Medical therapy for frontal fibrosing alopecia: A review and clinical approach

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Background: Guidelines for the treatment of frontal fibrosing alopecia (FFA) are limited, and the literature on treatment modalities consists mostly of case reports and cohort studies.

Objectives: In this review, we sought to assess the response of medical therapy for FFA and propose a clinical approach to management.

Methods: A literature search for "frontal fibrosing alopecia" on PubMed returned 270 items. In this review, only studies with treatment regimens and reported outcomes were considered. The majority of studies found were case reports and retrospective cohort studies. Response to therapy was assessed by reported ability to slow or arrest hair loss.

Results: Intralesional steroids and 5α-reductase inhibitors were the most commonly used therapies with the most positive treatment responses (88%, 181/204 for intralesional steroids and 88%, 158/180 for 5α-reductase inhibitors). Oral prednisone was seldom used and only temporarily delayed rapid hair loss. Other therapies evaluated included topical steroids, antibiotics, pioglitazone, systemic retinoids, and hair transplantation.

Limitations: Lack of placebo control studies and uniform outcome measures.

Conclusion: The natural course of FFA is variable. Recession of the frontal hairline might stabilize regardless of treatment. However, early intervention is encouraged in active disease because hair loss is presumed permanent and treatment could modify the disease course. (J Am Acad Dermatol 2019;81:568-80.)

Key words: frontal fibrosing alopecia; hair loss; inflammatory hair disorder; medical management; primary lymphocytic cicatricial alopecia.

Frontal fibrosing alopecia (FFA) is a primary lymphocytic cicatricial alopecia typically characterized by recession of the frontotemporal hairline.[1] It presents as scarring circumferential hair loss around the frontal hairline associated with perifollicular hyperkeratosis and erythema.[2,3] Lonely hairs (ie, isolated hairs in an area that is otherwise devoid of hair) in the vicinity of the hairline can be a clinical indicator when recession is subtle.[4] Eyebrow involvement has been reported in 50%-83% of patients.[5-7] Patients might also experience pruritus, burning, and scalp tenderness as a result of inflammation.

FFA, first described by Kossard in 1994, was thought to be a clinical variant of lichen planopilaris (LPP).[8,9] It was initially believed to be a condition in postmenopausal women; however, subsequent reports revealed cases in younger women and rarely in men.[8,10-12] The pathogenesis of FFA is complex and not well understood. One theory suggests an autoimmune reaction targeting follicular antigens, inducing the destruction of follicular stem-cell

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niches.[13] The role of androgens in FFA is also uncertain, but some believe a higher prevalence of FFA in postmenopausal women indicates a possible hormonal role.[14]

The histopathologic features of FFA resemble that of LPP. The destruction of sebaceous glands and replacement by sclerotic collagen occurs early in disease. Follicular lymphocytic interface dermatitis is seen around the infundibulum and isthmus in the upper portion of the follicles.[15-19] Chronic inflammation and perifollicular fibrosis is believed to be the primary cause of irreversible hair loss. FFA can be difficult to differentiate histologically from LPP but can be differentiated from chronic cutaneous lupus erythematosus, another primary lymphocytic cicatricial alopecia, by the absence of dermal mucin deposition and perivascular and perieccrine inflammation.[2,3]

CAPSULE SUMMARY

- Efficacy of treatment modalities for frontal fibrosing alopecia is difficult to assess because most reports in the literature are limited to case reports and case series.
- Intralesional steroids and 5α-reductase inhibitors might be effective at preventing the progression of hair loss.

Multiple therapies have been reported to be beneficial in the treatment of FFA. However, evidence supporting the benefits of these treatment modalities is sparse and limited only to case reports and cohort studies.[1] Treatment is also challenging when encountering refractory cases of FFA because no guidelines exist. In this article, we aim to review medical therapies used for the treatment of FFA and propose a clinical approach to managing this condition.

METHODS

All the literature on medical therapies for FFA was retrieved through PubMed. An electronic search of "frontal fibrosing alopecia" on July 19, 2018, resulted in 270 items. Only publications in English on the clinical outcomes of treatment modalities for FFA were considered. A total of 23 studies were identified, and we summarized the details of these studies in Table I.* Each study was assigned a level of evidence according to the 2009 Oxford Centre for Evidence-Based Medicine levels of evidence guidelines. No randomized clinical trials were found.

In this review, studies were separated by treatment regimen. Primary treatment modalities were categorized as either a topical agent, intralesional steroid, oral anti-inflammatory agent, 5α-reductase inhibitor (5α-RI), peroxisome proliferator-activated receptor γ (PPAR-γ) agonist, immunosuppressant, other medicinal therapy, or hair transplantation. The outcomes of therapy were attributed to the most recent agent added or to the most potent medication (with systemic therapies being more potent than intralesional steroids being more potent than topical agents).

Treatment response was measured by the extent of hairline recession after treatment (Table II), and positive response was defined as no further recession of the frontal hairline.† Other parameters assessed included prevention of further eyebrow loss, reduction in clinical signs of inflammation, and resolution of symptoms (Table III).[6,20,22,23,26-28] In several studies, the treatment response was measured by the Lichen Planopilaris Activity Index (LPPAI), which scores disease activity on the basis of the following parameters: pruritus, pain, burning, scalp erythema, perifollicular erythema and scale, shedding, and progression.[6,20] The LPPAI scoring system defines responders as patients with a >85% reduction in LPPAI posttreatment. Partial responders had a 25%-85% reduction in LPPAI and nonresponders had a <25% reduction in LPPAI.

RESULTS

The FFA treatment courses of 622 individuals (excluding those without treatments and those with hair transplants) were reviewed. The most common primary agent was intralesional corticosteroids, specifically intralesional triamcinolone acetonide (TAC), which represented 35% (215/622) of therapies, followed by 5α-RIs, which represented 29% (182/622) of therapies. Few studies reported the use of PPAR-γ agonists (1%, 5/622) and immunosuppressants (3%, 17/622).

