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Updates In Therapeutics for Lichen Planus Pigmentosus

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INTRODUCTION

Lichen planus pigmentosus (LPP) is a rare variant of lichen planus presenting most commonly in middle-aged patients of color and characterized by the insidious onset of violaceous, brown, or grayish patches on photo distributed areas. Currently, there is limited data regarding the efficacy of treatments for LPP. We, therefore, sought to provide an analysis of current treatment protocols for this condition. A PubMed search on articles detailing treatment regimens yielded 37 total studies. Outcomes were graded according to the American College of Physicians grading system.[1]

The highest level of evidence amongst all available studies was grade 2, largely consisting of prospective analyses (Table I).[2-5] In 13 patients treated with topical tacrolimus ointment 0.03% applied twice daily for 6–12 weeks, 7 (53.8%) demonstrated lightening of LPP after 12 weeks.[2] Twenty patients received oral tranexamic acid at 250mg daily for 4–6 months. Upon completion of the trial, partial improvement was evident in 10 patients, 3 patients showed no improvement, and 7 patients were lost to follow-up. Pruritus was evident in nine patients and completely resolved following treatment. After 12 months, there was no evidence of worsening of the disease.[3]

Muthu et. al demonstrated that a low dose of oral isotretinoin (20 mg/day) for 6 months with broad-spectrum sunscreen use was effective in stabilizing and decreasing hyperpigmentation associated with LPP. Based on the decrease in progression as well as the intensity of hyperpigmentation, 15 of 27 patients

TABLE 1.

Grade 2 Studies

Author	Study Design	Study Participants	Treatment	Scoring Method	Primary Outcome	Adverse Effects	Duration of Follow Up	ACP Grading
Prospective Studies								
Al-Mutairi et al [J Eur Acad Dermatol Venereol, 2010. 24(5): p. 535-40]	Open label, non-randomized, prospective study	13 patients; 21 M 12 F	Topical tacrolimus 0.03% ointment applied twice daily until complete clearance or up to 16 weeks	Grading for improvement in pigmentation: 0%, none; 1–25%, poor; 26–50%, moderate; 51–75%, good; >75%, excellent Photographs were taken before and after treatment	7/13 patients showed improvement in pigmentation: Graded as "excellent" in 4 and "good" in 3	None reported	Not reported	2
Zenjari et al [Ann Dermatol Venereol, 2020. 147(12): p. 818-822]	Prospective Study	20 patients; 18 F 2 M	Oral tranexamic acid at 250mg/d for 4- 6 months Sunscreen usage highly encouraged	Evaluation was carried out by clinical examination and by measuring the area affected by Visioface RD Hardware	Partial improvement in 10 patients 3 patients showed no improvement 9 patients with pruritus at start of study noticed improvement in symptoms 7 patients lost to follow-up	None reported	1 year, no evidence of relapse	2
Muthu et al [Int J Dermatol, 2016. 55(9): p. 1048-54]	Open label, non-randomized, prospective study	27 patients; 17 F 10 M	Fixed low dose of oral isotretinoin (20 mg/day) each day for 6 months in addition to topical sunscreen use	Response was graded as mild (<25%) moderate (26-50%) and good (>50%) improvement based on decrease in intensity and progression of hyperpigmentation.	Disease stabilized by 4–6 weeks in treatment-responsive patients 15 patients (55.7%) experienced moderate improvement 7 (21.8%) experienced good improvement 2 (6.2%) experienced mild improvement.	One patient who developed menorrhagia Mild cheilitis, xerosis, and transient transaminitis in a few patients	3 mo	2

TABLE 1. (CONTINUED)

