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Reviews in Clinical Medicine

Therapeutic Updates on Lichen planopilaris and Frontal Fibrosing Alopecia: A Systematic Review

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ABSTRACT

Introduction: Lichen planopilaris (LPP) and frontal fibrosing alopecia (FFA) are skin diseases that affect the quality of life. Although a systematic review on LPP and FFA treatment was published in 2013, further updates are needed. The aim of this study is to review systematically the studies published after the last systematic review.

Methods: We searched Scopus, PubMed, Embase, and ISI Web of Science. All the studies published during March 2012-June 2017 were included in this review. Two reviewers separately selected the studies and extracted the data. The results of studies were categorized as unimproved, stabilized, and improved based on the articles reports.

Result: Among the 38 studies, 20, 17, and one studies assessed LPP, FFA, and both treatments, respectively. The papers were case reports, case series, cohorts, and randomized controlled trials. Antimalarial agents and pioglitazone resulted in enhancement in 73 and 71% of the LPP patients, respectively. Improvement and stabilization were observed in almost one third of the topical steroid users and 6/12 of Tacrolimus/Pimecrolimus users in LPP. Improvement and stabilization in FFA was found in 68% of the individuals using antimalarial agents, 83% of intralesional steroid users, all cases of finasteride users, and 95% of the people utilizing dutasteride.

Conclusion: Contrary to the previous systematic review, we found antimalarial agents more effective than steroids in LPP. Finasteride/dutasteride may have favorable impacts on FFA. Intralesional steroids showed to be more effective than antimalarial agents in FFA. Still further studies are needed in order to define a treatment protocol. Low quality and heterogeneity of the articles were among the limitations for making a conclusion.

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Introduction

Lichen planus (LP) is an inflammatory skin disease which involves mucosa, skin, and hair follicles (1). Lichen planopilaris (LPP) is a morphological sub-group of LP that mainly affects the scalp and is classified as primary lymphocytic cicatricial al-

opecia (2,3). LPP causes alopecia and cicatricial alopecia in approximately 1.25% and up to 25% of the patients. The disease occurs 1.8 times more frequently in Caucasian and Indian females and is less common among Asians (3,4). It should be not-

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ed that the elderly are the main affected group (5-9).

Physiopathology of LPP arises from the infundibuloisthmic area, which is the main site of inflammation. A decrease in Ki-67⁺ cells in this area supports the hair follicle stem cell damage as a basis for physiopathology of the disease. In early active stages of LPP, Langerhans cells may play role in antigen presentation leading to CD8⁺-mediated cell response (10).

The three classes of LPP include the classic type (11), frontal fibrosing alopecia (FFA) or Kossard disease (12), and Graham-Little-Piccardi-Lassueur syndrome. Frontal hair loss, scalp skin atrophy and scarring, pricking pain, itching, scaling, as well as tenderness are the common signs and symptoms of these three classes (2). Ultraviolet light exposure, perspiration, scalp irritation, and stress may intensify the symptoms.

The FFA type was first described in 1994 by Kossard as a new variant of scarring alopecia (5). Clinically, FFA is similar to LPP with two exceptions. First, the disease is more common in post-menopausal women; however, there are few cases reported in pre-menopausal women and men (13-15). Second, it mainly affects frontal hairline, followed by the eyebrows. As a primary lymphocytic cicatricial alopecia, FFA is accompanied by some clinical findings, such as retrogressive frontal hair loss, perifollicular erythema, and hyperkeratosis. Patients also report itching in addition to pain or burning sensation (16).

Late diagnosis and treatment of LPP might decrease the quality of life in the patients. Therefore, different topical and systemic therapies have been developed to resolve the symptoms (3). Although spontaneous improvement may be found in some cases, the response to treatment is usually partial (17). Some studies proposed using superpotent topical corticosteroids or intralesional corticosteroid injections as the first-line treatment for moderate cases of LPP (4,18,19). On the other hand, some studies have reported antimalarial agents, namely hydroxychloroquine as the first-line systemic treatment (20,21). Other LPP medications include immunosuppressive agents, systemic retinoids, griseofulvin, thalidomide, Dapsone, pioglitazone, and minoxidil (4).

Likewise, a range of treatments has been proposed for FFA (22), including 5-alpha reductase inhibitors (5aRi) that are very popular in post-menopausal women (23). Furthermore, hydroxychloroquine may improve or stabilize the course of disease (9). Rácz et al. Published a systematic review in the field of FFA and LPP treatment in 2013 (24). However, several studies have been published since then providing a better insight

for management of LPP. Consequently, we aimed to update the findings of the previous systematic review.

Methods

This study was carried out based on the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) protocols (25).

Database Searching

Regarding the low prevalence of the disease, we planned a wide search strategy for this systematic review. A systematic electronic search was conducted in Scopus, PubMed, Embase, and ISI Web of Science. The keywords used for search included frontal fibrosing alopecia, Lichen planopilaris, follicular lichen planus, and LP acuminatus.

All the studies, namely the case reports, case series, case-control studies, randomized controlled trials (RCT), cohort and cross-sectional studies published during March 2012-June 2017 were entailed the review. Furthermore, the references of the included studies was checked and hand searched to find any relevant studies. We did not impose any language limitation and data extraction for non-English studies was performed applying the bilingual translators. Studies that did not report any treatment or outcome of the treatment, including those that provided epidemiologic findings, and review articles were excluded.

Data Screening

Two reviewers selected the data separately (A.O and S.A) utilizing the title and abstract screening at initial step, followed by full-text evaluation at the final step. All the related studies assessing different treatment alternatives for FFA and LPP were included.

Data Extraction

Two researchers performed the data extraction separately (T.S and A.O) based on the predefined parameters, such as the study title, name of the first author, type of the study, sample size, type of the disease, histology confirmation of the disease, as well as the type, dose, duration, and outcome of the treatment and measuring method in each study.

No standardized type of treatment outcome measuring has been introduced for LPP and FFA so far. Therefore, different qualitative and quantitative measurements were used to measure the treatment outcome in the studies. In order to compare the treatment outcomes, we categorized the findings of studies as improved, stabilized, and unimproved groups.

