Therapeutic updates for Lichen planopilaris and Frontal fibrosing alopecia: a systematic review

Abstract

Background: Lichen planopilaris (LPP) and frontal fibrosing alopecia (FFA) are skin diseases. A systematic review about LPP and FFA treatment was published in 2013 but further updates are needed.

Objectives: the aim of our study is to systematically review the studies that published after the publication of the last systematic review.

Method: We searched in Scopus, Pubmed, Embase, and ISI web. All studies from March 2012 to Jun 2017 were included. Study selection and extraction were separately done by two reviewers. Studies should report a treatment and treatment outcome to fulfill the inclusion criteria. The outcomes of the studies were categorized as unimproved, stabilization, and improvement based on articles reports.

Result: Of 38 studies, twenty studies assessed LPP treatment, seventeen FFA treatment and one study assessed both. Studies were case-report case series, cohort, and RCTs. Antimalarial agents and pioglitazone showed improvement in 73 % and 71% of LPP patients respectively. Improvement and stabilization was seen in about 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 antimalarial agent users, 83% of intralesional steroid users, all cases of finasteride users, and 95% of dutasteride users.

Conclusion: in contrast with the previous systematic review, we found that antimalarial agents may be more effective than steroids in LPP. Finasteride/dutasteride may have good effects in FFA.

Intralesional steroids showed to be more effective than antimalarial agents in FFA. Still further studies are needed to define a treatment protocol. Making a conclusion based on low quality and heterogeneous articles limited our study.

Keywords: lichen planopilaris, frontal fibrosing alopecia, LPP, FFA, treatment

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 alopecia (2, 3). LPP causes alopecia and cicatricial alopecia in approximately 1.25% and up to 25% of the patients, respectively. It occurs 1.8 times more frequently in Caucasian and Indian females and is less common among Asians (3, 4).

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 a role in presenting antigens that lead to $CD8^{+}$ mediated cell response (5).

The three classes of LPP are the classic type (6), frontal fibrosing alopecia (FFA) or Kossard disease (7), and Graham-Little-Piccardi-Lassueur syndrome. Frontal hair loss, scalp skin atrophy and scaring, pricking pain, itching, scaling, and tenderness are common signs and symptoms of these three classes (2). Ultraviolet light exposure, perspiration, scalp irritation, and stress may intensify the symptoms.

Frontal fibrosing alopecia (FFA) was first described in 1994 by Kossard as a new variant of scarring alopecia (8). Clinically, FFA is similar to lichen planopilaris (LPP) with two exceptions. First, the disease is more common in post-menopausal women; however, a few cases have been reported in pre-menopausal women and also in men (9-11). Second, it mainly affects frontal hairline and after that involves eyebrows. As a primary lymphocytic cicastricial alopecia, FFA accompanies with some clinical findings, including retrogressive frontal hair loss, perifollicular erythema, and hyperkeratosis. Patients also report itching, pain or burning sensation (12).

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 (13). Some studies proposed the use of superpotent topical corticosteroids or intralesional corticosteroid injections as the first-line treatment for moderate cases of LPP (4, 14, 15); however, some studies have reported Antimalarial agents including hydroxychloroquine as the first line systemic treatment (16, 17). 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 (18) including 5-alpha reductase inhibitors (5aRis) that are very popular in postmenopausal women (19). Furthermore, hydroxychloroquine may improve or stabilize the course of the disease (20). Rácz et al. Published a systematic review in the field of FFA and LPP treatment in 2013 (21); however, several studies have been published since then that provide a better insight for the management of LPP. We aimed to update the findings of the previous systematic review.

Method

This study was based on preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (22).

Data base searching

Regarding the uncommonness of the disease, we planned a wide search strategy for this systematic review. A systematic electronic search was conducted in Scopus, PubMed, Embase, ISI web of science using the following search terms "(frontal fibrosing alopecia) OR (Lichen planopillaris)". All published studies, including case reports, case series, case-control studies, randomized controlled trials, cohort and cross-sectional studies from March 2012 to Jun 2017 were included. Furthermore, the bibliography of the included studies was checked, and hand searched to find any relevant studies. No language limitation was imposed, and data extraction for non-English studies was performed with the help of 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

The data selection process was conducted separately by two reviewers (A.O and S.A) using the title and abstract screening at initial step and full-text evaluation at the final step. All related studies assessing different treatment alternatives for FFA and LPP were included.

