retrospective analysis of 23 patients with LPP who were treated with pioglitazone at a Hair and Scalp Disorders Clinic at New York University Langone Health (NYULH).

METHODS

A retrospective review of all patients with LPP who presented to NYULH between October 1, 2007 and August 18, 2018 was performed. A total of 252 unique patients were identified using International Classification of Disease billing codes and natural language corresponding to LPP, FFA, or GLPL. All individuals age 18 to 89 years of age with diagnosis of LPP, FFA, or GLPL were included. When necessary, biopsy was performed for diagnostic guidance. A total of 23 patients who were treated with pioglitazone were identified. All patients were started on 15 mg orally once daily and increased to 30mg if well-tolerated.

These patients were evaluated for clinical changes in degree of inflammation and progression of alopecia. Hairline measurements from bilateral outer canthi and glabella to the frontal and temporoparietal hairline were utilized as a means of tracking progression of disease. Improvement was defined as stabilization of disease (lack of further progression of hair loss or recession of hair line) and resolution of symptoms as assessed by the patient perception. This study was approved by the NYULH Institutional Review board.

TABLE 1.

Characteristics of 23 Patients With Lichen Planopilaris and Their Clinical Response to Pioglitazone Hydrochloride	
Baseline Characteristics	
Gender, F:M	21:2
Age, year (mean, range)	46.8 (39-69)
Caucasian	23
Diagnosis	
FFAFrontal Fibrosing Alopecia	9
LPPLichen planopilaris	13
Write this one out: GLPL	1
Top comorbidities	
Androgenetic alopecia	4
Hypothyroidism	3
Alopecia areata	2
Dyslipidemia	2
Treatment Regimen	
Concurrent use of topical medications	
Clobetasol 0.05% solution	19
Minoxidil 5% solution	13
Tacrolimus 0.3% in Cetaphil cleanser	12
Hydrocortisone butyrate lotion	2
Clobetasol shampoo	4
Concurrent use of intralesional triamcinolone acetonide	12
Concurrent use of systemic medications	
Hydroxychloroquine 200mg twice daily	17
Doxycycline 100mg twice daily	11
Naltrexone 3-4.5mg/day	6
Finasteride 1-5mg/day	10
Mycophenylate mofetil	1
Methotrexate 15mg/week	2
Prednisone 40mg, tapered	1
Response to Pioglitazone Hydrochloride	
Complete resolution*	0
Improvement, stabilization**	18
No change***	5
Progression****	0
Time to improvement after pioglitazone (months)	4
Total treatment duration with pioglitazone (months)	10.68

*Resolution of alopecia, complete regrowth
**Improvement or stabilization in subjective and objective measures
***No change in subjective or objective measures
****Worsening of condition, in objective or subjective measures
Subjective measures = patient-reported symptoms, clinical findings
Objective measures = hairline measurements, photographs

RESULTS

Table 1 summarizes the characteristics of 23 patients with LPP who were treated with pioglitazone hydrochloride. All patients were referred from an outside dermatologist for specialty evaluation and care. The average age at diagnosis was 46.8, (range, 39-69 years). All patients were Caucasian. The mean treatment duration on pioglitazone was 10.68 months (range 2-20 months). The mean time to improvement after initiation of pioglitazone was 4 months (range 1-12 months). All those biopsied had histopathologic features consistent with LPP including inflammatory lymphocytic infiltrates, interface dermatitis, and progressive perifollicular fibrosis and hyperkeratosis. None had concurrent oral or nail lichen planus. Concomitant disorders included: androgenetic alopecia (4/23), hypothyroidism (3/23), alopecia areata (2/23), and dyslipidemia (2/23).