Therapies that were associated with minimal to

maximal improvement, including hair regrowth, recovery from symptoms, remission, or any improvement in the course of disease were categorized as improved. Therapies that resulted in a halt in hair loss or a steady state of disease were classified as stabilized. In case no improvement or stabilization was observed for a therapy or worsening of the disease course was detected, it was classified as unimproved. In case of mere quantitative measurement, the results were reported in the text. The findings of the studies where patients were treated first with one medication, followed by another agent, were analyzed based on the final results. The outcomes of studies that used multiple therapies for one patient were included mentioning the result of combination therapy.

Appraisal

Oxford quality assessment checklist was used to check the quality of the RCT. This checklist includes several evaluation factors, including randomization, blinding, adjusting, intention to treat, lost to follow-up, equal treating in addition to allocated treatment, and objective outcome.

Results

Characteristics of the Studies

Initial electronic search results for LPP and FFA were as 347, 221, 209, and 170 studies in Embase, Scopus, PubMed, and ISI web of science, respectively. After removal of the duplicate references, 563 studies remained. Title and abstract screening resulted in exclusion of 470 articles, and the final full-text evaluation led to inclusion of 38 articles. The excluded studies did not propose any treatment or did not report the outcome of the treatment.

Among the 38 publications, 20 assessed the effect of treatment for LPP (1,26-44), 17 investigated treatment for FFA (27,35,45-57), and only one study evaluated treatment for both FFA and LPP (58). The process of screening is shown in Figure 1. All the studies were written in English except two, one of which was in Spanish (56) and one in Polish (43).

Twenty-one studies (1,29-31,34,35,37-41,43, 47-49, 51, 54-56,59,60) were case reports, six (32, 33,46, 53,57,61) were case series, eight (26-28, 36, 42,45,52,58) were retrospective case series, and only one article was a cohort study (50). In addition, there were two RCTs among the included papers (44,62) (Figure 1).

Several qualitative and quantitative outcome measurements ranging from subjective to objective assessments were used to assess the outcome of each medication in the included studies. The characteristics of studies, including the name of

first author, type of study, sample size and diagnosis, evidence of histology, treatment, as well as the approach for outcomes measurement are summarized in Table 1.

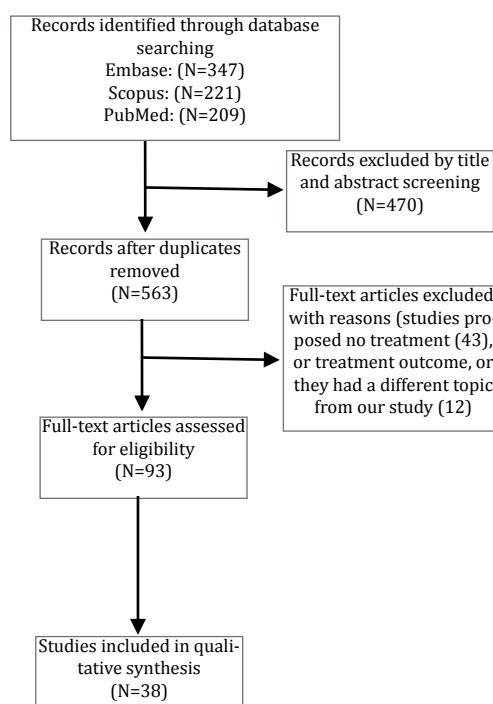


Figure 1. PRISMA flow chart of study selection process.

FFA Treatments

According to the studies, 483 patients received different therapies for FFA. Moreover, some publications tried various medications in the course of disease. Overall, 28 different monotherapies and combination therapies were investigated. Monotherapy with antimalarial medicines, such as Hydroxychloroquine/Chloroquine at the dose of 200-400 mg/d in 63 patients resulted in improvement and stabilization in 9 and 36 cases, respectively.

There was only one case report in a patient regarding monotherapy with oral administration of corticosteroid for FFA treatment with stabilization (45). Intralesional steroids were used in 146 patients and resulted in improvement in 57 (37.0%) and stabilization in 64 patients (43.8%). Administration of 5αRi, including Finasteride and Dutasteride led to improvement in 44.5% (58/127) of the patients. Stabilization of the disease was observed in three patients that applied topical corticosteroids as monotherapy.

Furthermore, Minoxidil administration in a report of FFA caused improvement during the disease course. Other monotherapies were less effective or ineffective. Table 2 indicates the administration doses and outcomes of different monotherapies, as well as combinatorial medications in each of the included studies. In addition, dose of each therapy is reflected in Table 1.

Table 1. General Information of Reviewed Articles.

