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View and Practice

Is Finasteride the future of Frontal Fibrosing Alopecia?

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Frontal Fibrosing Alopecia (FFA) is a primary lymphocytic cicatricial alopecia typically characterised by recession of the frontotemporal hairline. While FFA is usually seen in postmenopausal women, it has also been recognised in premenopausal women and men.[1] FFA is currently known as one of the leading causes of scarring alopecia, and without treatment it can lead to permanent hair loss.[2] Treatment remains difficult due to the lack of data on disease pathogenesis and treatment efficacy. At present, increasing evidence have shown that 5-alpha-reductase inhibitors (5ARIs) such as Finasteride can effectively control the disease process.

Treatment of Frontal Fibrosing Alopecia

Case reports and cohort studies have reported disease control of FFA through the use of various therapies including 5ARIs, topical and intralesional corticosteroids, topical and oral immunomodulators, hydroxychloroquine, doxycycline, retinoids and pioglitazone.

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Topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), and intralesional steroids are typically considered first-line local therapy for FFA. A systematic review on therapeutic options for FFA found that high or moderate potency TCS led to no response in 93% of cases.[3] A retrospective review of 22 FFA patients who received TCI therapy found a reduction of signs of inflammation but it did not slow the progression of disease.[4] In a systemic review assessing the response of various therapy for FFA, intralesional steroids resulted in a positive treatment response in 88% (181/204) of patients.[5] However, intralesional injection of steroids are limited by side effects such as pain, skin atrophy and telangiectasia.

Hydroxychloroquine (HCQ) and Doxycycline have been previously used as first-line systemic therapies due to their anti-inflammatory properties and low side effect profile. A systemic review found improvement of LPPAI score in 74% (17/23) of patients on HCQ 200-400 mg/d alone, and stabilisation of hairline recession was seen in 71% (41/58) on HCQ combination therapies.[5] However, data is only available from four retrospective cohort studies with 23 patients on HCQ alone and 58 patients on HCQ combination therapy.[1,6-8] In a retrospective report including 65 FFA patients treated with Doxycycline, Tetracycline, or Minocycline, no difference was found in outcomes compared to HCQ (n=32) but were more likely to experience adverse side effects compared

to other treatments. Adverse effects of these antimicrobials included nausea, candida infection, esophagitis, lightheadedness, photosensitivity, and skin eruption.[9]

Oral Retinoids have also been used as alternative treatment for FFA. A retrospective cohort study of 40 FFA patients treated with Isotretinoin 20 mg/d or Acitretin 20 mg/d for 12 months showed stabilisation in 79% (23/29) and 73% (8/11), respectively.[10] There are also case reports supporting the use of Isotretinoin for facial papules in FFA, although the hairline involvement showed no clinical change with this therapy.[11,12]

Systemic immunosuppressants such as methotrexate (MTX),[8] azathioprine,[8] mycophenolate mofetil (MMF),[13] have all been used in small numbers of patients with FFA, all with controversial results. Accordingly, potent immunosuppressive agents are generally reserved for refractory cases of FFA.

5-alpha-reductase inhibitors in treatment of Frontal Fibrosing Alopecia

Finasteride and dutasteride, well established in the treatment of androgenetic alopecia, are antiandrogens, and prevent the enzyme 5-alpha-reductase from converting testosterone into dihydrotestosterone. Finasteride, a type-II 5ARI, prevents this conversion in hair follicles, while dutasteride, a type I and II inhibitor, is less selective and inhibits conversion at hair follicles, and sweat and sebaceous glands.[14]

The lack of randomised clinical trials does not allow for definitive conclusions to be made regarding optimal treatment for FFA, but increasing available evidence have shown that 5ARIs are effective in stabilising the disease.