Topical agents

Topical corticosteroids, topical calcineurin inhibitors, and intralesional steroids are typically considered first-line therapy for FFA and other forms of inflammatory hair disorders. In FFA, monotherapy with topical corticosteroids was mostly unsuccessful.[7,9,21] Heppt et al reported that the combination of clobetasol propionate or betamethasone valerate

*5-7,12,14,20-31,34-37

†5,7,9,14,21,22,24-31,33-37

Abbreviations used:

5α-RI:	5α-reductase inhibitor
FFA:	frontal fibrosing alopecia
FFASS:	Frontal Fibrosing Alopecia Severity Score
LPP:	lichen planopilaris
LPPAI:	Lichen Planopilaris Activity Index
PPAR-γ:	peroxisome proliferator-activated receptor γ
TAC:	triamcinolone acetonide

with pimecrolimus 1% cream subjectively stabilized or improved hair loss in 64.6% (31/48) of patients in a cohort study.[22] Recession of the hairline continued at a rate of 0.4-0.5 cm per 6 months in 22.9% of patients (11/48); however, hair loss stabilized in all patients after 9 months of treatment. Combination therapy also resolved pruritus in 44% (11/25) of patients and reduced trichodynia in 33% (1/3).[22] In a retrospective cohort analysis comparing topical tacrolimus 0.3% and topical clobetasol, patients treated with tacrolimus 0.3% were more likely to have stabilized hair loss within 3 months of initiating treatment.[12]

Intralesional corticosteroids

Injection with intralesional TAC was one of the most beneficial therapies used; this therapy resulted in a positive treatment response in 88% (181/204) of patients.[5,7,9,21,23,24] In a retrospective cohort study of 57 patients, Banka et al demonstrated that injections of intralesional TAC 2.5 mg/mL into the frontal scalp was beneficial in the treatment of FFA.[1,21] After 4-5 sets of injections with intralesional TAC 2.5 mg/mL, hair loss stabilized in all patients with no further progression of disease. In a cohort study on intralesional steroids for eyebrow loss, Donovan et al showed that intralesional TAC 10 mg/mL with 0.125 mL per eyebrow can be beneficial with a low chance of atrophy.[23]

Oral anti-inflammatory agents

FFA unresponsive to localized therapy often requires systemic agents introduced to the treatment regimen. Hydroxychloroquine and doxycycline are first-line systemic therapies due to their anti-inflammatory properties and low side effect profile. Improvement of LPPAI score was seen in 74% (17/23) of patients on hydroxychloroquine 200-400 mg/d alone, and stabilization of hairline recession was seen in 71% (41/58) on hydroxychloroquine combination therapies.[6,7,20,24,25] Response to tetracyclines have been inconsistent in the few studies including this treatment.[6,25]

5α-Reductase inhibitors

Use of 5α-RIs was the most beneficial oral therapy for FFA. Finasteride 1-5 mg/d and dutasteride 0.5 mg/d stabilized hair loss in 88% (158/180) of patients.[14,24-30] In 1 case report, finasteride showed potential for reducing the redness and reversing the skin atrophy associated with FFA.[26] Dutasteride arrested hair loss in 81% (34/42) of patients.[24,25,27,28] In a patient with eyebrow and axillary loss, dutasteride in combination with pimecrolimus 1% cream was attributed to restoring eyebrow and axillary hairs.[28]

PPAR-γ agonists

PPAR-γ agonists are seldom used for the treatment of FFA.[25,31] Although only a few cases exist, PPAR-γ for the treatment of FFA appears promising, considering the theoretic role of PPAR-γ in the inflammatory role of LPP.[25,31] One retrospective cohort study on the PPAR-γ agonist pioglitazone demonstrated stabilization of hair loss and mild regrowth in 75% (3/4) of patients.[31]

Systemic immunosuppressive agents

Potent immunosuppressive agents are generally reserved for refractory cases of FFA; however, they have shown mixed results. Only a few cases have been reported on the use of systemic steroids (eg, methotrexate and mycophenolate mofetil) for the treatment of FFA. Oral prednisone 25-50 mg/d slowed rapid, temporary hair loss in 50% (2/4) of patients but demonstrated no response in patients with slowly progressive hair loss.[9] Mycophenolate mofetil use resulted in a reduction of the LPPAI score in 60% (3/5) of patients posttreatment.[6,9] Use of other agents are seldom reported in the literature, and future studies with larger sample sizes are necessary to further evaluate the utility of immunotherapy.[6,9,14,25,30]

Other medicinal therapies

A retrospective cohort study of 40 FFA patients treated with isotretinoin 20 mg/d or acitretin 20 mg/d for 12 months showed stabilization in 79% (23/29) and 73% (8/11), respectively.[29] No further progression was seen in 72% (21/29) of the patients on isotretinoin and 73% (8/11) of the patients on acitretin 12 months off therapy. This study suggests that the use of retinoids might be beneficial as an alternative treatment for FFA. Naltrexone is an opioid receptor antagonist that has been suggested for use in autoimmune disorders.[32,33] A case report on naltrexone 3 mg/d in combination with pioglitazone 15 mg/d used for scarring alopecias noted

Table I. Studies evaluating therapeutic modalities for frontal fibrosing alopecia

Level of evidence	Study	Study type	Patients, n	Therapeutic modalities	Outcome measurement
2b	Banka et al[21]	Retrospective cohort study	62	Topical: clobetasol, tacrolimus Intralesional steroids Oral hydroxychloroquine, doxycycline, tetracycline, finasteride, dutasteride	Hairline recession
2b	Chiang et al[20]	Retrospective cohort study	7	Oral hydroxychloroquine	LPPAI
2b	Donovan et al[23]	Retrospective cohort study	11	Intralesional TAC Oral hydroxychloroquine, doxycycline, MMF	Eyebrow loss
2b	Georgala et al[27]	Prospective cohort study	13	Oral dutasteride	Hairline recession
2b	Heppt et al[22]	Retrospective cohort study	72	Topical clobetasol, betamethasone valerate, mometasone furoate, methylprednisolone aceponate, hydrocortisone butyrate, pimecrolimus, tacrolimus Oral hydroxychloroquine and retinoids	Hairline recession
2b	Kossard et al[9]	Retrospective cohort study	16	Topical: minoxidil, steroids, retinoids Intralesional steroids Oral chloroquine, prednisone, isotretinoin, ultramicronized griseofulvin	Alopecia progression
2b	Ladizinski et al[25]	Retrospective cohort study	19	Oral hydroxychloroquine, minocycline, finasteride, dutasteride, pioglitazone, methotrexate, azathioprine, acitretin, imiquimod, and IFN α-2b	Alopecia progression
2b	Mesinkovska et al[31]	Retrospective cohort study	4	Oral pioglitazone	Hairline recession
2b	Moreno-Ramirez et al[5]	Retrospective cohort study	16	Topical minoxidil Intralesional TAC Oral finasteride	Hairline recession
2b	Rakowska et al[29]	Retrospective cohort study	54	Oral finasteride, isotretinoin, and acitretin	Hairline recession
2b	Rallis et al[30]	Retrospective cohort study	18	Topical minoxidil and steroids Oral finasteride and methylprednisolone	Hairline recession
2b	Samrao et al[6]	Retrospective cohort study	36	Oral hydroxychloroquine, doxycycline, and MMF	LPPAI

