Chapter

Treatment of Frontal Fibrosing Alopecia and Lichen Planopilaris

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Abstract

The aim of the treatment in frontal fibrosing alopecia and lichen planopilaris is to alleviate symptoms and to arrest the progression of the hair loss, since hair regrowth is not possible once the destruction of hair follicle has happened. Topical corticosteroids and tacrolimus are used to reduce inflammation, but with no clear benefit in slowing the alopecia. Intralesional corticosteroids may obtain hair regrowth in some patients, and they are especially useful in the treatment of eyebrow alopecia in frontal fibrosing alopecia. Regarding systemic treatments, the use of 5-alpha reductase inhibitors has been shown to be the most effective one to get stabilization in frontal fibrosing alopecia and even regrowth in the hairline. Hydroxychloroquine and oral immunomodulators are especially helpful as oral treatment in lichen planopilaris. Low-dose oral isotretinoin is the preferred treatment for facial papules in frontal fibrosing alopecia. The combination of oral and topical treatments is the best therapeutic choice.

Keywords: frontal fibrosing alopecia, lichen planopilaris, scarring alopecia, cicatricial alopecia, treatment

1. Introduction

Frontal fibrosing alopecia (FFA) and lichen planopilaris (LPP) are currently the most common types of scarring alopecia, especially the first one [1]. LPP was first described in 1895 by Pringle [2], while FFA was described in 1994 by Kossard [3], although the latter has become the most prevalent.

Both belong to the lymphocytic cicatricial alopecia subtype and share the main histopathologic features, although there are some differences between them [4, 5]. They are mainly characterized by a lichenoid lymphocytic infiltrate around the upper follicle, that is isthmus and infundibulum, including the bulge area, where the stem cells are located, and concentric perifollicular lamellar fibrosis [6].

FFA is clinically characterized by frontal or temporoparietal hairline recession, leading to a cicatricial alopecic band without follicular openings. FFA is frequently associated with eyebrow alopecia, and sometimes eyelash alopecia or peripheral hair body loss (limbs, axillary, pubic) can be observed. Facial papules are another typical finding in FFA, which are normally distributed on the temples, but also on the cheeks or chin [7]. The classic LPP usually appears as multifocal scarring areas that may

coalesce in large alopecic areas, and which are more commonly located at the vertex and parietal scalp [5]. However, sometimes both conditions can present concomitantly, since up to 25% of patients with FFA may have also the classic form of LPP [7, 8]. Pruritus and trichodynia may be present in some patients. FFA and LPP also share some trichoscopic features, such as follicular hyperkeratosis and perifollicular erythema, which are usually more intense in LPP. The background of FFA is typically ivory-white, whereas in LPP is usually milky-red [9].

The aim of the treatment in both FFA and LPP is to alleviate symptoms – if they are present – and to stop or slow down the progression of the disease, since hair regrowth is not possible once the destruction of the hair follicle has happened. Photographic and trichoscopic control is really useful to assess the progression of the disease and the response to the treatment. Moreover, in FFA, the size of the alopecic band and the measurement from the frontal hairline to the glabella and from the temporal hairline to the eyebrows is highly advisable.

2. Frontal fibrosing alopecia management

The therapeutic management of FFA remains still challenging due to its unclear pathophysiology, the lack of double-blind prospective studies and the progressive and refractory nature of the disease. In fact, most of the studies about treatment in FFA are based on retrospective cohort studies and case reports. The best therapeutic option in FFA usually combines oral and topical or intralesional treatments. Topical and intralesional corticosteroids are first-line treatments due to their security profile, and 5-alpha reductase inhibitors are currently considered one of the most effective therapies in terms of disease stabilization [10, 11]. FFA is progressive and mostly irreversible, so an early diagnosis and treatment is mandatory to achieve the best results. However, in some cases, a poor outcome can be predicted despite the treatment, especially in patients with the diffuse form [12].

2.1 Topical and intralesional treatments

Potent topical corticosteroids are considered the first-line treatment and are recommended especially when inflammation signs are present. There is no clear benefit in slowing the progression of the alopecia, but their security profile and capacity to relieve symptoms support their use [13, 14]. Similar indication has the use of topical calcineurin inhibitors, either alone or associated with topical corticosteroids, although one report found a better outcome with them, in terms of stabilization, compared to a group of patients treated with corticosteroids [15, 16]. Topical calcineurin inhibitors are also useful to spare topical corticosteroids. However, topical treatments are not usually used in monotherapy, which makes it difficult for a proper assessment of their real efficacy.