Grade 2 Studies								
Author	**Study Design**	**Study Participants**	**Treatment**	**Scoring Method**	**Primary Outcome**	**Adverse Effects**	**Duration of Follow Up**	**ACP Grading**
Shah et al [J Cosmet Laser Ther, 2019. 21(2): p. 108-115]	Open-label, non-randomized prospective pilot study	13 patients; 9 F 4 M	1064 nm Q-switched Nd-YAG laser (QSNYL) 5 mm spot, fluence of (3–4.6 J/cm^2) and 5-Hz frequency Fluence periodically increased Treatment every 4–8 weeks for an average of 5-6 sessions	Two independent dermatologists assessed final results by visual inspection and comparing serial photographs	All patients achieved satisfactory response 38.4% demonstrated significant improvement 38.4% demonstrated moderate improvement 23% demonstrated slight improvement	Some pain and swelling of the affected site One patient experienced depigmentation on forehead; another patient showed some scarring in supraorbital area	6 mo	2
Bhari et al [Dermatol Ther, 2020. 33(2): p. e13208]	Prospective pilot study	9 patients; all female	Six sessions of Q-switched Nd-YAG laser (1,064 nm/3 J/cm^2 /6 mm/10 Hz) with toning every 2 weeks	Photographic assessment, physician and patient assessment of improvement Measurement of melanin and erythema index Measurement of immunohistochemistry and mRNA expression	After 6 sessions: 25.7% average clinical improvement in lesions by physician assessment Mean melanin and erythema index not statistically significant Reduction in tyrosinase expression at mRNA level Reduced expression of immunohistochemical markers of cellular infiltrate	None reported	Not reported	2
Bhutani et al 1979 [Br J Dermatol, 1979. 100(4): p. 473-4]	Prospective Pilot study	140 patients	100,000 units of vitamin A each day 15 days Washout period of 15 days, after which vitamin A therapy resumed	Response to treatment was recorded by pre and post treatment photographs Response was graded as 'excellent' with an improvement of 76-100%, 'good' with an improvement of 51-75%, 'fair' with an improvement of 26-50%, or 'poor' with an improvement of < 25%	Of the 19 patients who had completed 4-6 courses, 6 demonstrated good-excellent improvement (32%) Of the 12 patients who completed 10 or more courses, 9 demonstrated good-excellent improvement (75%)	None reported	Not reported	2

(55.7%) experienced moderate improvement, 7 (21.8%) experienced good improvement, and 2 (6.2%) experienced mild improvement.[4]

The 1064 nm Q-switched Nd-YAG (QSNYL) laser has also demonstrated efficacy regarding LPP improvement. In a non-randomized prospective pilot study, thirteen patients were treated with a 5 mm spot size, fluence of 3–4.6 J/cm^2, and 5-Hz frequency. Patients underwent treatment every 4–8 weeks for an average of 5-6 total sessions. Roughly 38.4% demonstrated significant improvement (>90% clearance), 38.4% demonstrated good improvement (>75%), and 23% demonstrated marked improvement (51–75%). No patients experienced worsening of disease within 6 months post-treatment.[5]

Of note, many of the studies included in this analysis had small sample sizes and exhibited relatively low levels of evidence. There is very limited data regarding efficacious treatments for LPP, and the majority of available data is derived from case reports and series. This is likely a reflection of the rarity of the

TABLE 2.