In a retrospective multicentre study including 355 FFA patients, 5ARIs were used in 111 patients (31%) with improvement in 52 (47%) and stabilisation in 59 (53%) patients. The authors concluded that 5ARIs were the most effective treatment modalities for FFA.[1]

A recent large retrospective observational study found that the stabilisation rate for the frontal, right, and left temporal regions after 12 months was 62%, 64%, and 62% in the dutasteride group (n=148), 60%, 35%, and 35% with other systemic therapies (n=20), and 30%, 41%, and 38% without systemic treatment (n=56). After 24 months of treatment, the percentage of stabilised patients at the frontal regions was 57.1% with dutasteride (n=42), 50.0% with finasteride (n=6), 21.7% without systemic treatment (n=23) and 0% with HCQ (n=4), Doxycycline (n=2) and Isotretinoin (n=1). Dutasteride was well tolerated in all patients. The authors concluded that dutasteride was the most effective therapy for FFA compared with other systemic therapies or no systemic treatment.[15]

In an evidence-based analysis of articles on treatment efficacy and safety of 5ARIs in the treatment of FFA, the authors concluded that 5ARIs has a positive role in the treatment of FFA, either in achieving disease stability or reducing the rate of disease progression. 5ARIs are recommended for cases where disease control is not established with conventional treatment and prior to starting a systemic immunosuppressive agent.[14] In a systemic review assessing the response of treatments for FFA, the authors found that 5ARIs are the therapies with the most positive treatment responses and stabilised hair loss in 88% (158/180) of patients.[5]

Table 1.1 and 1.2 summarise the available evidence on the use of 5ARIs in FFA.

Treatment algorithm for Frontal Fibrosing Alopecia

Management of FFA has been difficult because of the limited guidelines available. However, due to the growing evidence on the effectiveness of 5ARIs in management of FFA, several authors have recently proposed updated treatment algorithm based on the current available data and clinical experience.

Ho and Shapiro proposed an approach to the management of FFA using the data from their systematic review.[5] In their algorithm (Figure 1), 5ARIs are used as first line therapy in combination with topical treatment and intralesional steroids for patients with hairline recession ≥1 cm. 5ARIs are also used for patients with hairline recession <1 cm when no improvement was noted after first line topical treatment and intralesional steroids. The authors

Table 1.1. The available evidence on the use of Finasteride in the treatment of Frontal Fibrosing Alopecia

Author(s)	Study type	No. of patients	Finasteride dosing	Concomitant treatment	Duration	Response
Vañó-Galván et al[1]	Retrospective cohort study	102	2.5-5 mg/d	–	–	Regrowth in 47% (48/102), stabilised in 53% (54/102)
Rakowska et al[21]	Retrospective cohort study	14	5 mg/d	–	12 months	Stabilised in 43% (6/14) after 12 months
Pindado-Ortega et al[15]	Retrospective cohort study	9	2.5-5 mg/d	–	24 months	Stabilsed at the frontal region in 78% (7/9) at 12 months and 50% (3/6) at 24 months
Tosti et al[22]	Retrospective cohort study	8	2.5 mg/d	Topical minoxidil	–	Arrested in 50% (4/8), slowly progressive in 50% (4/8)
Moreno-Ramirez et al[23]	Retrospective cohort study	7	2.5 mg/d	IL-TAC, topical minoxidil	2-4 years	Stopped progression
Rallis et al[24]	Retrospective cohort study	5	2.5 mg/d	Topical minoxidil	12 months	Stabilised in 60% (3/5) at 2-year follow-up
Ladizinski et al[8]	Retrospective cohort study	1	1-2.5 mg/d	–	3 months	Stabilised
Donovan et al[25]	Case report	1	2.5 mg/d	–	3 months	Regrowth in frontotemporal scalp

suggested the use of Finasteride 5 mg/d for premenopausal female and Dutasteride 0.5 mg/d for postmenopausal female.

Imhof and Tolkachjov also provided a practical guide for clinicians based on the evidence-based management options currently available in the literature.[16] In their algorithm (Figure 2), 5ARIs are included as first line treatment together with topical regimens and intralesional steroids for FFA patients of all severity. They suggested the use of Finasteride 1-5 mg/d or Dutasteride 0.5 mg/d. However, the authors suggested to consider HCQ or Doxycycline over 5ARIs for pre-menopausal females in view of their teratogenic nature.