Continued

Table I. Cont'd

Level of evidence	Study	Study type	Patients, n	Therapeutic modalities	Outcome measurement
2b	Strazzulla et al[12]	Retrospective cohort study	92	Topical minoxidil, clobetasol, hydrocortisone butyrate, and tacrolimus 0.3% in Cetaphil cleanser Intralesional TAC Oral hydroxychloroquine, doxycycline, tetracycline, minocycline, finasteride, dutasteride, spironolactone, pioglitazone, prednisone, methotrexate, and MMF	Hairline recession
2b	Tan et al[7]	Retrospective cohort study	18	Topical minoxidil, clobetasol, steroids, and tacrolimus Intralesional TAC Oral hydroxychloroquine	Hairline recession
2b	Tosti et al[14]	Retrospective cohort study	14	Topical minoxidil Intramuscular TAC Oral finasteride	Hairline recession
2b	Vano Galvan et al[24]	Retrospective cohort study	355	Topical minoxidil and steroids Intralesional steroids Oral hydroxychloroquine, finasteride, dutasteride, and pioglitazone	Hairline recession
5	Cranwell et al[34]	Case report	1	Sunscreen cessation Topical clobetasol Intralesional TAC Oral dutasteride and cyclosporine	Hairline recession
5	Donovan[26]	Case report	1	Topical betamethasone valerate and tacrolimus Oral hydroxychloroquine and finasteride	Hairline recession
5	Jimenez et al[36]	Case report	3	Hair transplant Topical minoxidil and steroids Intralesional TAC Oral finasteride	Hair density
5	Katoulis et al[28]	Prospective cohort study	1	Topical pimecrolimus Oral dutasteride	Hairline recession
5	Liu et al[35]	Case report	2	Hair transplant	Hair density
5	Nusbaum et al[37]	Case report	1	Hair transplant	Hair density
5	Strazzulla et al[29]	Case report	1	Oral doxycycline, finasteride, naltrexone, and pioglitazone	Hairline recession

IFN α-2b; Interferon α-2b; *LPPAI*, Lichen Planopilaris Activity Index; *MMF*, mychophenolate mofetil; *TAC*, triamcinolone acetonide.

Table II. Response of various frontal fibrosing alopecia treatment modalities in hair loss prevention

Primary agent	Study type	Patients, n	Treatment regimen	Duration	Response
No treatment					86% (6/7)
	Retrospective cohort study[30]	6	None	-	Stable at 2-yr follow-up
	Retrospective cohort study[5]	1	None	-	No improvement at 2-yr follow-up
Topical agents					53% (35/66)
Topical steroids	Retrospective cohort study[9]	9	Topical moderate potency steroids	-	No improvement
	Retrospective cohort study[7]	1	Topical steroids	-	Stabilized
	Retrospective cohort study[22]	48	Clobetasol propionate or betamethasone valerate tiw, pimecrolimus 1% cream tiw	20 mon	Improvement in 39.6% (19/48), stabilized in 25% (12/48), no improvement in 22.9% (11/48)
	Retrospective cohort study[30]	6	Topical clobetasol 0.05% solution daily	6 mon	Stabilized in 50% (3/6) at 2-yr follow-up
Topical minoxidil	Retrospective cohort study[9]	2	Topical 2% minoxidil solution	-	No improvement
Intralesional steroids					88% (181/204)
	Retrospective cohort study[5]	8	Intralesional TAC 20 mg/mL q3m	1-3 yr	Stopped progression
	Retrospective cohort study[9]	1	Intralesional steroids	-	No improvement
	Retrospective cohort study[7]	3	Intralesional TAC	-	Stabilized
		2	Intralesional TAC, minoxidil	-	Stabilized
		2	Intralesional TAC, topical tacrolimus	-	Stabilized
		1	Intralesional TAC, topical steroids, topical tacrolimus	-	Stabilized
	Retrospective cohort study[24]	130	Intralesional steroids q3-6m with nonspecific therapies	-	Regrowth in 34% (44/130), stabilized in 49% (64/130), no improvement in 5% (6/130), results unavailable in 12% (16/130)
	Retrospective cohort study[21]	57	Intralesional TAC 2.5 mg/mL x 0.5-3 mL q6-8w topical clobetasol, various other therapies	-	Stabilized
Anti-inflammatory					69% (45/65)
HCQ	Retrospective cohort study[25]	2	HCQ 400 mg/d	10-42 mon	Stabilized
		1	HCQ 400 mg/d, tacrolimus, class I steroid	18 mon	No improvement
		1	HCQ 400 mg/d, class I steroid	7 mon	No improvement
	Retrospective cohort study[24]	54	HCQ 200-400 mg/d with nonspecific therapies	-	Regrowth in 15% (8/54), stabilized in 59% (32/54), no improvement in 22% (12/54), results unavailable in 4% (2/54)
	Retrospective cohort study[7]	1	HCQ, clobetasol	1 yr	Stabilized
		1	HCQ, intralesional TAC	-	No improvement