| Author Reference Year Country | Type of study | Patients Diagnosis | Number | Histology | Agent | Dose | Treatment Duration | Outcome measure | Outcome |
|---------------------------------------|-----------------------------|--------------------|--------|-----------|--|--|---|--|--|
| Alegre-Sánchez et al. (50) 2017 Spain | retrospective case series | FFA | 12 | yes | 1.Topical corticosteroids + topical minoxidil 2.Topical corticosteroids + topical minoxidil + finasteride 3.Intralesional steroids + topical triamcinolone 4.Hydroxychloroquine 5.Prednisone | 1.n.i 2.n.i 3.Triamcinolone, one infiltration every 3 months; 4. 200 mg/d during 15 and 18 months 5. 0.5 mg/kg/d | 1.n.i 2.n.i 3.Four infiltrations in total 4. 15 and 18 months 5.n.i | Measuring the area of cicatricial skin in frontotemporal hairline. | 1.One of the patients (10%) received no treatment; improvement in two (33%) and stabilization in two (33%) patients. Worsening happened in two (33%) patients. 2.Stabilization in one of the cases. 3.Stabilization in one of the cases. 4.Stabilization in two patients. 5.Stabilization in one of the cases. |
| Contini et al. (68) 2017 Brazil | case series | FFA* | 4 | Yes | Hydroxychloroquine/ chloroquine | n.i | n.i | global photos and/or LPP activity index | Hydroxychloroquine did not halt the development or reveal any signs of stabilization of FFA. |
| Naeimi et al. (49) 2017 Iran | randomized controlled trial | LPP | 29 | Yes | Comparison of methotrexate with hydroxychloroquine | 15 mg per week / 200 mg twice a day | 6 months | comprehensive numeric Lichen Planopilaris Activity Index (LPPAI) | LPPAI difference between baseline and month 6 was 3.34±2.09 in Methotrexate group which was significantly higher than 1.39±0.91 in Hydroxychloroquine group (p value=0.003) |
| Anzai et al. (69) 2016 n.i | case report | FFA | 3 | Yes | intralesional triamcinolone + acetamide + hydroxychloroquine + topical tacrolimus + finasteride + topical minoxidil | 2.5mg/ml + 400 mg mg/d + 0.1% + 5mg day + 5% foam daily | n.i | eyebrow density and hair regrowth | Two patients maintained eyebrow density and one patient improved. |
| Granwell et al. (70) 2016 Australia | case report | FFA | 1 | Yes | 1.Intralesional triamcinolone 2.Dutasteride + minoxidil | 1.n.i 2. 0.1 mg daily + 1 mg daily | 1.n.i 2.n.i | progression of hair loss | This case report suggests that hydroxychloroquine and methotrexate have little role in preventing the onset and altering the progression of FFA. Oral dutasteride and minoxidil stabilised hair loss. |

| Author Reference Year Country | Type of study | Patients Diagnosis | Number | Histology | Agent | Dose | Treatment Duration | Outcome measure | Outcome |
|--|---------------------------|--------------------|--------|-----------|--|---|--------------------|---|---|
| De Quintana-Sancho et al. (61) 2016 Spain | case report | FFA | 1 | Yes | topical corticosteroids + inhibitors of 5 α reductase(-Finasteride) | n.i + 2.5mg / day | 5 month | Hair loss and clinical symptoms | Five months after the treatment, the patient presented a stabilization of the disease and a great improvement of pruritus. |
| Dhonncha et al. (71) 2016 Ireland | retrospective case series | LPP | 27 | Yes | hydroxychloroquine | 200 mg twice daily reducing to once daily if their condition was deemed well controlled | 1.n.i | clinical response | Fourteen of our patients (61%) achieved full clinical response with hydroxychloroquine, and two (9%) achieved partial clinical response. Four patients (18%) failed treatment. Three patients (13%) withdrew from treatment because of suspected adverse effects. |
| Ibison et al. (34) 2016 United Kingdom | case report | LPP | 1 | Yes | Topical + intralesional steroids | n.i | n.i | n.i | Treatment was ineffective |
| Jamil et al. (41) 2016 United Kingdom | case report | LPP | 1 | Yes | clobetasol propionate + amitriptyline | n.i | n.i | alleviate symptoms and signs and to arrest the progression of hair loss | The treatment resolved symptoms of the patient |
| Jayasekera et al. (35) 2016 United Kingdom | case report | LPP | 1 | Yes | topical clobetasol propionate | 0.05% | n.i | n.i | Majority of the lesions resolved |
| Lal et al. (72) 2016 India | case report | FFA | 1 | Yes | Intralesional triamcinolone + topical glucocorticoid + tacrolimus ointment | n.i | n.i | n.i | The treatment showed no benefit |
| Vendramini et al. (44) 2016 n.i | case report | LPP | 1 | Yes | Doxycycline + topical clobetasol | 100 mg/day + 3 times a week | 3 months | resolution of symptoms | Resolution after 3 months without hair regrowth |
| Donovan et al. (64) 2015 Canada | case report | FFA | 1 | Yes | finasteride, | 2.5 mg daily | 3 months | photography, dermoscopy, and a series of standardized measurements | The patient experienced a reduction in redness and reversal of skin atrophy, followed by hair regrowth in the frontotemporal scalp with further improvement in one-year follow-up |

| Author Reference Year Country | Type of study | Patients Diagnosis | Number | Histology | Agent | Dose | Treatment Duration | Outcome measure | Outcome |
|--------------------------------------|---------------------------|--------------------|--------|-----------|---|--|--|---|--|
| Lajvardi et al. (73) 2015 Iran | Randomized clinical trial | LPP | 60 | Yes | Comparison of Systemic Mycophenolate Mofetil with Topical Clobetasol | 0.05 % every night (minimum of 30 drops) / 2 g/day (1 g morning, 1 g night). | 6 months | comprehensive numeric Lichen Planopilaris Activity Index (LPPAI) | In Mycophenolate group 6/26 of cases failed treatment (< 25% reduction in LPPAI) and 20/26 showed partial response (25-85% reduction in LPPAI) In Clobetasol group 6/27 of cases failed treatment; 17/27 of patients showed partial response and 4/27 showed improvement (< 85% reduction in LPPAI) No significant difference was found between two groups in response |
| Lyakhovitsky et al. (31) 2015 Israel | retrospective case series | LPP | 46 | Yes | 1. mid-to high potency topical corticosteroids 2. topical calcineurin inhibitors as monotherapy (tacrolimus or pimecrolimus) 3. Intralesional injections of corticosteroids (methyl-prednisolone acetate) 4. Systemic hydroxychloroquine 5. Oral tetracyclines 6. Retinoids + corticosteroid 7. Oral corticosteroids + hydroxychloroquine + topical corticosteroids 8. Oral corticosteroids as monotherapy | 1.n.i 2.n.i 3.n.i 4.n.i 5.n.i 6.n.i 7.n.i 8.n.i | 1. Mean time interval of 2.2 months 2.n.i 3. Mean time interval of 2.6 months 4. Mean time interval of 2.2 months 5. Mean time interval of 1.6 months 6.n.i 7.n.i 8.n.i | hair loss progression, clinical signs of active inflammation, and subjective symptoms | 1.Improvement in eight (19%) and stabilization in two (4.8%) 2.Improvement in three cases worsening in two cases failure of response in two cases 3.Partial response in 13 (87%) patients and failure in two patients. 4.Remission in five (20%) partial improvement in 16 (64%), and failure in four (16%) patients 5.Partial improvement in four (36.4%) and no response in seven (63.7%) cases. 6.Improvement in two cases 7.Partial improvement in two cases 8.There was no effect in the patient |