Prior to initiating therapy with pioglitazone, all were treated with one or more other agents. However, no patients were controlled with these treatments alone or in combination. The average number of medications employed during the stabilizing regimen was 7 (range 4-10). The average number of medications employed for the maintenance regimen was 4 (range 2-7). First and second line medications are listed in Table 2. Patients with significant symptoms, rapid progression of disease, or marked activity on trichoscopy were also initiated on systemic immunosuppression, such as hydroxychloroquine and doxycycline. As part of the therapeutic ladder for LPP, pioglitazone was added after first and second line medications failed to achieve stabilization.

Response to treatment was recorded at baseline and all following visits. Patients were evaluated by the investigators and assessed via objective measures of hairline measurements, photographs, and subjective measure of symptoms of pruritus, pain, or burning. In our cohort, 18 patients (78%) achieved improvement or stabilization of disease activity while 5 patients (22%) did not report benefits. One patient achieved minor regrowth. Mean time to stabilization after initiation of pioglitazone was 4 months (range, 1-12 months), with a mean treatment duration of 10.68 months (range, 4-20 months). No patient experienced significant adverse effects with either topical, intralesional, or systemic therapies. Several patients exhibited significant improvement with the addition of pioglitazone, after being refractory to other first line therapies. One such patient demonstrated improvement after 1 month of pioglitazone, complete cessation of disease activity after 2 months, and was stabilized on pioglitazone monotherapy for 12 months. Despite initial improvement on pioglitazone, three patients discontinued therapy citing concerns regarding the medication's black box warning of increased risk of bladder cancer.

TABLE 2.

Therapeutic Ladder for the Treatment of Lichen Planopilaris

Intervention Type	Medication	Line	Dosage	Notes
Topical	Tacrolimus 0.3% compounded in Cetaphil cleanser	1st	BIDtwice daily	Patient applies thin layer to affected areas first. Compounded in Cetaphil cleanser as an effective, convenient, and inexpensive delivery mechanism.
Topical	Clobetasol solution	1st	BIDtwice daily	Patient applies thin layer to affected areas second.
Topical	Minoxidil 5% solution	1st	BIDtwice daily	Patient applies third, creating 5 parts in the hair and applying 5 drops per part, equivalent to 1mL
Systemic	Finasteride	1st	1mg/day	5α-reductase inhibition has shown efficacy in the treatment of FFA, as well as concurrent androgenetic alopecia.[18,19]
Intralesional	Triamcinolone acetanide	1st	2.5mg/cc	3 cc applied intralesionally 1cm behind frontal hairline. 0.5cc applied to each eyebrow. Maximum of 20mg per month.
Systemic	Hydroxychloroquine	2nd	100-200mg BID	Therapy starts at 100mg BID and can increase to 200mg BID as needed. Care is taken to ensure patient follows with ophthalmology for yearly retinal exams,
Systemic	Doxycycline	2nd	50-200mg BID	Therapy starts at 50mg BID and can increase to 200mg BID. Counseling regarding possible gastrointestinal and photosensitive side effects is recommended.
Systemic	Naltrexone	3rd	3mg/day	Low dose naltrexone has shown efficacy in reducing symptoms and inflammation in LPP.[10]
Systemic	Pioglitazone	3rd	15-30mg/day	Low dose pioglitazone has shown efficacy in reducing symptoms and inflammation in LPP.[8]
Systemic	Mycophenylate mofetil	3rd	500-1000mg BID	Mycophenylate mofetil has shown efficacy as an adjunctive anti-inflammatory therapy in FFA.[12]
Systemic	Dapsone	3rd	50-100mg/day	Dapsone inhibits neutrophilic and lymphocytic inflammatory responses and may therefore provide adjunctive benefit in LPP.[16]