Data extraction

The data extraction was conducted separately by two researchers (T.S and A.O) based on predefined parameters, including the title of the study, the name of the first author, type of the study, sample size, type of the disease, histology confirmation of the disease as well as type, dose, duration, and outcome of the treatment and the measuring method in each study. No standardized type of treatment outcome measuring has been introduced for LPP and FFA so far; thus different qualitative and quantitative measurements were used to measure treatment outcome in the studies. In order to compare treatment outcomes, the findings of the studies were categorized into improved, stabilized, and unimproved. Therapies that accompanied minimal to maximal improvement, including hair regrowth, recovery from symptoms, remission, or any improvement in the course of the disease were classified as improved. Therapies that resulted in a halt in hair loss or resulted in a steady state of the disease were classified as stabilized. If no improvement or stabilization was observed for a therapy or worsening of the course of the disease 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 drug and with another medication after that were analyzed based on the final results. The findings of the studies that used multiple therapies for one patient were included mentioning the outcome of the combination therapy.

Appraisal

Oxford quality assessment checklist was used to check the quality of the randomized controlled trials. 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.

Result

Characteristics of the studies

Initial electronic search results for LPP and FFA is as follows: Embase (347), Scopus (221), Pubmed (209), and ISI web of science (170) studies. After removal of duplicate references, 563 studies remained. Title and abstract screening resulted in the exclusion of 470 studies, and the final full-text evaluation resulted in the inclusion of 38 articles. 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, 23-41), 17 studies assessed treatment for FFA (24, 32, 42-54), and only one study assessed treatment for both FFA and LPP (55). The process of screening is shown in Figure 1. All the studies were written in English except two studies (one study in Spanish (53) and one in Polish (40) language). Twenty one studies (1, 26-28, 31, 32, 34-38, 40, 44-46, 48, 51-53, 56, 57) were case reports, six studies (29, 30, 43, 50, 54, 58) were case series, and eight studies (23-25, 33, 39, 42, 49, 55) were retrospective case series. Only one article was a cohort study (47). There were only two randomized controlled trials (RCT) among the included studies (41, 59). 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 the studies, including the name of the first author, type of study, patients' number and diagnosis, evidence of histology, treatment and the way the outcomes were measured are shown in Table 1.

FFA treatments

A total of 483 patients received different therapies for FFA. Also, some publications tried various medications in the course of the disease. Overall, 28 different monotherapies and combination therapies were investigated. Monotherapy with antimalarial drugs such as Hydroxychloroquine/Chloroquine with a 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 about the use of oral corticosteroid monotherapy for FFA treatment with stabilization in one patient (42). Intralesional steroids were used in 146 patients and resulted in improvement in 57 (37.0%) and stabilization in 64 patients (43.8%). Administration of 5α-reductase inhibitors (5aRis) including Finasteride and Dutasteride resulted in improvement in 44.5% (58/127) of the patients. Stabilization of the disease was observed in three patients that used topical corticosteroids as monotherapy. Also, a case report about Minoxidil administration in FFA reported improvement of the disease course. Other monotherapies were less effective or ineffective. Table 2 shows the administration doses and outcomes of different monotherapies and combinatorial medications for each of the included studies. Also, dose of each therapy is reflected in table 1.