| Author Reference Year Country | Type of study | Patients Diagnosis | Number | Histology | Agent | Dose | Treatment Duration | Outcome measure | Outcome |
|--|---------------------------|--------------------|--------|-----------|--|---|-----------------------------------|---|--|
| Macpherson et al. (52) 2015 India | case report | FFA | 1 | n.i | oral dutasteride + topical clobetasole propionate | 0.5 mg + 0.05% | 3 months | dermoscopic examination | Reduction of signs of follicular inflammation by dermoscopic examination |
| Mesinkovska et al. (32) 2015 United states | retrospective case series | LPP | 22 | n.i | Pioglitazone | 15 mg per day | mean time interval of 10.5 months | Clinical grading, including subjective measures (pain, tenderness, pruritus), objective measures (perifollicular erythema, scale), and hair loss extent | Complete remission in 0 (0). Marked improvement in 16 (72.7). Stabilization in 5 (22.7). Progression in 1 (4.5) |
| Ramanauskate et al. (53) 2015 Switzerland | case report | FFA | 1 | n.i | oral hydroxychloroquine + topical clobetasol propionate + topical minoxidil solution + combination of topical minoxidil triamcinolone acetonide solution | 200 mg bid + 0.05% + 5% + 0.2% | n.i | n.i | The patient was treated successfully |
| Seastrom et al. (33) 2015 United states | case report | LPP | 1 | yes | 1.Oral methylprednisolone + intralesional triamcinolone 2.Methotrexate + clobetasol | 1.n.i 2.Five days a week | 1. n.i 2.Three months | patient complained of hair loss | 1.No improvement 2.No response 3.improvement and cessation of further hair loss |
| Sutton et al. (4) 2015 United states | case report | LPP | 1 | Yes | 1.Acitretin + oral prednisone 2.Mycophenolate mofetil + acitretin | 25mg three times a week/ five times a week + n.i 500mg twice daily/ 500mg once daily + 25mg three times per week | One month/five months | n.i | 1.Despite some improvement in the pruritic eruption, large painful plaques remained on the extremities 2.LPP significantly improved |
| Revol et al. (74) 2015 France | case report | LPP | 1 | Yes | topical clobetasol | Daily | three weeks | Clinical assessment of patches | The patches were no longer inflammatory |

| Author Reference Year Country | Type of study | Patients Diagnosis | Number | Histology | Agent | Dose | Treatment Duration | Outcome measure | Outcome |
|--|---------------------------|--------------------|--------|-----------|---|---|---|--|---|
| Webster et al. (75) 2015 United states | case report | LPP | 1 | n.i | 1.Ustekinumab 2.Topical steroids 3.Hydroxychloroquine | 1.45 mg 2.n.i 3.200 mg twice daily | 1.10 months 2.n.i 3.5 months | n.i | 1.No effect on the LPP after 10 months of therapy 2.No benefit was observed 3.Treatment had minimal effect |
| Zaouak et al. (76) 2015 Tunisia | case report | FFA | 1 | Yes | minoxidil | 2% | n.i | Assessment of scarring alopecia | slight improvement in scarring alopecia |
| Krasowska et al. (48) 2014 Poland | case report | LPP | 1 | Yes | Topical glucocorticosteroids | n.i | n.i | n.i | Therapy had good effect |
| Spano et al. (30) 2014 Canada | retrospective case series | LPP | 21 | yes | Retinoid + acitretin + isotretinoin | n.i | 2-4 months | clinical improvement | Five of 21 (24%) of patients benefit from adjunctiveoral retinoid therapy |
| Vañó-Galván et al. (51) 2014 Spain | case series | FFA | 355 | yes | 1.Topical steroids and topical minoxidil 2.Intralesional steroids 3.Oral hydroxychloroquine 4.Finasteride 5.Dutasteride | 1.n.i 2. 1 infiltration every 3-6 months 3. 200-400 mg/d 4. 2.5-5 mg/d 5. 0.5 mg/wk | 1.n.i 2. Mean number of 8 per patient 3.n.i 4.n.i 5.n.i | Measuring the area of cicatricial skin in frontotemporal hairline. | 1.Variable results depending on the associated systemic therapy. 2.Improvement in 44 (34%), stabilization in 64 (49%), and worsening in 6 (5%) patients (data available for 16 patients). 3.Improvement in 8 (15%), stabilization in 32 (59%), and worsening in 12 (22%) patients (data on effectiveness was not available for 2 patients). 4.Improvement in 48 (47%) and stabilization in 54 (53%) patients. 5.Improvement in 8 (44%) and stabilization in 10 (56%) patients |
| Dlova et al. (54) 2014 South Africa | case report | FFA | 1 | Yes | Hydroxychloroquine + topicalsteroid (clobetasol dipropionate) + tacrolimus + minoxidil | 200 mg twice per day + n.i + 0.1% + 2% | 6 months | n.i | Good response to treatment |