Continued

Table II. Cont'd

Primary agent	Study type	Patients, n	Treatment regimen	Duration	Response
Chloroquine	Retrospective cohort study[9]	3	Chloroquine phosphate 150 mg/d	3-9 mon	Temporary response in 33% (1/3)
Minocycline	Retrospective cohort study[25]	1	Minocycline, topical tacrolimus	25 mon	Stabilized
		1	Minocycline, topical imiquimod	5 mon	No improvement
5α-reductase inhibitor					88% (158/180)
Finasteride	Retrospective cohort study[29]	14	Finasteride 5 mg/d	12 mon	Stabilized after 12 mon in 43% (6/14)
	Case report[26]	1	Finasteride 2.5 mg/d	3 mon	Regrowth in frontotemporal scalp
	Retrospective cohort study[25]	1	Finasteride 1-2.5 mg/d	3 mon	Stabilized
	Retrospective cohort study[5]	7	Finasteride 2.5 mg/d, intralesional TAC 20 mg/mL q3m, topical 5% minoxidil bid	2-4 yr	Stopped progression
	Retrospective cohort study[24]	102	Finasteride 2.5-5 mg/d	-	Regrowth in 47% (48/102), stabilized in 53% (54/102)
	Retrospective cohort study[14]	8	Finasteride 2.5 mg/d, topical minoxidil	-	Arrested in 50% (4/8), slowly progressive in 50% (4/8)
	Retrospective cohort study[30]	5	Finasteride 2.5 mg/d, topical 5% minoxidil solution	12 mon	Stabilized in 60% (3/5) at 2-yr follow-up
Dutasteride	Prospective cohort study[27]	13	Dutasteride 0.5 mg/d	12 mon	12 mon: regrowth 15% (2/13), arrested 46% (6/13), slow progression 38% (5/13); 18 mon: no recurrence in responders
	Retrospective cohort study[25]	5	Dutasteride 0.5 mg/wk	15-44 mon	Stabilization in 80% (4/5)
		3	Dutasteride 0.5 mg/wk, doxycycline	18-52 mon	Stabilization in 67% (2/3)
		1	Dutasteride 0.5 mg/wk, class I steroid, topical tacrolimus	17 mon	Stabilized
		1	Dutasteride 0.5 mg/wk, class I steroid	13 mon	No improvement
	Retrospective cohort study[24]	18	Dutasteride 0.5 mg/wk	-	Regrowth in 44% (8/18), stabilized in 56% (10/18)
	Case report[28]	1	Dutasteride 0.5 mg/d, pimecrolimus 1% cream bid	6 mon	Moderate regrowth
PPAR-γ agonist					60% (3/5)
Pioglitazone	Retrospective cohort study[31]	4	Pioglitazone 15 mg/d	10 mon	Regrowth in 75% (3/4)
	Retrospective cohort study[25]	1	Pioglitazone	8 mon	No improvement
Immunosuppressants					33% (4/12)
Systemic steroids	Retrospective cohort study[9]	4	Prednisone 25-50 mg/d	1 mon	Temporarily slowed rapid hair loss in 50% (2/4)
	Retrospective cohort study[14]	3	Intramuscular TAC 40 mg q3w, topical minoxidil	-	Slowly progressive
	Retrospective cohort study[30]	1	Methylprednisolone 16 mg/d	1 mon	Stable

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Table II. Cont'd

Primary agent	Study type	Patients, n	Treatment regimen	Duration	Response
Methotrexate	Retrospective cohort study[25]	2	Methotrexate 15-25 mg/wk	13-19 mon	Stabilized in 50% (1/2)
		1	Methotrexate 15-25 mg/wk, finasteride 1-2.5 mg/d	16 mon	No improvement
Azathioprine	Retrospective cohort study[25]	1	Azathioprine	4 mon	No improvement
Other medicinal therapies					70% (33/47)
Systemic retinoids	Retrospective cohort study[29]	29	Isotretinoin 20 mg/d	12-16 mon	Stabilized after 12 mon in 79% (23/29)
		11	Acitretin 20 mg/d	12-16 mon	Stabilized after 12 mon in 73% (8/11)
	Retrospective cohort study[9]	1	Isotretinoin 50 mg/d	2 mon	No improvement
	Retrospective cohort study[25]	1	Acitretin	4 mon	No improvement
		1	Acitretin, finasteride 1-2.5 mg/d, topical imiquimod	20 mon	No improvement
Griseofulvin	Retrospective cohort study[9]	1	Griseofulvin 330 mg/d	1 mon	No improvement
Naltrexone	Retrospective cohort study[33]	1	Naltrexone 3 mg/d, pioglitazone 15 mg/d, finasteride 5 mg/d, doxycycline 100 mg bid	1 mon	Stable
Imiquimod	Retrospective cohort study[25]	1	Imiquimod, class I steroid	40 mon	Improvement (nonspecific)
Interferon α-2b	Retrospective cohort study[25]	1	Interferon α-2b	2 mon	No improvement
Hair transplant					33% (2/6)
FU extraction method	Case report[35]	1	Transplanted 360 FUs (630 hairs) using FU extraction method to frontal and temporal hairline 2 yr after stabilized and off medication 2 yr	-	Transplant hair: best results at 13 mon, 56 hairs/cm^2, distance from glabella to hairline 8.6 cm after transplant, stable at 4 yr with no reactivation
		1	Transplanted 551 FUs (938 hairs) using FU extraction method to frontal hairline and vertex 3 yr after stabilized and off medication 3 yr	-	Transplant hair: best results at 10 mon, vertex hair densities (12 cm from glabella) 58-126 hairs/cm^2, stable at 3 yr and 4 mon
Elliptical strip excision	Case report[37]	1	Transplanted 82 FUs with elliptical strip excision after stabilization with finasteride 1 mg/d, intralesional TAC 2.5 mg/mL, halcinonide 0.1% solution bid	-	Transplant hair: regrowth at 3 mon, excellent hair growth at 15 mon, 6 hairs remain at 5 yr (stopped all therapy at 15 mon); hair loss: progression at 5 yr
	Case report[36]	1	Transplanted 50 FUs, topical tacrolimus, topical steroids	-	Transplant hair: 90% remaining at 14 mon, 20 FUs at 2.5 yr, and 16 FUs at 6 yr