LPP treatments

A total of 599 patients experienced different therapies through 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 with improvement in 6 (50.0%) cases. Pioglitazone also had an improving effect on 71.7% (33/46) of patients. The administrated dose of each medication is demonstrated

in Table 1. Treatment strategies and their observed outcomes are presented in Table 3. Among the two randomized control trials (RCTs), one compared Systemic Mycophenolate Mofetil 2 g/day with Topical Clobetasol 0.05 % lotion in the treatment of LPP and the other RCT compared the effect of methotrexate with a 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 having a sample size of 60 patients with histologically proved LPP. Pregnant and lactating patients, those with other underlying diseases, those consumed any drug 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) that was conducted by another blinded physician. Treatment responders were defined as those who had more than 85% reduction in LPPAI and treatment failure was defined as less than 25% reduction in LPPAI. The range between 25 and 85 was defined 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 improved cases were Clobetasol-treated patients. Also, the number of non-responders were similar between 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 showed that the study was analyst-blinded. Also, 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 two groups. For

instance, some patients received isoniazid and vitamin B6 besides Mycophenolate Mofetil, and this can somehow obscure the result of the treatment. Computerized randomization was conducted properly, and each of the groups contained a sample size of 30 patients equally at the beginning of the study. In order to measure outcomes of the study in an objective way, the authors suggested Lichen Planopilaris Activity Index. The study has the intention to treat and reported 6/60 (10.0%) lost to follow-up (59).

The other RCT was conducted by Naeini et al. (41) in which 29 patients completed the six-month course of the study. Subjects were allocated to two groups: methotrexate (15mg per week) and hydroxychloroquine (200mg twice a day). Pregnant and breastfeed women and those patients suffered 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 (more 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 used as the outcome measure in the study by Naeini et al. Standardized scaled photography was used in order to fill items in LPPAI.

The quality assessment of the study revealed that the allocation was identical between 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 measurements of 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 hydroxychloroquine group. The study had intention to treat analysis with a quantitative outcome.

Progressive improvement was observed in methotrexate and hydroxychloroquine group. Overall, the study found notably methotrexate more effective than hydroxychloroquine.

Discussion

The aim of this study was to update the findings of the previous systematic review about treatments of LPP and FFA. We faced most of the limitation that Rácz et al. faced in their study (21). The studies were mainly case-reports, case series, or retrospective case series that belong to the lowest level of evidence. Currently, there is no standardized objective measurement for disease progression and most of the studies proposed different qualitative measuring scales using several measuring tools. The outcome measuring was mainly based on clinical signs of inflammation and hair loss progression. Various ways were used to measure the outcome of treatment, including dermoscopy, standardized photographs, and patients' self-reports. One of the included RCTs found no difference between Systemic Mycophenolate Mofetil 2 g/day and Topical Clobetasol 0.05 % lotion using Lichen Planopilaris Activity Index (LPPAI) as a numerical measurement. However, the study had some methodological problems in randomization (59).

We found no predefined quantitative measurement for assessing FFA progression and response to treatment. However, a study on 4 cases used LPPAI as an outcome measure. Other studies, mostly used cicatricial skin area measurement in frontotemporal hairline (42, 43) and dermoscopy (44, 56) as their outcome measures. Also, Anzai et al. exploited eyebrow density as an outcome measure (32). As a whole, we should declare that our study was limited by

heterogeneous and imprecise way of outcome measurement of the treatment in most of the studies.

Another RCT that was conducted in Iran suggested methotrexate as a more efficient drug than hydroxychloroquine (41). The study also proposed that both treatments were effective in reducing LPPAI and improving some of the signs and symptoms of the 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 that antimalarial agents, including hydroxychloroquine and chloroquine may be amongst the most effective treatments in LPP patients with around 73% improvement and 4% stabilization. A dose of 200 mg twice a day was used in all the studies that mentioned their administrated dosage (24, 33, 37, 55). Among the studies that mentioned period of treatment, one reported a mean time interval of 2.2 months (24) and the other a period of 5 months (37). In line with the findings of our study, some other studies have proposed antimalarial drugs as first-line treatment (16, 17). Chiang et al. and Spenser et al. reported some improvement in 55% of patients who were treated with a common dosage of 6.5 mg/kg/day or 200 mg twice daily within 6 months (16, 17). The best-proposed duration in Chiang et al. study was 12 months (16). Only one of the RCTs reported a superiority in efficiency for methotrexate over hydroxychloroquine in the treatment of LPP (41). 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 the 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, 15, 16, 21, 60-64). However, due to low evidence of the published studies, both in this study and the previously published systematic review, a conclusion is still on the debate.