| Author Reference Year Country | Type of study | Patients Diagnosis | Number | Histology | Agent | Dose | Treatment Duration | Outcome measure | Outcome |
|---|---------------------------|--------------------|--------|-----------|--|---|--------------------|---|--|
| Pandhi et al. (36) 2014 India | case series | LPP | 316 | Yes | 1.Systemic steroids 2. Dapsone | n.i | n.i | n.i | 1.Minimum response in 3 (9.7%) patients, response and recurrence in 7 (22.6%), response in 12 (38.7%), Partial in 8 (25.8) Not known 1 (3.2), Side effects 7 (22.6) |
| Rossi et al. (55) 2014 Italy | cohort | FFA | 40 | Yes | Minoxidil + hydrocortisone butyrate + 17 α -estradiol + ciclo silicone + pentamer + alcohol | 2% + 0.08% + 0.05% + 16% + 96 $^{\circ}$ 2 ml/die once a day in the evening | 36 months 2 ml/die | Standardized global photographs that captured hair density in the vertex and in the anterior regions. | no improvement: 12.5% stabilized: 37.5 % improved: 25 % greatly improved: 25 % |
| Pérez-Rodríguez et al. (56) 2014 Mexico | case report | FFA | 1 | Yes | Dutasteride + pimecrolimus | 0.5 mg q.d + 1% b.i.d. | 5 months | n.i | The patient reported a 40% improvement in erythema and even showed slight hair regrowth |
| Russell et al. (57) 2013 United kingdom | retrospective case series | FFA | 15 | Yes | 1.Super-potent topical steroids 2.Lymecycline 3.Dutasteride 4.Azathioprine / ciclosporin | 1.n.i 2.408 mg once daily 3.n.i 4.n.o | n.i | n.i | 1.stabilization or improvement in 4/9 (44%) of cases 2.Improvement in two cases 3.One patient don't tolerate the medication, one deriving some benefit, and one experiencing progression on treatment 4.Improvement in both cases |
| Spring et al. (37) 2013 Switzerland | case series | LPP | 22 | yes | pioglitazone | 15 mg/d | One year | n.i | 3 patients showed cessation of disease activity, others experience negative outcomes |
| Walsh et al. (38) 2013 United Kingdom | case report | LPP | 1 | Yes | topical clobetasol propionate | n.i | n.i | n.i | the majority of the lesions resolved |
| Delova et al. (77) 2013 South Africa | case series | FFA | 20 | Yes | Hydroxychloroquine + clobetasol dipropionate + Tacrolimus + Minoxidil | 200 mg bid + n.i + 0.1% + 2% | 6-12 months | progression of alopecia | The progression of alopecia in five patients was stopped |

| Author Reference Year Country | Type of study | Patients Diagnosis | Number | Histology | Agent | Dose | Treatment Duration | Outcome measure | Outcome |
|---|---------------|--------------------|--------|-----------|---|------|--------------------|---|---|
| Ladizinski et al. (78) 2013 United states | case series | FFA | 19 | Yes | 1.Dutasteride monotherapy 2.Dutasteride + doxycycline 3.Dutasteride + class I steroid + topical tacrolimus 4.Dutasteride + class I steroid 5.Finasteride monotherapy 6.Finasteride + methotrexate 7.Finasteride + acitretin + topical imiquimod 8.Methotrexate monotherapy 9.Hydroxy-chloroquine monotherapy 10.Hydroxy-chloroquine + tacrolimus + class I steroid 11.Hydroxy-chloroquine + class I steroid 12.Minocycline + topical tacrolimus 13.Minocycline + topical imiquimod 14.Imiquimod + class I steroid 15.Acitretin 16.Interferon alfa-2b 17.Azathioprine 18.Pioglitazone | n.i | n.i | clinical notes and global photographic assessment | 1.Stabilization in 4/5 of patients 2.Stabilization in 2/3 of patients 3.Stabilization in 1/1 of patients 4.Stabilization in 0/1 of patients 5.Stabilization in 1/3 of patients 6.Stabilization in 1/1 of patients 7.Stabilization in 0/1 of patients 8.Stabilization in 1/2 of patients 9.Stabilization in 2/2 of patients 10.Stabilization in 0/1 of patients 11.Stabilization in 0/1 of patients 12.Stabilization in 1/1 of patients 13.Stabilization in 0/1 of patients 14.Stabilization in 1/1 of patients 15.Stabilization in 0/1 of patients 16.Stabilization in 0/1 of patients 17.Stabilization in 0/1 of patients 18.Stabilization in 0/1 of patients |

| Author Reference Year Country | Type of study | Patients Diagnosis | Number | Histology | Agent | Dose | Treatment Duration | Outcome measure | Outcome |
|--|---------------------------|--------------------|--------|-----------|--|------|--------------------|---|---|
| Khalid et al. (79) 2013 United kingdom | retrospective case series | LPP,FFA | 21,6 | Yes# | 1.Topical corticosteroids 2.Topical calcineurin inhibitors 3.Oral/intrale-sional cortico-steroids 4.Antimalarials | n.i | n.i | n.i | 1.Control of disease in 35.3% (6/17) and re-growth in 23.5% (4/17) 2.Stabilization of the dis-ease in 60% (3/5) 3.Stopping progression in 1/4 4.Regrowth in 1/2 |
| Abid et al. (46) 2012 United kingdom | case report | LPP | 1 | Yes | topical mometasone furoate | 0.1% | 1 month | Assessment of the viola- ceous changes and lesions | The violaceous changes resolved and lesions be-came post inflammatory |
| Baibergenova et al. (47) 2012 Canada | retrospective case series | LPP | 24 | n.i | pioglitazone | n.i | n.i | Decrease in or disappear- ance of symptoms and per- ifollicular erythema in the context of halted spread of old patches | Disappearance of symp- toms including pain, pru- ritus, burning and stop- page of lesions spread and absence of signs of activity and negative pull test (remission) in 5 cases Improvement in 12 cases, no change in 3 cases and discontinuation due to side effects in 14 cases |

Biopsy confirmation was only conducted for 56 patients

#Biopsy confirmation was conducted for a part of patients

*The cases have simultaneous discoid lupus erythematosus

Table 2. Treatment results of frontal fibrosing alopecia.