Mechanism of Finasteride in treatment of Frontal Fibrosing Alopecia

Finasteride is a competitive inhibitor of 5-alpha-reductase, an enzyme that catalyzes the conversion of testosterone to DHT. Finasteride specifically acts on isoenzyme II, which is found in the hair follicle root sheath, uterus, endometrium, fallopian tube, prostate, male genitalia, and liver. The mean circulating levels of testosterone are concomitantly increased since Finasteride inhibits the conversion of testosterone to DHT. Elevated testosterone may negatively compete with estrogen in the blood. It is

Table 1.2. The available evidence on the use of Dutasteride in the treatment of Frontal Fibrosing Alopecia

Author(s)	Study type	No. of patients	Finasteride dosing	Concomitant treatment	Duration	Response
Pindado-Ortega et al[15]	Retrospective cohort study	148	0.5 mg/d to 0.5 mg/wk	–	24 months	Stabilised at the frontal region in 62% (91/148) at 12 months and 58% (24/42) at 24 months
Vañó-Galván et al[1]	Retrospective cohort study	18	0.5 mg/wk	–	–	Regrowth in 44% (8/18), stabilised in 56% (10/18)
Georgala et al[26]	Prospective cohort study	13	0.5 mg/d	–	12 months	12 months: regrowth 15% (2/13), arrested 46% (6/13), slow progression 38% (5/13); 18 months: no recurrence in responders
Ladizinski et al[8]	Retrospective cohort study	5	0.5 mg/wk	–	15-44 months	Stabilisation in 80% (4/5)
		3	0.5 mg/wk	Doxycycline	18-52 months	Stabilisation in 67% (2/3)
		1	0.5 mg/wk	TCS, TCI	17 months	Stabilised
		1	0.5 mg/wk	TCS	13 months	No improvement
Katoulis et al[27]	Case report	1	0.5 mg/d	TCI	6 months	Moderate regrowth
Cranwell et al[28]	Case report	1	0.5 mg/d	Minoxidil 1 mg/d	3 years	Stabilisation

estimated that Finasteride use results in a 15% increase in both testosterone and estradiol compared to baseline, which is still considered within the physiologic range.[17]

The mechanism of action of Finasteride in FFA remains unclear. Considering the preferential involvement of the frontotemporal hairline and the high prevalence in postmenopausal women, an androgen-related stimulus has been proposed as a trigger for FFA. It has been hypothesised that Finasteride might interfere with the pathogenic pathway by acting against androgenic influence on androgen dependent hair follicles of the frontal scalp.[18] Moreover, it was postulated that a currently unknown antigenic stimulus triggers a lichenoid reaction in genetically susceptible individuals. Accordingly, Finasteride may reverse the miniaturisation of terminal hairs into vellus hairs, which can prevent lichenoid inflammation.[19]

Recommendations for Finasteride in management of Frontal Fibrosing Alopecia

Indications

In mild cases of FFA (hairline recession <1 cm), topical treatments including TCS and TCI, and