Khalid et al. and Lyakhovitsk et al. have also tried Tacrolimus/Pimecrolimus regimen in 12 patients with improvement in half of the cases. It seems that Calcineurin inhibitors may have notable therapeutic effects. However, studies in the case of Calcineurin inhibitors efficacy are not sufficient to draw any recommendation, but it can be assumed that Calcineurin inhibitors may be useful as a treatment modality or at least used as an adjuvant to other treatments (14, 60).

Pioglitazone was used in two studies as LPP treatment with around 71% improvement. Peroxisome proliferator-activated receptor (PPAR) agonists are transcription factors that regulate differentiation, development, proliferation, and metabolism via gene transcription. This drug is used in metabolic and inflammatory diseases (65), but there are studies that reported their benefits in dermatology in lipodystrophies, psoriasis, melanoma, and atopic dermatitis (39).

Combination therapy with oral corticosteroids, hydroxychloroquine, and topical corticosteroids showed improvement in all of the two patients that underwent the treatment. Also, 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, but none of them were permanently useful in the management of the disease (4, 15, 16, 21, 60-64).

Although FFA is a variant of LPP, our finding showed that the effectiveness of treatment modalities for FFA differ from that of LPP. It seems that other more substantial factors besides inflammation lie in the physiopathology of the FFA. Maybe, small differences in the pathology

of the diseases can be an evidence of the various treatment outcomes in LPP and FFA (66). There is no predefined protocol, or first-line treatment for FFA; however, several different mono and combination therapies have been proposed for the disease. General treatments are categorized as topical or intralesional corticosteroids, antimalarial agents, or 5aRis. However, no RCTs that assess their efficacy against each other have been published so far.

The good response to antimalarial agents in LPP patients was not seen in FFA sufferings. In case of antimalarial drugs, improvement and stabilization were observed in about 14% and 54% of the patients with FFA and LPP, respectively. A good response was found in 30% of the patients who used antimalarial agents in the last published systematic review (59). Corticosteroids are among the mostly used FFA therapies and may have a fundamental role in the treatment of FFA according to our findings. Respectively, around 40% of the patients experienced improvement and 43% showed stabilization with intralesional steroids (24, 43, 51). This was somehow in line with the previous published systematic review that reported partial improvement in 60% of the patients (59). Only one study tried oral corticosteroids in FFA. The only case that used oral corticosteroids showed stabilization of the disease (42). Also, another study used topical corticosteroids that showed stabilization in 60% (3/5) of patients (55). In contrast with the findings of our study, the previous systematic review showed no efficacy for topical steroid treatment (21). Stabilization (49/103) or improvement (54/103) was seen in all cases of finasteride monotherapy (43, 56). Improvement and stabilization of the disease were respectively observed in about 37% and 58% of the patients with the administration of Dutasteride (43, 54, 56). Totally, 5aRIs seem to have a effect in the disease improvement. An androgenic alopecia may accompany FFA (20) and this may explain the efficacy of 5aRIs in FFA. Only one case report used minoxidil as monotherapy that showed improvement in the only case of the study (52). Combination therapy was mainly based

on corticosteroids, minoxidil, finasteride, triamcinolone, and hydroxychloroquine that showed stabilization in most of the cases (32, 42, 44, 51, 57, 58).

Conclusion

As an update for a previous systematic review in 2013, our study resulted in some complementary suggestions. We found two admissible RCTs in our systematic search that one of them prposed methotrexate as a preferable medication for LPP patients than hydroxychloroquine. However, other studies in the field of LPP treatment stated that antimalarial agents may be effective drugs. Pioglitazone may be one of the most effective treatments in LPP. Thus, further study is advisable to add pioglitazone to LPP treatment regimen. Also, some therapeutic effects have been suggested for topical steroids and calcineurin inhibitors. Our findings showed no established regimen for FFA, but it seems that 5aRIs and intralesional steroids are the most effective drugs. Further studies, including high-quality multicenter RCTs, are needed to find a first choice medication for FFA. Coming into conclusion based on low quality and heterogeneous studies or only a few randomized controlled trials limited our study.

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