| Author Reference | Treatment | Number of Patients | Improved | Stabilized | Unimproved |
|----------------------------|---|--------------------|----------|------------|------------|
| Alegre-Sánchez et al. (80) | Topical corticosteroids + topical minoxidil | 6* | 2 | 2 | 1 |
| Alegre-Sánchez et al. (80) | Topical corticosteroids + topical minoxidil + finasteride | 1 | | 1 | |
| Alegre-Sánchez et al. (80) | Intralesional steroids + topical triamcinolone | 1 | | 1 | |
| Alegre-Sánchez et al. (80) | | 2 | | 2 | |
| Vañó-Galván et al. (51) | Hydroxychloroquine / chloroquine | 54 | 8 | 32 | 12 |
| Ramanauskate et al. (53) | | 1 | 1 | | |
| Arsie Contin et al. (68) | | 4 | | | 4 |
| Ladizinski et al. (78) | | 2 | | 2 | |
| Alegre-Sánchez et al. (80) | Oral corticosteroid | 1 | | 1 | |
| Vañó-Galván et al. (51) | Intralesional steroids | 130## | 44 | 64 | 6 |
| Lyakhovitsky et al. (31) | | 15 | 13 | | 2 |
| Cranwell et al. (70) | | 1 | | | 1 |
| Vañó-Galván et al. (51) | Finasteride | 102 | 48 | 54 | |
| Donovan et al. (64) | | 1 | 1 | | |
| Vañó-Galván et al. (51) | Dutasteride | 18 | 8 | 10 | |
| Donovan et al. (64) | | 1 | 1 | | |
| Ladizinski et al. (78) | | 5 | | 4 | |
| Macpherson et al. (52) | Oral dutasteride + topical clobetasole propionate | 1 | 1 | | |
| Alegre-Sánchez et al. (80) | triamcinolone + topical corticosteroids + topical minoxidil | 1 | | 1 | |
| Anzai et al. (39) | Intralesional triamcinolone acetonide + hydroxychloroquine + topical tacrolimus + finasteride + topical minoxidil | 3*** | 1 | 2 | |
| Cranwell et al. (70) | Dutasteride + minoxidil | 1 | | 1 | |
| Lal et al. (72) | Intralesional triamcinolone + topical glucocorticoid + tacrolimus ointment | 1 | | | 1 |

| Author Reference | Treatment | Number of Patients | Improved | Stabilized | Unimproved |
|--------------------------------|---|--------------------|----------|------------|------------|
| Khalid et al. (79) | Topical corticosteroids | 5 | | 3 | |
| Zaouak et al. (76) | Minoxidil | 1 | 1 | | |
| Delova et al. (77) | Hydroxychloroquine + clobetasol dipropionate + Tacrolimus + Minoxidil | 20 | | 5 | |
| Ladizinski et al. (78) | Dutasteride + doxycycline | 3 | | 2 | |
| Ladizinski et al. (78) | Dutasteride + class I steroid + topical tacrolimus | 1 | | 1 | |
| Ladizinski et al. (78) | Dutasteride + class I steroid | 1 | | | 1 |
| Ladizinski et al. (78) | Finasteride + methotrexate | 1 | | | 1 |
| Ladizinski et al. (78) | Finasteride + acitretin + topical imiquimod | 1 | | | 1 |
| Ladizinski et al. (78) | Methotrexate monotherapy | 3 | | 1 | |
| Ladizinski et al. (78) | Hydroxychloroquine + tacrolimus + class I steroid | 1 | | | 1 |
| Ladizinski et al. (78) | Hydroxychloroquine + class I steroid | 1 | | | 1 |
| Ladizinski et al. (78) | Minocycline + topical tacrolimus | 1 | | 1 | |
| Ladizinski et al. (78) | Minocycline + topical imiquimod | 1 | | | 1 |
| Ladizinski et al. (78) | Imiquimod + class I steroid | 1 | | | 1 |
| De Quintana-Sancho et al. (61) | Topical corticosteroids + Finasteride | 1 | | 1 | |

*One of the patients received no treatment

**Variable results depending on the systemic therapy

***Only two patients received intralesional triamcinolone acetonide, one received finasteride, and one received topical minoxidil

#Three patients withdrew from treatment because of suspected adverse effects

##Data were not available for 16 patients

###Four patients discontinued treatment due to side effects.

+Dose changes did not make difference in the course of the disease

LPP Treatments

Overall, 599 patients experienced various therapies as mentioned in the publications. Hydroxychloroquine/Chloroquine monotherapy was administered to 51 patients and resulted in remission and improvement in 27 patients (52.9%). Tacrolimus/Pimecrolimus treatment was tried in 12 patients leading to improvement in six (50.0%) cases. Pioglitazone also had an improving effect on 71.7% (33/46) of the individuals. The administered dose of each medication is demonstrated in Table 1. Treatment strategies and their observed outcomes

are presented in Table 3. Among the two RCTs, one compared systemic Mycophenolate Mofetil 2 g/day with topical Clobetasol 0.05% lotion for treating LPP. The other RCT compared the influence of methotrexate with at the dose of 15 mg per week and 200 mg hydroxychloroquine twice a day on LPP.

The first RCT was a single-center, parallel-group, assessor- and analyst-blinded RCT with a sample size of 60 patients affected by histologically proved LPP. Pregnant and lactating patients, those with other underlying diseases, those consumed every

Table 3. Treatment results of Lichen Planopilaris.

| Author Reference | Treatment | Number of Patients | Improved | Stabilized | Unimproved |
|--------------------------|---|--------------------|----------|------------|------------|
| Lyakhovitsk et al. (27) | | 25 | 21 | | 4 |
| Dhonncha et al. (70) | | 23# | 14 | 2 | 4 |
| Webster et al. (71) | Hydroxychloroquine / chloroquine | 1 | 1 | | |
| Khalid et al. (72) | | 2 | 1 | | |
| Lyakhovitsk et al. (27) | Oral corticosteroid | 1 | | | 1 |
| Spano et al. (26) | Adjunctive oral retinoid | 21 | 5 | | |
| Lyakhovitsk et al. (27) | Mid to high potency topical corticosteroids | 42 | 8 | 2 | 32 |
| Lyakhovitsk et al. (27) | | 7 | 3 | | 4 |
| Khalid et al. (72) | Tacrolimus/pimecrolimus | 5 | 3 | | |
| Lyakhovitsk et al. (27) | Tetracyclines | 12 | 4 | | 7 |
| Lyakhovitsk et al. (27) | Retinoids + corticosteroid | 5 | 2 | | |
| Lyakhovitsk et al. (27) | Oral corticosteroids + hydroxychloroquine + topical corticosteroids | 2 | 2 | | |
| Mesinkovska et al. (28) | | 22 | 16 | 5 | 1 |
| Baibergenova et al. (42) | Pioglitazone | 24### | 17 | | 3 |
| Anzai et al. (35) | Intralesional triamcinolone acetonide + hydroxychloroquine + topical tacrolimus + finasteride + topical minoxidil | 3*** | 1 | 2 | |
| Jamil et al. (37) | Clobetasol propionate + amitriptyline | 1 | | 1 | |
| Sutton et al. (73) | Acitretin + prednisone+ | 1 | 1 | | |
| Sutton et al. (73) | Mycophenolate mofetil + acitretin+ | 1 | 1 | | |
| Revol et al. (74) | | 1 | 1 | | |
| Lajevardi et al. (75)++ | Clobetasol | 26 | 4 | 17 | 5 |
| Vendramini et al. (39) | Doxycycline + topical clobetasol | 1 | 1 | | |
| Webster et al. (71) | Ustekinumab | 1 | | | 1 |