Topical minoxidil has not shown clinical improvement in slowing down the alopecia, but it is useful when androgenetic alopecia is associated or to improve the remaining hair [13].

In the case of eyebrow and eyelash alopecia, the use of a prostaglandin analogue, such as bimatoprost 0.03% eye drops, applied twice daily, may be a therapeutic option [17].

Eyebrow alopecia in FFA usually does not improve with systemic treatment alone, so another associated therapy is recommended [18]. In that case, the use

of intralesional corticosteroids, 10 mg/ml of triamcinolone acetonide every three months, may obtain hair regrowth in some patients, especially when the hair loss is partial. A higher concentration of triamcinolone acetonide – 20 mg/ml - can be used in the hairline implantation, every 3 to 6 months, and it may obtain stabilization and even hair regrowth in a considerable number of patients [19].

There is only one study about platelet-rich plasma (PRP) in FFA. These authors reported one patient who had an improvement in the trichoscopic signs and a stoppage in the progression of the alopecia after five treatments, with a one-month interval of injections in the frontotemporal hairline and eyebrows [20].

2.2 Systemic treatments

Nowadays, oral 5-alpha reductase inhibitors are considered the most effective treatment for FFA. In a report about 102 patients with FFA treated with finasteride (2.5–5 mg/day), which inhibits the isoenzyme type II of 5-alpha reductase, 47% of them showed improvement and 53% of them showed stabilization of the alopecia [19]. Dutasteride is about three times as potent as finasteride at inhibiting type II 5-alpha reductase and more than 100 times as effective at inhibiting type I [21]. A recent study including 224 FFA patients found a significantly higher stabilization rate in those under treatment with dutasteride – around 64% - compared to other systemic treatments, such as finasteride, hydroxychloroquine, doxycycline and isotretinoin [11]. Moreover, the response was dose-dependent, and the most effective dose was five to seven capsules of dutasteride (0.5 mg) per week. Thus, 5-alpha reductase inhibitors are considered, by most authors, the first therapeutic option in patients with FFA, [22] while others considered them as a second-line therapy [23]. Due to its higher effectivity, dutasteride may be a suitable first option, except for childbearing age women, in which finasteride should be considered because of its shortest wash-out period [22].

Antimalarials, such as hydroxychloroquine, may improve symptoms and signs of FFA, with better results seen within the first six months of therapy, although they normally achieve partial responses [24]. Other reports have not found any consistent benefit with the use of hydroxychloroquine [14]. A recent systematic review found that hydroxychloroquine and 5-alpha reductase inhibitors resulted to be the most effective therapies in terms of disease stabilization [10].

Tetracyclines, such as doxycycline, have been used for their anti-inflammatory effects in patients with FFA, often after antimalarial failure, but the response rates are low and not consistent [24, 25].

Treatment with oral prednisone (0.5–1 mg/kg/day), for 3 to 18 months, has been shown to produce a stoppage of the progression of the alopecia in almost 43% of patients, but relapse occurs after its discontinuation [13]. Therefore, the worse security profile in long-lasting treatments, and the relapse when the treatment is stopped, move this therapeutic option from the first-line treatments.

Oral retinoids, isotretinoin (20 mg/day) and acitretin (20 mg/day) have been shown to produce a stoppage in the hairline recession in 76% and 73% of patients, respectively, in a retrospective analysis, in which they were even more effective than finasteride (5 mg/day) in stopping the progression of the alopecia [26]. Isotretinoin may be useful in patients with facial papules, which may improve in two to four months with low doses such as 10 mg/day or even less. The improvement of erythema and perifollicular hyperkeratosis has also been reported in patients under treatment with isotretinoin (10–20 mg/day) [27]. Regarding other oral retinoids, such as

alitretinoin, only one report of a woman has been published, in which she showed improvement after one month with 30 mg/day [28]. Facial papules improvement has also been noted with the use of oral prednisone and hydroxychloroquine, after at least 6 months of treatment [29, 30].

Other treatments, such as griseofulvin or azathioprine have shown inconsistent outcomes or no efficacy [3, 24, 31–33]. Partial responses have been described in around 60% of patients who were treated with mycophenolate mofetil [24]. Stabilization of a few patients who were under treatment with methotrexate has been observed [25, 34].