Continued

Table II. Cont'd

Primary agent	Study type	Patients, n	Treatment regimen	Duration	Response
		1	Transplanted 80 FUs while on finasteride 2.5 mg/d, intralesional TAC, topical steroids, minoxidil	-	Transplant hair: full growth at 10 mon, 68 FUs remaining at 18 mon, 21 FUs at 3 yr, 6 FUs at 7 yr; signs: perifollicular hyperkeratosis, miniaturization of hairs
		1	Transplanted 20 FUs (35 terminal hairs) when stable on topical steroids	-	Transplanted hair: 100% growth at 1 yr, 8 FUs (11 hairs) remaining at 4 yr
Sunscreen cessation					100% (1/1)
	Case report[34]	1	Sunscreen cessation, clobetasol, intralesional TAC 5 mg/mL, dutasteride 0.1 mg/d, cyclosporine 25 mg/d	6 mon	Regrowth

bid, Twice daily; *FU*, follicular unit; *HCQ*, hydroxychloroquine; *PPAR-γ*, peroxisome proliferator-activated receptor gamma; *q3m*, every 3 months; *q3-6m*, every 3-6 months; *q3w*, every 3 weeks; *q6-8w*, every 6-8 weeks; *TAC*, triamcinolone acetonide; *tiw*, thrice weekly.

stabilization of hair loss and resolution of inflammation after 1 month of treatment.[33]

Hair transplantation

In FFA and other scarring alopecias, the extent of medical therapy is limited to stabilization of hair loss without restoration. Scar tissue prevents hair regrowth and leaves permanent patches of alopecia. Patients often seek hair transplantation to reconstruct the hairline in FFA; however, trauma from transplanting grafts might worsen hair loss.[35,38] Hair transplants often demonstrate positive results early after the procedure is performed; however, only 33% (2/6) of patients show lasting results 2 years after transplantation.[35-37] A biopsy of a follicular unit from a failed transplant patient 4 years after the procedure demonstrated histologic findings of FFA.[36] Negative results might be due to the length of disease stabilization before initiating hair transplant or method of transplantation.

Sunscreen cessation

Because of the increased incidence of FFA since its first description in 1994, environmental triggers are believed to play a role in FFA pathogenesis. Survey studies on men and women with FFA suggest a possible association with sunscreens.[39,40] This hypothesis is supported by a report that detected titanium nanoparticles, an active ingredient in ultraviolet-blocking sunscreens, in hair shafts of a patient with FFA and a case study that reported regrowth after sunscreen cessation.[34,41] However, the diagnosis of FFA in the patient demonstrating regrowth was made clinically and does not rule out the possibility of hair loss secondary to alopecia areata. Although evidence suggests an association between FFA and sunscreen use, the role sunscreens play in the pathogenesis of FFA is unclear and remains controversial.

DISCUSSION

Evaluating the response of individual therapeutic agents is difficult. Monotherapy is seldom used, and most patients reported in the literature are treated with a combination of therapies. The responses of patients on multiple treatment modalities could be attributed to other therapies or the combination of therapies. The natural disease course of FFA is also obscure, and hair loss might be self-limiting if left untreated.[1,2] In a retrospective cohort study, Rallis et al reported that in 6 patients with FFA not on any treatment, all 6 patients demonstrated no further hair loss on 2-year follow-up.[30] However, in a retrospective analysis by Moreno-Ramirez et al, 1 patient not on treatment continued to have progressive hair loss.[5] FFA can also present as a slowly progressive disease, which introduces limitations to measuring disease progression. In studies with short durations of therapy, it is unclear whether the disease process has truly stabilized or significant change was not appreciated. Patients should be counseled and informed that the disease might still be active even after hair loss has stabilized and that a prolonged treatment process might be necessary to ensure resolution.

Table III. Outcomes of various frontal fibrosing alopecia treatment modalities in eyebrow loss prevention, clinical activity reduction, symptom resolution and LPPAI response

Primary agent	Study type	Patients, n	Treatment regimen	Duration, mon	Outcomes
Topical steroids	Retrospective cohort study[22]	48	Clobetasol propionate or betamethasone valerate tiw, pimecrolimus 1% cream tiw	20	Symptoms: resolved pruritis in 44% (11/25), improvement of trichodynia in 33% (1/3)
Intralesional steroids	Retrospective cohort study[23]	11	Intralesional triamcinolone acetonide 10 mg/mL x 0.125 mL/eyebrow, systemic therapy	1-72	Eyebrow regrowth in 91% (10/11) after 3-6 mon
HCQ	Retrospective cohort study[6]	16	HCQ	12	LPPAI at 6 mon: 27% (4/15) responders, 47% (7/15) partial responders, 27% (4/15) nonresponders; LPPAI at 12 mon: 56% (5/9) responders, 33% (3/9) partial responders, <25% reduction in 11% (1/9) nonresponders
HCQ	Retrospective cohort study[20]	7	HCQ 200 mg bid	12	LPPAI at 6 mon: 14% (1/7) responders, 57% (5/7) partial responders, 29% (2/7) nonresponders; LPPAI at 12 mon: 57% (4/7) responders, 29% (2/7) partial responders, 14% (1/7) nonresponders
Doxycycline	Retrospective cohort study[6]	4	Doxycycline	18	LPPAI at 6 mon: 25% (1/4) responders, 25% (1/4) partial responders, 50% (2/4) nonresponders; LPPAI at 12 mon: 33% (1/3) responders, 33% (1/3) partial responders, 33% (1/3) nonresponders
Finasteride	Case report[26]	1	Finasteride 2.5 mg/d	3	Signs: reduction in redness, reversal of skin atrophy
Dutasteride	Prospective cohort study[27]	13	Dutasteride 0.5 mg/d	12	Eyebrows regrowth in 71% (5/7)
Dutasteride	Case report[28]	1	Dutasteride 0.5 mg/d, pimecrolimus 1% cream bid	6	Eyebrows restored; axillae regrowth
Mycophenolate mofetil	Retrospective cohort study[6]	5	Mycophenolate mofetil	6	LPPAI at 6 mon: 20% (1/5) responders, 40% (2/5) partial responders, 40% (2/5) nonresponders; LPPAI at 12 mon: 100% (1/1) nonresponders

bid, Twice daily; *HCQ*, hydroxychloroquine; *LPPAI*, Lichen Planopilaris Activity Index; *tiw*, thrice weekly.