Grade 3-4 Studies								
Author	**Study Design**	**Study Partici-pants**	**Treatment**	**Scoring Method**	**Primary Outcome**	**Adverse Effects**	**Duration of Follow Up**	**ACP Grading**
Retrospective Analyses								
Sonthalia et al [J Cosmet Dermatol, 2019.]	Retrospective analysis	17 patients; 15 F 2 M	6 sessions of Croton oil free phenol combination (CFPC) peel administered every 3 weeks	Patient reported, physician assessed, and Dermoscopy-based improvement	Excellent improvement in 29% of patients with more than a 75% reduction in pigmentation Moderate-excellent improvement in 76 % of patients with at least a 25% reduction in pigmentation	None reported	1 year	3
Cheng et al [Australas J Dermatol, 2018. 59(4): p. 322-327]	Retrospective analysis	29 patients	Topical tacrolimus only (n = 1), topical corticosteroid only (n = 1), topical corticosteroid in combination with either topical tacrolimus (n = 2), hydroquinone (n = 1), or a combination of all the above in addition to topical tretinoin (n = 1) *treatments for the n=6 patients who responded. All other treatment combinations produced no response	Not specified	11/29 treated patients had follow up. Of the 11 with follow up, 6 patients showed improvement The rest experienced stable disease Mean time of improvement was 1-6mo	None reported	1-3 mo	3
Mahajan et al [Pigment Inter, 2014. 1: 9]	Retrospective analysis	8 patients	Fluticasone/mometasone, and/or topical calcineurin inhibitors (tacrolimus 0.1% ointment)	Patient reported	All patients experienced stabilization of disease with 3/8 reporting satisfactory improvement in pigmentation. The remaining 5 patients were lost to follow up.	None reported	6-18 mo	3
Rutnin et al [Biomed Res Int, 2019. 2019: p. 5829185]	Retrospective analysis	71 patients; 54 F 17 M	Topical corticosteroid (steroid not specified) and vitamin A (dosage not specified)	Patient reported	Complete resolution reported in 1 patient after 3 years 47.9% of patients reported partial resolution in 15.5 weeks	None reported	Not reported	3
Sindhura et al [J Eur Acad Dermatol Venereol, 2016. 30(11): p. e142-e144.]	Retrospective analysis	6 patients; 4 F 2 M	Oral mini pulse with dexamethasone 2.5 mg twice/week Topical mometasone furoate 1% cream and tacrolimus 0.1% ointment	Not specified	Disease stabilization over 10.7 ± 3.2 weeks in all patients 1 patient showed improvement in pigmentation	None reported	Not reported	3
Dabas et al [Clin Exp Dermatol, 2019. 44(2): p. 190-193]	Retrospective analysis	10 patients; 6 F 4 M	Oral mini pulse therapy with dexamethasone at 2.5 mg twice weekly for 4 patients Oral isotretinoin (20mg/day) for remaining 6 patients Topical mometasone furoate 0.1% cream and tacrolimus 0.1% ointment for all 10 patients	Not specified	Stabilization of disease at around 11.2 ± 3.01 weeks. There was no statistically significant difference in time to stabilization between groups 1 patient experienced >50% improvement 2 patients experienced moderate improvement 4 patients experienced mild improvement 3 patients experienced no change from baseline	None reported	Not reported	3

TABLE 2. (CONTINUED)

Grade 3-4 Studies								
Author	**Study Design**	**Study Participants**	**Treatment**	**Scoring Method**	**Primary Outcome**	**Adverse Effects**	**Duration of Follow Up**	**ACP Grading**
Retrospective Analyses								
Vinay et al [Int J Dermatol, 2020. 59(2): p. 245-252]	Retrospective analysis	344 patients; 229 F 115 M *Adequate follow up available for 187 patients	Treatment groups Category 1: topical steroid therapy (steroid not specified) n= 86 Category 2: non-steroidal topical therapy (tacrolimus or other depigmenting agents such as azelaic acid, kojic acid) n= 52 Category 3: oral mini pulse (OMP) with or without systemic agents n= 44 Category 4: systemic agents other than OMP (isotretinoin 20 mg/day, colchicine 0.5 mg twice daily, dapsone 100 mg/day, mycophenolate mofetil 2 g/day n= 26 *overall sum of treatment modalities >187 due to switching of modalities for some patients after 3 mo.	Patient and physician global assessment	No significant difference in response to treatment across categories 49.2% noted satisfactory response 63% of those treated with OMP alone or OMP along with systemic agents had notable improvement 42.3% treated with only systemic agents other than OMP demonstrated satisfactory improvement (Isotretinoin, Dapsone, Colchicine, Mycophenolate mofetil)	Adverse effects seen in 12% (mainly those treated with systemic therapies)	> 3 mo	3
Case Reports/ Case Series								
Verma et al [Skinmed. 2015 Oct 1;13(5): 351-4.]	Case Report	5 patients; 1 M 4 F	Topical 0.1% tacrolimus ointment twice daily in combination with oral dapsone 100mg once daily	Comparison of pretreatment and posttreatment photos	No further progression of lesions in all cases; reduction in pigmentation in all cases	None reported	4 months	4
Kumar et al [Indian Dermatol Online J, 2014. 5(2): p. 157-9]	Case Report	40 yo M	Topical mometasone and tacrolimus ointments for 4 weeks, followed by hydroquinone cream	Not specified	Lesions responded well with significant pigment reduction	None reported	Not reported	4
Lemes et al [An Bras Dermatol, 2016. 91(5 suppl 1): p. 20-22]	Case Report	56 yo F	Clobetasol cream once daily for 15 days, followed by topical tacrolimus 0.1% once daily	Not specified	Partial improvement of lesions	None reported	Not reported	4
Chaoui et al [Our Dermatol Online, 2020. 2020; 11(e):e33. 1-e33.2]	Case Report	45 yo F	Topical tacrolimus 0.1% twice daily, along with sunscreen adherence for 4 months	Not specified	Partial improvement	None reported	Not reported	4