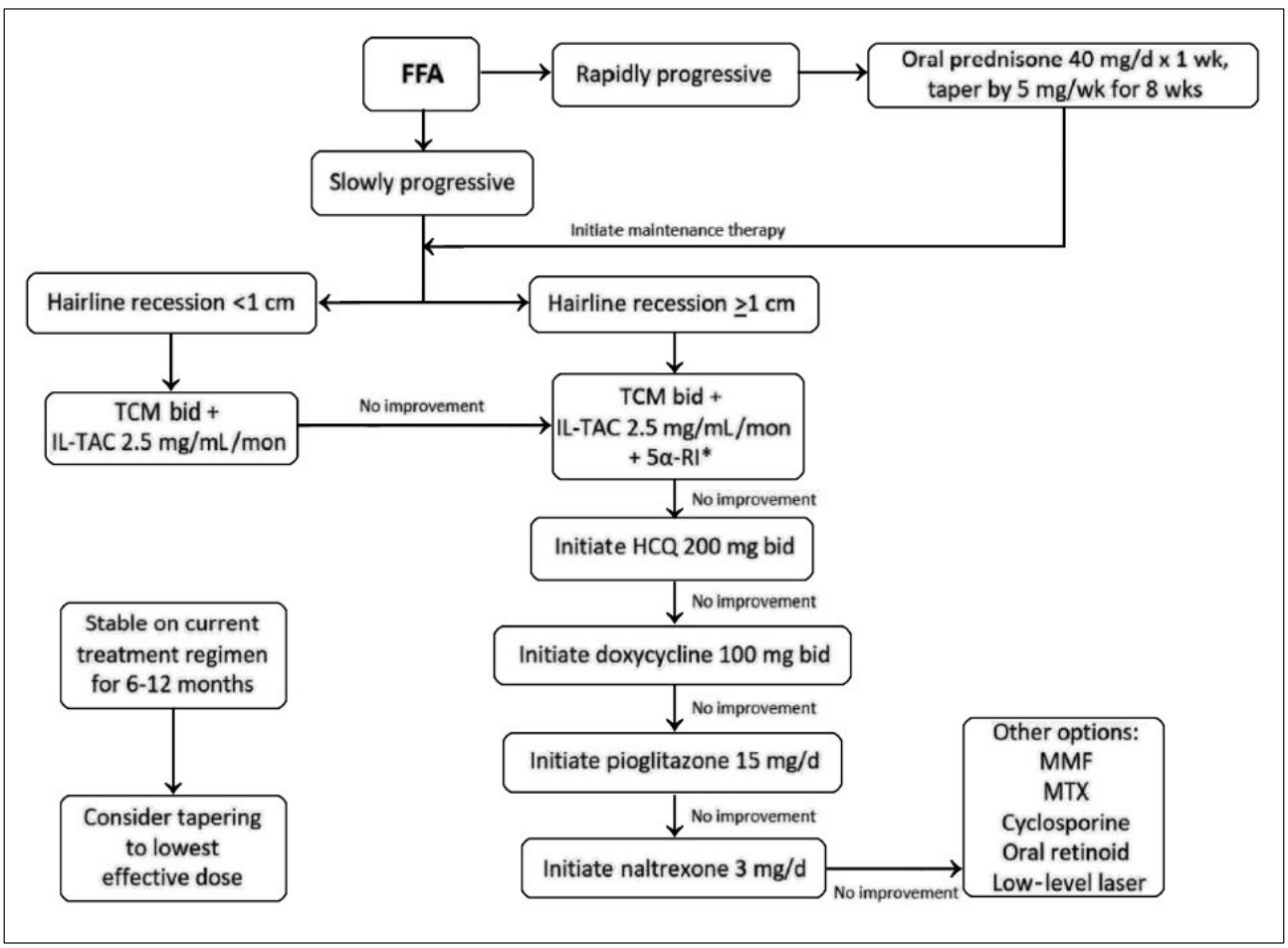

Figure 1. Algorithm for management of Frontal Fibrosing Alopecia (Ho & Shapiro)[5]

*Finasteride 5 mg/d (premenopausal) or Dutasteride 0.5 mg/d (postmenopausal)

Abbreviations: 5αRI, 5-alpha-reductase inhibitors; bid, twice daily; IL-TAC, intralesional triamcinolone acetonide, TCM, tacrolimus 0.3% in Cetaphil cleanser + clobetasol solution + minoxidil 5% solution.

intralesional steroids could be used as first line. Finasteride should be considered when these first line local therapies are unsuccessful in controlling the disease. In severe cases of FFA (hairline recession >1 cm), Finasteride could be considered in combination with topical treatments and intralesional steroid to halt the progression and prevent permanent hair loss.[5]

Finasteride can be used in post-menopausal females and men without worrying about