Low-dose oral minoxidil may improve the background hair thickness, although further studies about its use in FFA are needed [35]. Its addition to the treatment may be interesting to increase hair volume, especially when androgenetic alopecia is present [36]. In some patients with FFA and concomitant androgenetic alopecia, who were treated with oral minoxidil, partial or complete eyebrow regrowth was noted [37]. Therefore, low-dose oral minoxidil (0.25–2.5 mg/day) may be an interesting adjuvant therapy for the treatment of eyebrow alopecia in patients with FFA, particularly in early disease.

Regarding the use of the oral pioglitazone hydrochloride (15 mg/day), a peroxisome proliferator-activated receptor γ (PPAR- γ) agonist, inconsistent results have been found when using it in LPP, but no successful outcomes have been observed in FFA patients [25, 38, 39].

The pan-Janus Kinase (JAK) inhibitor, tofacitinib, 10–15 mg/day, was used in some patients with refractory LPP (8/10) and FFA (2/10), from two to nineteen months; 80% of patients showed a clinical response, including clinical improvement in both FFA patients [40]. Baricitinib, a JAK 1 and 2 inhibitor, was used in a woman with refractory subacute cutaneous lupus erythematosus and FFA and resulted in completed clearance of the former and no further progression of the latter [41]. JAK inhibitors might be used as a therapeutic option in the future. An isolated report about a woman with recalcitrant FFA and LPP, who improved after the treatment with tildrakizumab, an anti p19 interleukin 23 monoclonal antibodies, was also published; the dose the authors used was 100 mg subcutaneously at week zero, 4 and subsequently 12 weekly, for around 4 to 13 months [42].

2.3 Treatments based on light devices

Some authors found that the excimer laser may be useful in reducing inflammation and perifollicular hyperkeratosis in patients with active LPP and FFA [43]. Photobiomodulation therapy, also known as low-level laser (light) therapy (LLLT), using light-emitting diodes (LEDs), may be an adjuvant option to consider in patients with FFA or LPP. A report found that LEDs may produce an improvement in symptoms and perifollicular hyperkeratosis, because of their anti-inflammatory and immunomodulatory effects, and may even increase the number of thick hairs within the treated area [44]. Moreover, LEDs treatment can also improve eyebrow alopecia in FFA patients, as was found in a study carried out on 16 women, in which an increase in hair count and in the number of thick and mid-thick hairs were noted, especially in cases of partial eyebrow alopecia [45].

A study about Nd:YAG (1064) non-ablative laser, carried out on 5 FFA patients, found improvement in symptoms and in perifollicular hyperkeratosis and follicular erythema in some patients [46]. Moreover, facial papules, lichen planus pigmentosus and hair loss spreading, also improved in some patients.

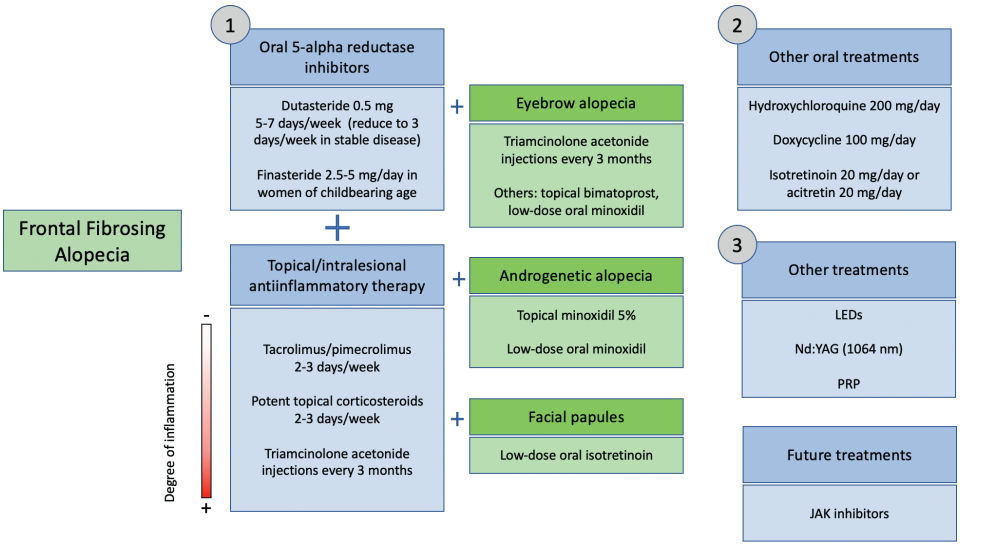
2.4 Hair transplant and covering options

Hair transplant may be considered in selected cases of FFA, but a minimum of one to five years without activity is recommended [47, 48]. However, patients with FFA should be warned about the hair graft survival rates, since a rate lower than 60% has been reported, independently of the period of time since clinical remission [49]. Therefore, hair transplant may be considered only in small areas of the scalp or in eyebrows, and always after discussing with the patient the long-term survival rates of the hair grafts [49, 50].