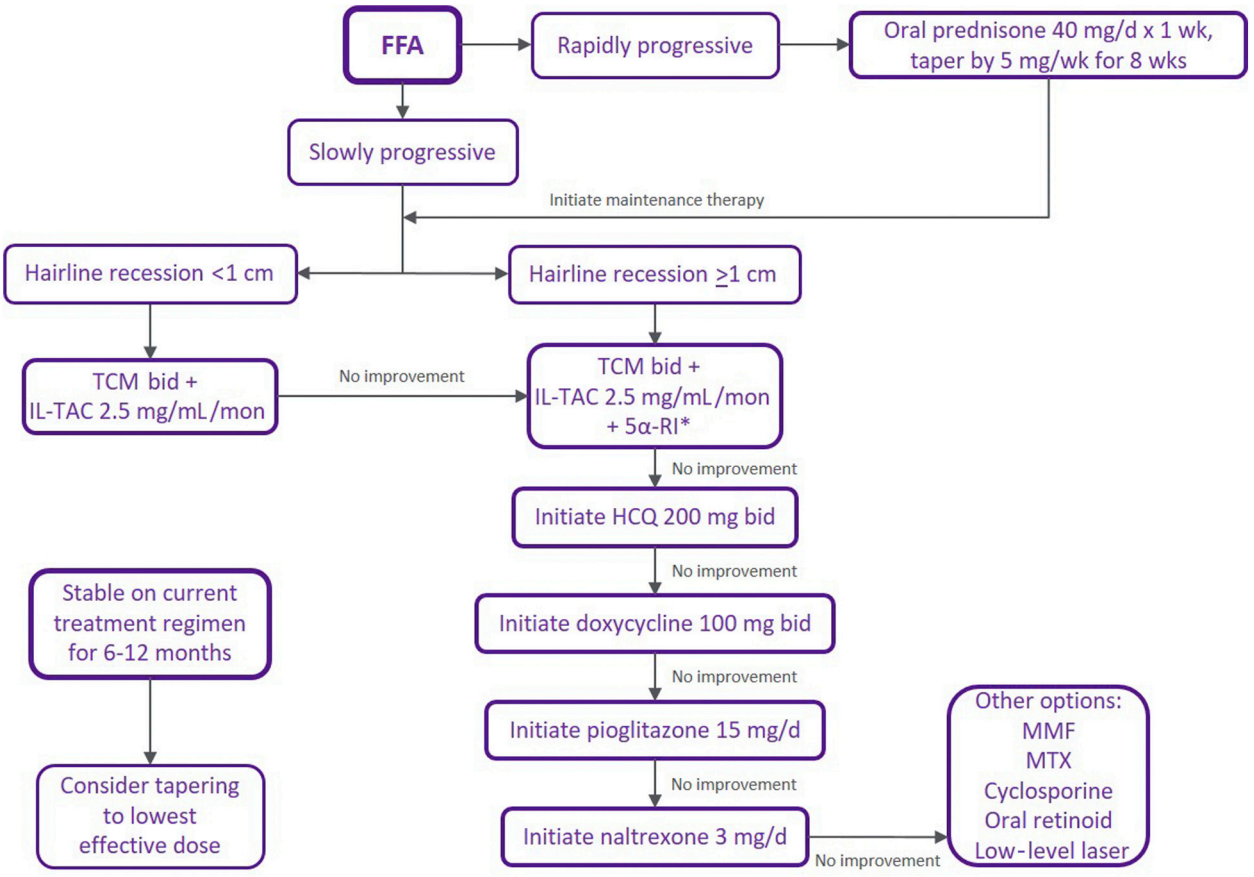

Fig 1. FFA treatment algorithm. *Finasteride 5 mg/d (premenopausal) or dutasteride 0.5 mg/d (postmenopausal). *5α-RI*, 5α-Reductase inhibitor; *bid*, twice daily; *FFA*, frontal fibrosing alopecia; *HCQ*, hydroxychloroquine; *IL-TAC*, intralesional triamcinolone acetonide; *MMF*, mycophenolate mofetil; *MTX*, methotrexate; *TCM*, tacrolimus 0.3% in Cetaphil cleanser + clobetasol solution + minoxidil 5% solution.

Unexpectedly, multiple studies reported improvement or regrowth of hair loss after treatment, which contradicts the accepted mechanism of FFA as a scarring alopecia.[‡] These findings could be attributable to a misdiagnosis of FFA or poor evaluation methods or could suggest that treatment can potentially rescue hair follicles before fibrosis occurs. Although FFA might eventually stabilize without intervention, the time course is unknown, and treatment is recommended in active cases to prevent further hair loss, as well as possibly rescue hair follicles.

Limitations of this review on the management of FFA include the variable nature of the disease, low level of evidence in the literature, frequent use of multiple simultaneous therapies, and lack of standardized disease and treatment measurements.

‡22,24,25,27,28,31,34,42

Management of FFA

Management of FFA can be difficult because of the limited guidelines available. Here, we propose an approach to the management of FFA, as well as a treatment algorithm created using the data from this systematic review and our personal experience treating these patients in an academic tertiary referral hair clinic. In our clinic, we utilize objective measurements to determine progression of disease and response of treatment. Hairline recession is assessed by the distance of hairline to landmarks on the face (glabella and both outer canthi). Photographs can be taken as a reference for global assessment of hair loss. Factors of disease activity evaluated also include eyebrow involvement, clinical signs of activity, and symptoms. Other methods to evaluate the activity of FFA are available, such as the LPPAI and Frontal Fibrosing Alopecia Severity Score (FFASS).[6,20,43]

As a scarring alopecia, FFA causes permanent damage to hair follicles and immediate intervention

is encouraged to stabilize the frontal hairline and prevent further permanent loss of hair. Fig 1 illustrates our treatment algorithm, and treatment is as aggressive as the degree of hair loss. Patients with slowly progressive hair loss are initiated on topical and intralesional therapy. Our topical protocol consists of tacrolimus 0.3% compounded in Cetaphil cleanser, clobetasol 0.05% solution, and topical minoxidil 5% solution. Although the role of minoxidil is not apparent in the pathogenesis of FFA, we initiate minoxidil in all patients with alopecia to help mask the deficit from the primary process. In clinical practice, primary cicatricial alopecias are typically treated with intralesional TAC 10 mg/mL. However, injections with intralesional TAC 2.5 mg/mL were reported to be successful in stabilizing hair loss and should be considered to avoid side effects from steroid injections.[21] Higher concentrations of intralesional TAC may be used if treatments are unsuccessful.