DISCUSSION

The proposed mechanism and efficacy of pioglitazone hydrochloride in the treatment of LPP is debated.[5,6] Diminished tissue expression the peroxisome proliferator-activated receptor gamma (PPAR- γ) has been shown to result in toxic accumulation of lipids and fibrotic destruction of the pilosebaceous unit.[6] Studies of PPAR- γ-deficient mice demonstrated progressive hair loss, cutaneous hyperkeratosis, erythema, and complete loss of follicular ostia, as well as scratching behavior, all reminiscent of the clinical presentation and symptomotology of LPP.[5,6] On histology, these mice had interstitial lymphocytic infiltrates, dystrophic hair follicles, and destruction of sebaceous glands with follicular fibrosis, while microarray analysis revealed significant increase in gene expression of chemokines and apoptosis-related genes, resulting in increased activation of macrophages and T-lymphocytes. Such findings underscore the importance of PPAR- γ in the clinical and histologic presentation of LPP, confirming that decreased PPAR- γ expression results in activation of pro-inflammatory pathways that lead to aberrant lipid metabolism and ultimately contribute to a cicatricial alopecia. Thus, as a PPAR- γ agonist, pioglitazone hydrochloride may be an effective means of combating the underlying pathogenesis of LPP. [8,9]

This single-center retrospective analysis of 23 patients supports the utility of pioglitazone for treatment of LPP. As shown in Table 1, 78% of patients achieved stabilization or significant improvement with the addition of pioglitazone. While these patients were also receiving intralesional glucocorticoids and systemic and topical immunosuppression, their disease was recalcitrant prior to initiation of pioglitazone, suggesting that PPAR- γ agonism can be a beneficial tool in the therapeutic armamentarium for LPP via other pathways implicated in disease pathogenesis. Two studies, of 24 and 22 patients with LPP, found pioglitazone to be effective in controlling symptoms, disease progression, and inflammation in a majority of patients.[8,9] However, these conclusions differ from another study of 22 patients in which only a minority of patients benefited from pioglitazone in recalcitrant LPP.[5] Variable response rates to pioglitazone have been well described in literature for the treatment of diabetes mellitus, with response rates ranging from 57.1%-71.4% for responders and 28.6%-42.9% for non-responders.[11,12] A majority of studies found an average non-responder rate of 20-30%,[14] corresponding to our findings of 22% of patients who did not achieve stabilization with pioglitazone therapy. While some have postulated that the insulin resistance index may be a useful predictor of response rates to pioglitazone, no significant differences were found between responder and non-responder groups in terms of age, sex, body mass index, fasting plasma glucose, or the homeostatsis model assessment for evaluating insulin resistance.[11,13] Further

investigation found that the two most common polymorphisms of the PPAR- γ gene, Pro12Ala and Pro12Pro, are not associated with differing response rates to pioglitazone in vivo.[14] Thus, while it is clear that some individuals demonstrate decreased response to therapy with pioglitazone, factors determining response remain uncertain. Further randomized controlled trials are necessary to understand the true mechanism and efficacy of this therapeutic modality.

The findings of this study are limited by several factors. This was a retrospective study, without a control population, which evaluated patients on several concurrent immunosuppressive therapies. Therefore, patient improvement may not be due solely from pioglitazone itself, but rather a function of continued use of concurrent medications on other medications or spontaneous resolution. Furthermore, patient evaluation and assessment of disease activity was based on one provider's clinical expertise.

CONCLUSION

Pioglitazone is a beneficial adjunctive therapy in the treatment of LPP, as supported by 78% of patients who demonstrated significant improvement in disease activity with the addition of pioglitazone to their therapeutic regimen. For a subset of patients, the addition of pioglitazone to their therapeutic regimen represented a key step toward stabilization, after being recalcitrant to all other first line therapies. These findings, in accordance with current literature supporting the role of PPAR- γ in cicatricial alopecia, suggest that pioglitazone's mechanism of action may combat a key contributor in the pathogenesis of LPP. However, given mixed evidence in current literature regarding pioglitazone's efficacy, a prospective, randomized trial evaluating the treatment of LPP with pioglitazone as the sole therapeutic agent is necessary to confirm or refute its potential beneficial effect.

DISCLOSURES

The authors have no conflict of interest to declare.

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AUTHOR CORRESPONDENCE

Jerry Shapiro MD
E-mail:..... jerry.shapiro@nyulangone.org