In advanced cases of FFA, wigs or hair systems could be interesting options to add to the medical therapy, as well as eyebrow micropigmentation in cases of eyebrow alopecia.

2.5 Therapeutic algorithm for FFA

A therapeutic algorithm for FFA is proposed in **Figure 1**, with different lines of treatment indicated with the circled numbers.



LEDs: light-emitting diodes; PRP: platelet-rich plasma; JAK: Janus Kinase.

Figure 1.
Therapeutic algorithm for FFA.

3. Lichen planopilaris management

There is no curative therapy for LPP. Therefore, the main goal of the treatment is to reduce the inflammatory symptoms and to slow the progression of hair loss, since hair regrowth is not possible when scarring has happened.

No gold standard approach exists to the treatment of LPP. Moreover, the publications about the treatment of LPP are quite sparse and the therapies they are referred to have limited evidence. Only a few of them are controlled trials. Furthermore, the

evidence shows a varied response to therapy, with frequent reports showing poor outcomes [51–53]. There are some recommendations for the treatment of LPP, but no specific therapy guidelines. Hence, daily clinical practice often relies on disease activity, age, comorbidities, and the physician's personal experience [54]. Patients with LPP experience significantly impaired quality of life and mental health associated with disease activity, and the potentially permanent hair loss highlights the importance of early disease detection and treatment [55].

3.1 Topical and intralesional treatments

Topical steroids are often reported as a first-line treatment, especially the ultrapotent corticosteroid clobetasol propionate, for cases with a limited extent. They help to reduce inflammation and associated symptoms, including burning sensation and itchiness [12, 35]. A proposed protocol consists of using topical steroids twice daily for the first month, followed by an application once a day for 3 months, and then every other day for 3 more months [56].

Monthly intralesional high potency corticosteroids have similar outcomes to topical steroids regarding efficacy. Injections of triamcinolone acetonide at a concentration of 10 mg/mL –2 mL in total - every 4 to 6 weeks until disease stabilization, are recommended for the treatment of LPP by the researchers of the University of British Columbia [57]. They also suggest that if there is no improvement after three months of injections, other treatment options should be considered. There is no clear evidence about which delivery mode is better, although Lyakhovitsky et al. and Mehregan et al., propose that topical and intralesional corticosteroids can be used together to achieve a faster clinical response [58, 59].

Topical calcineurin inhibitors also reduce inflammation and help to induce the early anagen phase of the hair cycle. However, the largest study of topical calcineurin inhibitors, which included ten patients with LPP, reported inflammation improvement in only two patients (one on monotherapy and another one associated with hydroxychloroquine) [58].

Topical minoxidil improves the caliber and condition of the hairs of the background, but irritative and allergic contact dermatitis, in an already inflamed scalp, are common adverse effects [60]. A combination of topical tacrolimus 0.3%, clobetasol propionate 0.05%, and minoxidil 5%, can be applied twice daily as first-line therapy, along with intralesional triamcinolone acetonide. When the disease stabilizes, the clobetasol dose is the one to be decreased or discontinued first, followed by the tacrolimus dose [54].

The efficacy and safety of PRP in cicatricial alopecia, including LPP, remain unknown. In a recent case series of 10 patients with LPP and FFA, who received PRP mesotherapy, no koebnerization or development of new areas of involvement were noted, although the clinical improvement was unclear due to the multitherapy regimens done by the patients [61].

3.2 Systemic treatments

Oral treatments are indicated for patients with local treatment resistance, more extensive manifestations, scalp involvement ≥10% and those with rapid progression.

Hydroxychloroquine is often preferred as the first-line systemic agent because of its relatively good side-effect profile. There are several case series regarding hydroxychloroquine as monotherapy or in combination with other agents, with

varied outcomes, and overall, treatment response was seen in approximately 50–60% of cases [58, 62, 63]. Conversely, other small case series or single case reports showed little or no response [64]. Action onset occurs after two to three weeks, and the peak of response is achieved after six months. Hydroxychloroquine may be initially administered at 200 mg, twice daily, with the goal to decrease to weight-based dosing of 5 mg/kg/day, for a 6 to 12-month period [54].

Immunomodulators are therapeutic alternatives for patients with difficult-to-control disease. Some options pointed out in the literature are methotrexate, cyclosporine and mycophenolate mofetil [65].