| Author Reference | Treatment | Number of Patients | Improved | Stabilized | Unimproved |
|-------------------------|------------------------------------|--------------------|----------|------------|------------|
| Webster et al. (71) | | 1 | | | 1 |
| Krasowska et al. (43) | Topical corticosteroids | 1 | 1 | | |
| Khalid et al. (72) | | 17 | 4 | 6 | 7 |
| Abid et al. (41) | Topical mometasone furoate | 1 | 1 | | |
| Khalid et al. (72) | Oral/intralesional corticosteroids | 4 | | 1 | |
| Lajevardi et al. (75)++ | Systemic Mycophenolate Mofetil | 25 | | 22 | 3 |

*One of the patients received no treatment.

**Variable results depending on the systemic therapy.

***Only two patients received intralesional triamcinolone acetonide, one received finasteride, and one received topical minoxidil.

#Three patients withdrew from treatment because of suspected adverse effects.

##Data were not available for 16 patients.

###Four patients discontinued treatment due to side effects.

+Dose changes did not make difference in the course of the disease.

++These are the two arms of one RCT

medicine for their disease, and those with erosive mucosal or generalized cutaneous LPP were excluded from their study. The patients underwent a six-month follow-up to assess the efficacy of each treatment using comprehensive numeric Lichen Planopilaris Activity Index (LPPAI) conducted by another blinded physician.

Response to treatment was defined as > 85% reduction in LPPAI and treatment failure was defined as < 25% decrease in LPPAI. The range of 25-85% was considered as partial responders. After two months, 33% of Mycophenolate Mofetil consumers experienced side effects that were significantly higher than Clobetasol consumers with no evident complications. At the end of six-month follow-up, the significant difference between Mycophenolate Mofetil group and Clobetasol group ended. Most of the patients showed stabilization in both groups while all the improved cases were Clobetasol-treated patients. Furthermore, the number of non-responders was similar between the two groups. The course of LPPAI reduction did not differ significantly between the two treatment groups during the six-month follow-up.

Quality assessment of this RCT demonstrated that the study was analyst-blinded. In addition, they used blood and urine analysis in order to rule out other confounding diseases, but no data were expressed regarding the adjustment for confounding factors in the two groups. For instance, some patients received isoniazid and vitamin B6 besides Mycophenolate Mofetil, which can somehow obscure the result of treatment.

Computerized randomization was conducted

properly, and each group contained a sample size of 30 patients equally at the beginning of the study. The authors suggested LPPAI in order to measure the outcomes of study in an objective way. The investigation intended to treat and reported 6/60 (10%) lost in follow-up (62).

Naeni et al. conducted the other RCT (44), in which 29 patients completed the six-month course of study. Subjects were allocated to the two groups of methotrexate (15 mg per week) and hydroxychloroquine (200 mg twice a day).

Pregnant and breastfeeding women, in addition to the patients who were suffering from gastrointestinal diseases, vision problems, porphyria, psoriasis, anemia (hemoglobin < 9 mg/dl), leukopenia (white blood cell counts < 4000/dl), thrombocytopenia (platelet count < 100,000/dl), elevated liver enzymes (higher than three times of the upper normal limit), notable liver disorder, positive viral hepatic markers, history of convulsion, and excessive alcohol intake were excluded from the study. Similar to the previous RCT, LPPAI was utilized as the outcome measure. The authors used standardized scaled photography in order to fill the items in LPPAI.

Quality assessment of the study revealed that the allocation was identical between the study groups. The analysts of the photographs were blinded to group allocation. The two groups were adjusted according to several confounding factors, including gender, age, diagnosis mean age, family history, organ involvements, and previous medications. The groups were not similar according to baseline pull test, but were

matched for other clinical findings. Furthermore, notable higher levels of baseline LPPAI were found in the methotrexate group, compared to the hydroxychloroquine group.

The investigation aimed to treat analysis with a quantitative outcome. A progressive improvement was observed in methotrexate and hydroxychloroquine group. Overall, the study found methotrexate considerably more effective than hydroxychloroquine.

Discussion

The objective of this study was to update the findings of the previous systematic review about treatments of LPP and FFA. We faced most of the limitations that Rác et al. had in their study (24). Similarly, in the previous systematic review, the studies were mainly case-reports, case series, or retrospective case series that belonged to the lowest level of evidence.

Currently, there is no standardized objective measurement for disease progression and most studies proposed different qualitative measuring scales using several measuring tools. The outcome measuring was mainly based on the clinical signs of inflammation and hair loss progression. Various methods are used to measure the outcome of treatment, including dermoscopy, standardized photographs, and self-reports by the patients.

One of the included RCTs found no difference between systemic Mycophenolate Mofetil 2 g/day and topical Clobetasol 0.05 % lotion according to LPPAI as a numerical measurement. However, the investigation had some methodological problems in randomization (62).

We found no predefined quantitative measurement for evaluating FFA progression and response to treatment. However, a study on four cases applied LPPAI as an outcome measure. Other studies mostly used cicatricial skin area measurement in frontotemporal hairline (45,46) and dermoscopy (47,59). Moreover, Anzai et al. exploited eyebrow density as an outcome measure (35). In fact, we should declare that our study was limited by heterogeneous and imprecise methods of measuring the outcome of treatments in most studies.