5α-RIs are relatively safe in the treatment of FFA; however, potential side effects include feminization of the male fetus in a pregnant woman.[44] Patients must be warned not to get pregnant while on these medications and are recommended to start birth control before initiating treatment. In women of childbearing age, finasteride is preferred over dutasteride due to the shorter half-life of finasteride.[44] Although rare, retinopathy is an undesirable side effect of chronic hydroxychloroquine and chloroquine use. For patients on hydroxychloroquine or chloroquine, the American Academy of Ophthalmology recommends baseline ophthalmologic examination within the first year of use and annual screening after 5 years of exposure.[45] Patients experiencing vision loss are advised to immediately stop the medication and follow up with their ophthalmologists for further recommendations.

Evidence supporting the use of pioglitazone or naltrexone is lacking; however, we believe that they are safe as adjunct therapy if alopecia or symptoms are not managed. Patients with rapidly progressive hair loss may start a short course of oral prednisone during the first week of treatment to bridge therapy. Other potential therapies for the treatment of FFA not addressed in this review include low-level lasers. There is no published data quantifying the response of FFA to low-level lasers. However, low-level lasers are anecdotally reported to be beneficial and may be considered if other therapies have failed.[46,47]

Conclusion

The management of FFA can be challenging because of the absence of available guidelines. Multiple therapies were reported to be beneficial in the literature. However, studies on these therapies were limited to studies with low levels of evidence. In this review, we propose an approach to the management of FFA derived from evidence in the literature and our clinical experiences. Further studies with higher levels of evidence are necessary to accurately evaluate the efficacy of each therapy.

REFERENCES

1. Bolduc C, Sperling LC, Shapiro J. Primary cicatricial alopecia: lymphocytic primary cicatricial alopecias, including chronic cutaneous lupus erythematosus, lichen planopilaris, frontal fibrosing alopecia, and Graham-Little syndrome. *J Am Acad Dermatol*. 2016;75(6):1081-1099.
2. Shapiro J, Otberg N. *Hair Loss and Restoration*. 2nd ed. Boca Raton, FL: CRC Press, Taylor & Francis Group; 2015.
3. Tan E, Martinka M, Ball N, Shapiro J. Primary cicatricial alopecias: clinicopathology of 112 cases. *J Am Acad Dermatol*. 2004;50(1):25-32.
4. Sundberg JP, Hordinsky MK, Bergfeld W, et al. Cicatricial Alopecia Research Foundation meeting, May 2016: progress towards the diagnosis, treatment and cure of primary cicatricial alopecias. *Exp Dermatol*. 2018;27(3):302-310.
5. Moreno-Ramirez D, Camacho Martinez F. Frontal fibrosing alopecia: a survey in 16 patients. *J Eur Acad Dermatol Venereol*. 2005;19(6):700-705.
6. Samrao A, Chew AL, Price V. Frontal fibrosing alopecia: a clinical review of 36 patients. *Br J Dermatol*. 2010;163(6):1296-1300.
7. Tan KT, Messenger AG. Frontal fibrosing alopecia: clinical presentations and prognosis. *Br J Dermatol*. 2009;160(1):75-79.
8. Kossard S. Postmenopausal frontal fibrosing alopecia. Scarring alopecia in a pattern distribution. *Arch Dermatol*. 1994;130(6):770-774.
9. Kossard S, Lee MS, Wilkinson B. Postmenopausal frontal fibrosing alopecia: a frontal variant of lichen planopilaris. *J Am Acad Dermatol*. 1997;36(1):59-66.
10. Meinhard J, Stroux A, Lunnemann L, Vogt A, Blume-Peytavi U. Lichen planopilaris: epidemiology and prevalence of subtypes-a retrospective analysis in 104 patients. *J Dtsch Dermatol Ges*. 2014;12(3):229-235, 229-236.
11. Soares VC, Mulinari-Brenner F, Souza TE. Lichen planopilaris epidemiology: a retrospective study of 80 cases. *An Bras Dermatol*. 2015;90(5):666-670.
12. Strazzulla LC, Avila L, Li X, Lo Sicco K, Shapiro J. Prognosis, treatment, and disease outcomes in frontal fibrosing alopecia: a retrospective review of 92 cases. *J Am Acad Dermatol*. 2018;78(1):203-205.
13. Tziotzios C, Stefanato CM, Fenton DA, Simpson MA, McGrath JA. Frontal fibrosing alopecia: reflections and hypotheses on aetiology and pathogenesis. *Exp Dermatol*. 2016;25(11):847-852.
14. Tosti A, Piraccini BM, Iorizzo M, Misciali C. Frontal fibrosing alopecia in postmenopausal women. *J Am Acad Dermatol*. 2005;52(1):55-60.
15. Childs JM, Sperling LC. Histopathology of scarring and nonscarring hair loss. *Dermatol Clin*. 2013;31(1):43-56.
16. Matta M, Kibbi AG, Khattar J, Salman SM, Zaynoun ST. Lichen planopilaris: a clinicopathologic study. *J Am Acad Dermatol*. 1990;22(4):594-598.
17. Mehregan DA, Van Hale HM, Muller SA. Lichen planopilaris: clinical and pathologic study of forty-five patients. *J Am Acad Dermatol*. 1992;27(6 Pt 1):935-942.