A randomized clinical trial comparing hydroxychloroquine (400 mg daily) and methotrexate (15 mg weekly), for a 6-month period in recalcitrant LPP, found a significant superiority of methotrexate over hydroxychloroquine. Moreover, patients in the hydroxychloroquine group showed only a significant improvement in erythema, while patients in the methotrexate group showed efficacy on pruritus as well as on all the objective variables assessed in the study (erythema, perifollicular erythema, perifollicular scaling, spreading, and follicular keratosis). The negative outcomes observed in the patients belonging to the hydroxychloroquine group could be due to the fact that the study was only focused on recalcitrant cases [66]. In a retrospective study, the response rates of cyclosporine and methotrexate were similar (100% and 85%, respectively), and those treated with cyclosporine achieved partial and complete remission faster than the methotrexate group patients. However, both treatments were less safe compared to mycophenolate mofetil [52].

On the other hand, a randomized controlled trial for evaluating the safety and efficacy of methotrexate (15 mg, oral, per week) versus cyclosporine (3–5 mg/kg/day), for six months, in patients with refractory LPP, found similar efficacy at the end of the study with both treatments. Nevertheless, the authors proposed methotrexate as the first choice over cyclosporine because of its easier administration, fewer tolerable side effects and lower recurrence rates [67]. Other studies regarding cyclosporine in LPP also revealed considerable outcomes, although high relapse rates are common after its discontinuation [53, 56, 68].

Mycophenolate mofetil may be another potential treatment for patients with severe or recalcitrant LPP who have failed hydroxychloroquine and other immunomodulators [69, 70]. Six studies were included in a recent systematic review and meta-analysis, including 94 patients, in which 69.2% of patients had a good response (partial or complete), with dosages ranging from 1 to 6 g daily, and treatment duration ranging from 2 to 12 months [71].

Limited evidence supports the therapeutic potential of JAK inhibitors for the treatment of recalcitrant LPP, and in most published reports the patients were treated with other concomitant therapies [40]. A report which investigated the usefulness of topical and oral tofacitinib as an adjuvant treatment in 9 patients with recalcitrant LPP, found that both formulations were effective in achieving a positive clinical response. The median time to see any treatment response was 3 months. Authors concluded that although oral tofacitinib led to a more pronounced and sustained improvement, topical therapy may be considered a feasible alternative in some patients [72]. A report about the use of baricitinib in patients with refractory LPP (7/12) and FFA (5/12) (median dose of 3.4 mg and concomitant treatments in all of the patients), showed that 46.5% and 83.8% of patients, respectively, demonstrated an initial reduction in the median Lichen Planopilaris Activity Index (LPPAI) score. However, the response was maintained in only 3 out of 7 LPP patients and in 2 out

of 5 FFA patients, after a median duration of 6 months. Furthermore, 4 patients had previously had a failure with oral tofacitinib treatment, which may predict a possible absence of response to another JAK inhibitor [73].

Oral glucocorticoids should be reserved for very symptomatic patients and those with rapid progression, due to their potential adverse effects and the very high degree of relapse (around 80% of patients) after treatment discontinuation [54, 74]. Some authors utilize short courses in rapidly progressive cases, usually prescribed at 40 mg daily for 1 week, then tapered by 5 mg weekly for 8 weeks, acting as a bridge to the effect of longer-lasting drugs, such as methotrexate [75].

The first study describing the use of low-dose of oral minoxidil (LDOM) in LPP showed that LDOM (median dosage 1 mg/day), with a mean duration of therapy of 21 months, can help to maintain or increase hair thickness in the majority of patients with LPP, in unaffected and potentially affected areas, with an acceptable safety profile. Better results were reported in patients presenting diffuse LPP and with the higher doses of LDOM used in male patients [35].

Regarding low dose naltrexone for the treatment of LPP, only one case series including four patients has been published, which showed some therapeutic benefits, including a decrease in inflammation and in the presence of inflammatory symptoms, along with slowing in the disease progression [76].

Other systemic treatment options, such as doxycycline (100 mg twice daily), have shown limited outcomes [58, 60, 77].

3.3 Treatments based on light devices

LLLT is an emerging light therapy that has shown effectiveness in treating several inflammatory skin disorders, such as lichen planus. Nevertheless, the reports about its use are limited [78], and there are just two studies about LLLT for the treatment of LPP. The first study, which included a total of 8 patients, showed a global reduction of symptoms, erythema, and perifollicular hyperkeratosis in all patients after 6 months of intervention [79]. Another report showed consistent improvement with reduction of inflammation, the disappearance of symptoms, and evident hair regrowth after 3 and 6 months, in a total of 4 patients whose disease had remained active despite topical and/or systemic treatments [80]. Limitations of this treatment could be the daily regimen and the lack of clear treatment protocol and parameters.