TABLE 2. (CONTINUED)

Grade 3-4 Studies								
Author	Study Design	Study Participants	Treatment	Scoring Method	Primary Outcome	Adverse Effects	Duration of Follow Up	ACP Grading
Wolff et al [J Clin Aesthet Dermatol, 2016. 9(11): p. 44-50]	Case Report	18 yo M	Topical 5% azelaic acid foam applied to the face each morning, tretinoin 0.1% cream applied to the face and arms each evening. Jessner's chemical peels applied to arms and glycolic acid peels to face every 2 weeks	Not specified	Marked improvement in facial lesions after 16 weeks Dyschromia on arm lesions mildly improved, but not as clinically dramatic as facial response	None reported	Not reported	4
Sonthalia et al [Indian J Dermatol, 2016. 61(2): p. 237]	Case Report	5 yo boy	2% hydroquinone and sunscreen for 1 month.	Not specified	60-70% of improvement in lesions	None reported	Not reported	4
Pinzani et al [Acta Derm Venereol, 2019. 99(2): p. 218-219]	Case Report	34 yo M	0.05% betamethasone valerate cream once daily in conjunction with 0.1% tacrolimus twice daily for 4 mo	Not specified	Partial remission	None reported	Not reported	4
Falkenhain-López et al [Dermatol Ther, 2020: p. e1468]	Case Report	69 yo F	Topical corticosteroid (specific corticosteroid not reported)	Not specified	Improvement in lesions and pruritus after 2 mo	None reported	Not reported	4
Vega et al [Int J Dermatol, 1992. 31(2): p. 90-4]	Case Series	11 patients; 6 M 5 F	Combination of topical steroid and keratolytics: Some patients used 10% topical aqueous solution of dimethyl sulfoxide, others used either griseofulvin, prednisone (1mg/kg), retinoids (etretinate), or chloroquine (Number of patients per treatment category unspecified)	Not specified	1 patient experienced complete resolution with the use of topical steroids	None reported	Not reported	4
Ghorbel et al [Indian J Dermatol Venereol Leprol, 2014. 80(6): p. 580]	Case Series	60 yo F	Topical Betamethasone (dosage not specified)	Not specified	Slight improvement	None reported	Not reported	4
Mohamed et al [Int J Dermatol, 2016. 55(10): p. 1088-91]	Case Report	10 patients with LPPI; 8 F 2 M	Topical Betamethasone (dosage not specified)	Not specified	Slight improvement in all patients	None reported	Not reported	4
Dizen et al [J Eur Acad Dermatol Venereol, 2016. 30(3): p. 450-2]	Case Series	5 patients; 3 F 2 M	Mometasone furoate (dosage not specified) applied twice daily for 3 months	Not specified	2/5 achieved moderate improvement 3/5 achieved minimal improvement	None reported	Not reported	4
Ohshima et al [J Dermatol, 2012. 39(4): p. 412-4]	Case Report	54 yo F with LPPI	Mometasone furoate ointment application twice/day for 9 months	Not specified	Gradual improvement in lesions	None reported	Not reported	4
Rieder et al [Skin Appendage Disord, 2020. 6(4):235-239]	Case Report	31 yo M	Acitretin 25 mg daily with topical mometasone twice daily	Not specified	After 2 months, originally erythema-rimmed patches and macules on the patient's neck had become grouped with a central clearing. Erythema had resolved	Trans-aminitis	Not reported	4

TABLE 2. (CONTINUED)