18. Sperling LC, Cowper SE. The histopathology of primary cicatricial alopecia. *Semin Cutan Med Surg*. 2006;25(1):41-50.
19. Sperling LC, Solomon AR, Whiting DA. A new look at scarring alopecia. *Arch Dermatol*. 2000;136(2):235-242.
20. Chiang C, Sah D, Cho BK, Ochoa BE, Price VH. Hydroxychloroquine and lichen planopilaris: efficacy and introduction of Lichen Planopilaris Activity Index scoring system. *J Am Acad Dermatol*. 2010;62(3):387-392.
21. Banka N, Mubki T, Bunagan MJ, McElwee K, Shapiro J. Frontal fibrosing alopecia: a retrospective clinical review of 62 patients with treatment outcome and long-term follow-up. *Int J Dermatol*. 2014;53(11):1324-1330.
22. Heppt MV, Letule V, Laniauskaite I, et al. Frontal fibrosing alopecia: a retrospective analysis of 72 patients from a German academic center. *Facial Plast Surg*. 2018;34(1):88-94.
23. Donovan JC, Samrao A, Ruben BS, Price VH. Eyebrow regrowth in patients with frontal fibrosing alopecia treated with intralesional triamcinolone acetonide. *Br J Dermatol*. 2010;163(5):1142-1144.
24. Vano-Galvan S, Molina-Ruiz AM, Serrano-Falcon C, et al. Frontal fibrosing alopecia: a multicenter review of 355 patients. *J Am Acad Dermatol*. 2014;70(4):670-678.
25. Ladizinski B, Bazakas A, Selim MA, Olsen EA. Frontal fibrosing alopecia: a retrospective review of 19 patients seen at Duke University. *J Am Acad Dermatol*. 2013;68(5):749-755.
26. Donovan JC. Finasteride-mediated hair regrowth and reversal of atrophy in a patient with frontal fibrosing alopecia. *JAAD Case Rep*. 2015;1(6):353-355.
27. Georgala S, Katoulis AC, Befon A, Danopoulou I, Georgala C. Treatment of postmenopausal frontal fibrosing alopecia with oral dutasteride. *J Am Acad Dermatol*. 2009;61(1):157-158.
28. Katoulis A, Georgala, Bozi E, Papadavid E, Kalogeromitros D, Stavrianeas N. Frontal fibrosing alopecia: treatment with oral dutasteride and topical pimecrolimus. *J Eur Acad Dermatol Venereol*. 2009;23(5):580-582.
29. Rakowska A, Gradzinska A, Olszewska M, Rudnicka L. Efficacy of Isotretinoin and acitretin in treatment of frontal fibrosing alopecia: retrospective analysis of 54 cases. *J Drugs Dermatol*. 2017;16(10):988-992.
30. Rallis E, Gregoriou S, Christofidou E, Rigopoulos D. Frontal fibrosing alopecia: to treat or not to treat? *J Cutan Med Surg*. 2010;14(4):161-166.
31. Mesinkovska NA, Tellez A, Dawes D, Piliang M, Bergfeld W. The use of oral pioglitazone in the treatment of lichen planopilaris. *J Am Acad Dermatol*. 2015;72(2):355-356.
32. Brown N, Panksepp J. Low-dose naltrexone for disease prevention and quality of life. *Med Hypotheses*. 2009;72(3):333-337.
33. Strazzulla LC, Avila L, Lo Sicco K, Shapiro J. Novel treatment using low-dose naltrexone for lichen planopilaris. *J Drugs Dermatol*. 2017;16(11):1140-1142.
34. Cranwell WC, Sinclair R. Frontal fibrosing alopecia: regrowth following cessation of sunscreen on the forehead. *Australas J Dermatol*. 2019;60(1):60-61.
35. Liu YS, Jee SH, Chan JL. Hair transplantation for the treatment of lichen planopilaris and frontal fibrosing alopecia: a report of two cases. *Australas J Dermatol*. 2018;59(2):e118-e122.
36. Jimenez F, Poblet E. Is hair transplantation indicated in frontal fibrosing alopecia? The results of test grafting in three patients. *Dermatol Surg*. 2013;39(7):1115-1118.
37. Nusbaum BP, Nusbaum AG. Frontal fibrosing alopecia in a man: results of follicular unit test grafting. *Dermatol Surg*. 2010;36(6):959-962.
38. Kossard S, Shiell RC. Frontal fibrosing alopecia developing after hair transplantation for androgenetic alopecia. *Int J Dermatol*. 2005;44(4):321-323.
39. Aldoori N, Dobson K, Holden CR, McDonagh AJ, Harries M, Messenger AG. Frontal fibrosing alopecia: possible association with leave-on facial skin care products and sunscreens; a questionnaire study. *Br J Dermatol*. 2016;175(4):762-767.
40. Debroy Kidambi A, Dobson K, Holmes S, et al. Frontal fibrosing alopecia in men: an association with facial moisturizers and sunscreens. *Br J Dermatol*. 2017;177(1):260-261.
41. Brunet-Possenti F, Deschamps L, Colboc H, et al. Detection of titanium nanoparticles in the hair shafts of a patient with frontal fibrosing alopecia. *J Eur Acad Dermatol Venereol*. 2018;32(12):e442-e443.
42. Donovan J. Lichen planopilaris after hair transplantation: report of 17 cases. *Dermatol Surg*. 2012;38(12):1998-2004.
43. Saceda-Corralo D, Moreno-Arrones OM, Fonda-Pascual P, et al. Development and validation of the Frontal Fibrosing Alopecia Severity Score. *J Am Acad Dermatol*. 2018;78(3):522-529.
44. Rogers NE, Avram MR. Medical treatments for male and female pattern hair loss. *J Am Acad Dermatol*. 2008;59(4):547-566. quiz 567-548.
45. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF, American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). *Ophthalmology*. 2016;123(6):1386-1394.
46. Fertig R, Tosti A. Frontal fibrosing alopecia treatment options. *Intractable Rare Dis Res*. 2016;5(4):314-315.
47. Navarini AA, Kolios AG, Prinz-Vavricka BM, Haug S, Trueb RM. Low-dose excimer 308-nm laser for treatment of lichen planopilaris. *Arch Dermatol*. 2011;147(11):1325-1326.