3.4 Hair transplant

The outcomes of transplantation in patients with LPP vary because of the autoimmune nature, so surgical procedures may trigger the Köebner phenomenon and induce new lesions in recipient and donor areas [47]. Hence, most of the authors believe that transplantation can be considered in patients with clinical remission of at least two years in order to keep the final outcome of transplantation and induce hair regrowth. Regarding the technique, FUE (follicular unit extraction) is preferred due to the following advantages: the absence of suture wounds and linear scars, less bleeding and less postoperative discomfort. Furthermore, these patients require close postoperative follow and long-term observation to determine the final outcomes of the treatment. If perifollicular keratosis or erythema is noted, medical modalities such as topical/intralesional steroid injections and/or oral medications should be given to prevent further hair loss [81, 82].

3.5 Therapeutic algorithm for LPP

A therapeutic algorithm for LPP is proposed in **Figure 2**, with different lines of treatment indicated with the circled numbers.

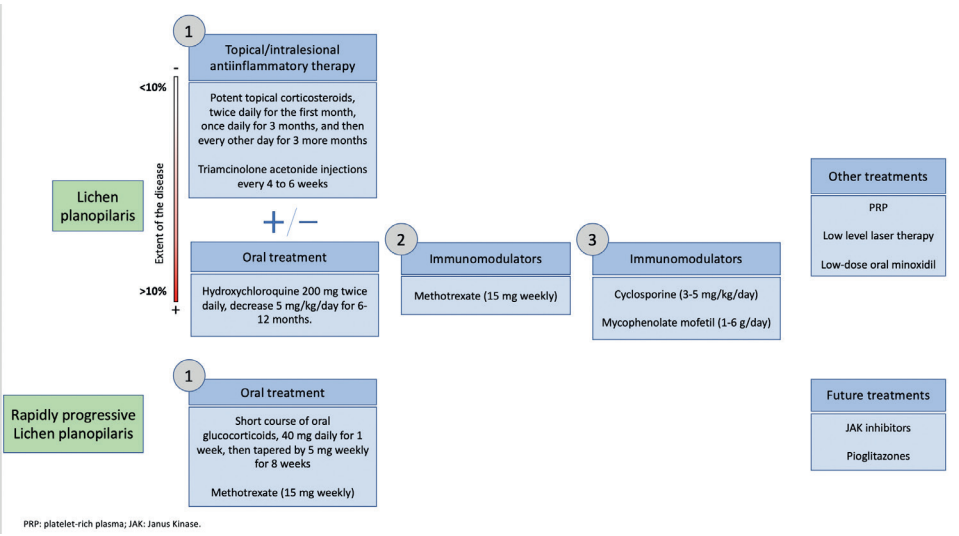


Figure 2.
Therapeutic algorithm for LPP.

4. Conclusions

The best therapeutic option in FFA should include both topical and oral treatments. Five-alpha reductase inhibitors, especially dutasteride, have shown to be one of the most effective treatments in stopping hairline recession, and they should be used as first-line therapy in FFA patients. A topical anti-inflammatory drug should be added with a maintenance frequency regimen, that is, topical calcineurin inhibitors or topical corticosteroids, or even intralesional corticosteroids, depending on the degree of inflammation. When androgenetic alopecia is associated, adding topical or oral minoxidil may achieve better outcomes. In the case of eyebrow alopecia, especially in early stages, intralesional corticosteroids are recommended, although the use of oral minoxidil may also be helpful. In patients with facial papules, low-dose oral isotretinoin should be added to the treatment.

Regarding LPP, treatment commonly involves the use of high potency topical and/or intralesional corticosteroids in cases with limited involvement and orally administered hydroxychloroquine in cases of progressive course or extensive cases. When therapy with hydroxychloroquine fails, methotrexate could be used as a second-line therapy, while mycophenolate mofetil and cyclosporine could be considered as third-line therapies. A short course of systemic steroids should be considered only in rapidly progressive and severe cases, acting as a bridge to the effect of longer-lasting drugs, such as methotrexate. Pioglitazone could be a promising and effective therapeutic option, although more evidence is needed to confirm its precise role in LPP management.

Conflict of interest

The authors declare no conflict of interest.

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