Grade 3-4 Studies								
Author	Study Design	Study Participants	Treatment	Scoring Method	Primary Outcome	Adverse Effects	Duration of Follow Up	ACP Grading
Shah et al [JAAD Case Rep, 2020. 6(9): p. 812-814]	Case Report	46 yo F	20 mg of oral isotretinoin daily for 9 months	Not specified	Complete resolution of her facial and body dyschromia	Mild xerosis and cheilitis	Not reported	4
Chen et al [Chin J Integr Med, 2019. 25(12): p. 922-925]	Case Series	3 patients; all female	Bushen Huayu Decoction twice daily, 30 min after breakfast and dinner 10 mg acitretin capsules twice daily with meals	Not specified	Noticeable improvement in hyperpigmentation after 3 months	None reported	Not reported	4
Sharma et al [Indian J Dermatol, 2016. 61(6): p. 700]	Case Report	70 yo F	40 mg Prednisolone	Not specified	Notable improvement in pruritus and flattening of plaques at 1 month	None reported	Not reported	4
Cozzani et al [Dermatol Ther, 2019. 32(2): p. e12809]	Case Report	50 yo F	1 mg/day of colchicine for 3 months, tapered for 6 months	Not specified	Significant improvement in appearance of lesions on trunk, arms, neck No evidence of recurrence at 9 month follow up	None reported	Not reported	4
Han et al [Dermatol Ther, 2014. 27(5): p. 264-7]	Case Report	50 yo F	Q-switched neodymium yttrium aluminum garnet (QS Nd:YAG) laser 6-mm spot size, fluence of 3 J/cm^2 pulse duration of 5 ns 10 passes/cheek Repeated bi-weekly for 28 sessions	Not specified	Significant improvement in pigmentation	Small guttate hypomel-anotic macules on her left cheek	1 year	4
Kim et al [Dermatol Ther, 2014. 27(5): p. 264-7]	Case Report	61 yo M	Topical tacrolimus 0.1% with low fluenced (1.8 J/cm^2) 1064-nm Q-switched neodymium:yttrium–aluminum– garnet laser (QSNYL every 3 weeks	Not specified	Lesions cleared w/o scarring after 4 mo of treatment No recurrence at 6 mo	None reported	6 mo	4
Wu et al [Australas J Dermatol, 2019. 60(4): p. e336-e337]	Case Report	50 yo F	Topical tacrolimus ointment (0.1%) and hydroxychloroquine 200 mg applied twice/day 1064 nm picosecond neodymium-doped yttrium–aluminium–garnet (Nd:YAG) laser: toning (spot size of 9 mm, 400 mJ of energy, and frequency of 10 Hz) and fractional (spot size 8 mm, energy 200 mJ, frequency 5 Hz). 3 total treatment sessions	Physician global assess-ment	Significantly reduced hyperpigmentation within 4 mo.	None reported	Not reported	4
Dimova et al [Dermatol Ther, 2020. 33(6): p. e14073]	Case Report	13 yo M	Narrow band ultraviolet B phototherapy 2x/week starting at 50 mJ/cm^2	Not specified	Complete resolution of lesions after 20 expositions	None reported	3 mo	4
Kashima et al [Int J Dermatol, 2007. 46(7): p. 740-2]	Case Series	51 yo F 62 yo M	None	Not specified	Spontaneous resolution within 6 mo	N/A	Not reported	4
Bennàssar et al [Actas Der-mosifiliogr, 2009. 100(7): p. 602-5]	Case Series	63 yo F	Initially treated with topical calcineurin inhibitor therapy with no improvement. Treatment was discontinued	Not specified	Lesions spontaneously regressed within 6 mo	None reported	Not reported	4
Barros et al [An Bras Dermatol, 2013. 88(6 Suppl 1): p. 146-9]	Case Report	25 yo M	Initially treated with oral prednisone at 20 mg/day for 30 days with little improvement. Treatment was discontinued	Not specified	Spontaneous notable improvement in cervical and popliteal lesions within 4 months	None reported	Not reported	4

*Level of Evidence Grading: Based on recommendation from the American College of Physicians

condition, but highlights a need for more robust prospective clinical trials exploring the few effective treatments that have been described, as well as to investigate novel therapies. Additionally, in assessing these studies it became clear the limitation in evaluating for improvement of LPP lesions with various treatments. A more standardized and validated protocol for scoring clinical improvement in the clinical trial setting is needed.

DISCLOSURES

The authors have no conflicts of interest of declare.

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