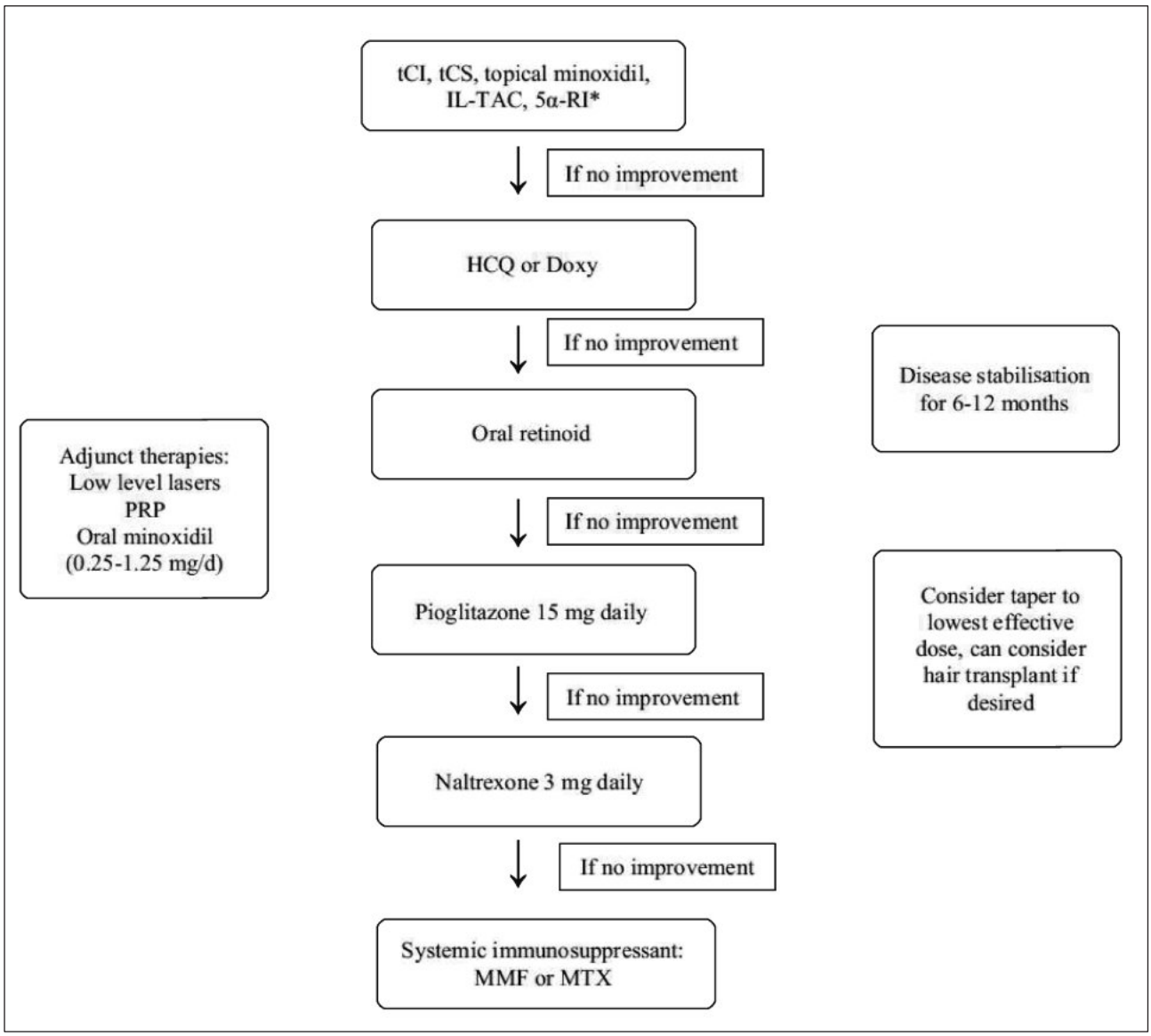

Figure 2. Algorithm for management of Frontal Fibrosing Alopecia (Imhof & Tolkachjov)[16]

Abbreviations: 5α-RI, 5-α-reductase-inhibitors; Doxy, doxycycline (100 mg bid); HCQ, hydroxychloroquine (150-400 mg/d); IL-TAC, intralesional triamcinolone acetonide; MMF, mycophenolate mofetil (0.5-1 g bid); MTX, methotrexate (15-25 mg/wk); PRP, platelet-rich plasma; tCS, topical corticosteroids; tCI, topical calcineurin inhibitors.

its teratogenicity side effect. While in pre-menopausal females, HCQ and Doxycycline can be considered as first line systemic treatment instead of Finasteride.[16] Finasteride can still be used in pre-menopausal females if there are no plan for pregnancy, with the importance of effective contraception emphasized.

Dosage

Doses of Finasteride 1-5 mg/d has been used in literature for the treatment of FFA. Finasteride can be started at a medium dose of 2.5 mg/d and the dose can be increased to 5 mg/d if there is no improvement after 6 months, i.e. progression of hair loss.[20] For patients more prone to side effects, Finasteride can be started at a low dose of 1 mg/d.

Summary

FFA has become an emerging cause of scarring alopecia and increasing cases have been described in the literature leading to its development in evidence-based management. With the growing evidence in the management of FFA, Finasteride is currently considered to be the most supported systemic treatment to stop the scarring process and to prevent irreversible hair loss. With the suitable patient population and careful patient education, Finasteride can be of great benefit in treating this disease which have an immense negative impact on the patient's quality of life.

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