Another RCT completed in Iran suggested methotrexate as a more efficient medication than hydroxychloroquine (44). The mentioned study also proposed that both treatments were effective in reducing LPPAI and improving some of the signs and symptoms in patients. Unlike the study by Naeini et al., Lajevardi et al. used no qualitative outcome besides the quantitative assessment of their study outcome.

We found antimalarial agents, including hy-

droxychloroquine and chloroquine as the most effective treatments in LPP patients with about 73% improvement and 4% stabilization. A dose of 200 mg twice a day was utilized in all the studies that mentioned their administrated dosage (27,36,40,58). Among the studies that mentioned the period of treatment, mean time intervals of 2.2 months (27) and 5 months (40) were reported.

In line with the findings of our study, some other studies have proposed antimalarial medicines as the first-line treatment (20,21). Chiang et al. and Spenser et al. reported some improvement in 55% of the patients who were treated with a common dosage of 6.5 mg/kg/day or 200 mg twice daily within 6 months (20,21). The best-proposed duration in Chiang et al. study was 12 months (20). Only one of the RCTs revealed a superiority in efficiency for methotrexate over hydroxychloroquine in treating LPP (44). No other studies used methotrexate as a medication.

Administration of topical corticosteroids as a monotherapy in LPP resulted in improvement and stabilization in nearly one third of the cases. The only conducted study about the efficacy of oral corticosteroids monotherapy showed no improvement in the course of disease. Khalid et al. also used oral/intralesional steroids and found only stabilization in one of the four included patients. They found response to treatment in 54.5% of topical corticosteroid users that is around 20% higher than the findings of this study.

Our findings oppose the previous systematic review that proposed topical corticosteroids as the first-line treatment modality for LPP patients (4,19,20,24,63-67). However, due to low evidence presented by the published studies, both this study and the previous systematic review have debate regarding a conclusion.

Khalid et al. and Lyakhovitsk et al. have also tried Tacrolimus/Pimecrolimus regimen in 12 patients reaching improvement in half of the cases. It seems that calcineurin inhibitors can have notable therapeutic effects. Although, studies concerning the efficacy of calcineurin inhibitors are not sufficient to draw any recommendation, it can be assumed that these agents may be useful as a treatment modality or at least be used as an adjuvant to other treatments (18,63).

Pioglitazone was administered in two studies as LPP treatment causing almost 71% improvement. Peroxisome proliferator-activated receptor (PPAR) agonists are transcription factors that regulate differentiation, development, proliferation, and metabolism through gene transcription. This medicine is applied in metabolic and inflammatory diseases (68). Furthermore, some investigations reported their benefits in dermatology,

lipodystrophies, psoriasis, melanoma, and atopic dermatitis (42).

Combination therapy with oral corticosteroids, hydroxychloroquine, and topical corticosteroids revealed improvement in two patients who underwent the treatment. Moreover, administration of retinoid in combination with corticosteroid resulted in improvement in 40% (2/5) of the patients. Many treatment modalities have been proposed in the literature. However, none of them were found to be permanently useful in management of the disease (4,19,20,24,63-67).

Although FFA is a variant of LPP, our findings showed that the influence of treatment modalities on FFA differs from that of LPP. It seems that other more substantial factors besides inflammation account for physiopathology of FFA. Small differences in the pathology of the diseases might be responsible for various treatment outcomes in LPP and FFA (69).

There is no predefined protocol, or first-line treatment for FFA. However, several mono- and combination therapies have been proposed for the condition. General treatments are categorized as topical or intralesional corticosteroids, anti-malarial agents, and 5aRIs, while no RCTs have examined their efficacy so far.

The good response to antimalarial agents in LPP patients was not observed in FFA ones. In case of antimalarial medicines, improvement and stabilization were observed in about 14 and 54% of the patients with FFA and LPP, respectively. A proper response was found in 30% of the patients who used antimalarial medications in the last published systematic review (62).

Corticosteroids are among the mostly used FFA therapies and may have a fundamental role in treatment of FFA according to our findings. About 40 and 43% of the patients experienced improvement and stabilization with intralesional steroids, respectively (27,46,54). This was somehow consistent with the previous systematic review that reported partial improvement in 60% of the patients (62).

Only one study tried oral corticosteroids in FFA which resulted in stabilization of the disease (45). Furthermore, another study used topical corticosteroids showing stabilization in 60% (3/5) of the patients (58). In contrast to the findings of our study, the previous systematic review did not report efficacy for topical steroid treatment (24). Stabilization (49/103) and improvement (54/103) were observed in all cases of finasteride monotherapy (46,59). Improvement and stabilization of the disease were found in about 37 and 58% of the patients following administration of Dutasteride, respectively (46,57,59).

5aRIs seem to have a notable effect on disease improvement. An androgenic alopecia may accompany FFA (9) and this may explain the efficacy of 5aRIs in FFA. Only one case report utilized minoxidil as monotherapy and demonstrated improvement (55). Combination therapy was mainly based on corticosteroids, minoxidil, finasteride, triamcinolone, and hydroxychloroquine and reported stabilization in most cases (35,45,47,54,60,61).

Conclusion

As an update for a previous systematic review in 2013, our study revealed several considerable findings. We observed two admissible RCTs in our review, one of which found methotrexate as the preferable medication for LPP patients, in comparison with hydroxychloroquine. However, other studies concerning LPP treatment stated antimarial agents as effective medications. In addition, Pioglitazone is listed as one of the most effective treatments in LPP. As a result, further study is recommended to add pioglitazone to LPP treatment regimen.

Moreover, some therapeutic effects have been found for topical steroids and calcineurin inhibitors. Although, our findings showed no established regimen for FFA, 5aRIs and intralesional steroids seem to be the most effective agents. Further studies, including high-quality multicenter RCTs are needed to find the first choice medication for FFA. Low quality and heterogeneity of the studies, as well as the low number of RCTs limited conclusion in our study.

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Conflict of Interest

The authors declare no conflict of interest.

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