Effectiveness of dutasteride in a large series of patients with frontal fibrosing alopecia in real clinical practice

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Background: Dutasteride has been proposed as an effective therapy for frontal fibrosing alopecia (FFA).

Objectives: We sought to describe the therapeutic response to dutasteride and the most effective dosage in FFA compared with other therapeutic options or no treatment.

Methods: This was a retrospective observational study including patients with FFA with a minimum follow-up of 12 months. Therapeutic response was evaluated according to the stabilization of the hairline recession.

Results: A total of 224 patients (222 females) with a median follow-up of 24 months (range 12-108 months) were included. The stabilization 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; P = .000, .006, and .006, respectively). Stabilization showed a statistically significant association with an increasing dose of dutasteride (88%, 91%, and 84% with a weekly treatment of 5 or 7 doses of 0.5 mg [n = 32], $P < .005$). Dutasteride was well tolerated in all patients.

Limitations: Limitations included the observational and retrospective design.

Conclusions: Oral dutasteride was the most effective therapy with a dose-dependent response for FFA in real clinical practice compared with other systemic therapies or no systemic treatment. (J Am Acad Dermatol 2021;84:1285-94.)

Key words: 5-alpha-reductase inhibitors; cicatricial alopecia; finasteride; lichen planopilaris; scarring hair loss.

Frontal fibrosing alopecia (FFA) is a primary lymphocytic cicatricial alopecia characterized by a recession of the frontal hairline and eyebrow alopecia.[1] The etiology of FFA is unknown. However, there are several theories, some of them extrapolated from studies of pathogenesis of lichen planopilaris,[2] which propose that after an unknown initial trigger a chain of events leads to the destruction of the stem cells in the bulge by T lymphocytes with ends in the destruction of the hair follicle.[3] The role of sexual hormones is uncertain, although there are several theories supporting a potential androgenic trigger in the pathogenesis of FFA.[4]

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Treatment of FFA is challenging and there are no randomized clinical trials evaluating the available therapeutic modalities. For this reason, there is no consensus on which is the optimal therapeutic regimen, having tried both topical therapies (corticosteroids, calcineurin inhibitors, and minoxidil) and systemic therapies with different targets (hydroxychloroquine, oral corticosteroid therapy, and oral retinoids, etc).[5] Results from retrospective studies reveal that the 5-alpha reductase inhibitors (5ARIs) finasteride and dutasteride seem to be effective in stabilizing the disease.[6]

Dutasteride is a competitive, potent, selective, and irreversible inhibitor of all 3 isoforms of the 5AR enzyme. Compared with finasteride, dutasteride inhibits 5AR type 1with an affinity 50 times higher and type 2 with an affinity 11 times higher.[7] Therefore, dutasteride achieves a greater suppression of serum dihydrotestosterone than finasteride (71% vs 94.7%)[7] and, theoretically, it might be more effective in treating FFA than finasteride.

The objective of this study was to analyze whether dutasteride was the most effective treatment for FFA in real clinical practice compared with other therapeutic modalities or no systemic treatment. The secondary objective was to assess the most effective dose of dutasteride. In addition, prognostic factors associated with a better therapeutic response were analyzed.

CAPSULE SUMMARY

- Oral dutasteride was the most effective therapy for patients with frontal fibrosing alopecia in real clinical practice compared with other systemic therapies or no systemic treatment.
- The response was associated with an increasing dose of dutasteride, with the most effective dose being 5 to 7 capsules of dutasteride 0.5 mg per week.

MATERIALS AND METHODS

Study design

A retrospective study including all patients with a confirmed diagnosis of FFA at a specialized trichology consultation from 2010 to 2018 was designed. Diagnosis of FFA was made by a dermatologist specialized in trichology fulfilling the updated diagnostic criteria for FFA.[8,9] Skin biopsy specimens were obtained in routine clinical practice in patients with a doubtful diagnosis. The selection of treatment in our patients was done in a real clinical practice following this algorithm: dutasteride was tried as a first-line therapy in all patients except for those patients with a personal or family history of breast cancer. There was a subgroup of patients not receiving systemic therapies because they refused to take oral treatments. Only patients receiving a systemic treatment in monotherapy were included.

Response to dutasteride was addressed and compared with other systemic therapies and no systemic treatment during patients' medical visits every 6 months. Therapeutic response was evaluated with the glabellar frontal and lateral distances by a single observer (Dr Vañó-Galván). Left and right lateral distances were measured following a line from the external eye canthus to the upper helix, indicating the intersection with the temporal hairline implantation. Patients were classified as "responders" when measures kept equal to the initial one after ≥6 months' follow-up. FFA patterns were classified according to the prognostic classification of Moreno-Arrones et al.[10] Institutional review board approval was obtained before the beginning of the study (IRB approval 289/17). Several clinical, diagnostic, and therapeutic variables were recorded.

Statistical analysis

Data are presented as mean ± standard deviation, median (25th percentile-75th percentile), or crude numbers (percentage). A comparison was made between the different treatment groups using the chi-square, Fisher exact, Mann−Whitney *U*, or Kruskal−Wallis tests. $P < .05$ was considered statistically significant. Logistic regression analysis was performed to identify the best combination of independent factors associated with a better therapeutic response.

RESULTS

A total of 224 patients (222 women [99.1%] and 2 men [0.9%] with a mean age of 61.2 years [range, 34-85 years]) were included in the study. The median follow-up was 24 months (range 12-108 months).

The dutasteride dose ranged from 1 to 7 capsules per week (Avodart capsules 0.5 mg [GlaxoSmithKline, Brentford, United Kingdom]). Altogether, 148 (66.1%) patients received dutasteride (36 patients [24.3%] 1 capsule/week, 10 patients [6.8%] 2 capsules/week, 70 [47.3%] 3 capsules/week, 17 patients [11.5%] 5 capsules/week, and 15 patients [10.1%] 7 capsules/week; no patient received 4 capsules/week or 6 capsules/week). No systemic treatment was prescribed to 56 (25%) patients, finasteride 2.5 to 5 mg per day was prescribed to 9 (4%) patients, hydroxychloroquine

Table I. Clinical characteristics of the 224 patients with frontal fibrosing alopecia

Variable	No systemic therapy, n = 56 (25.0%)	Other systemic therapies, n = 20 (8.9%)	Dutasteride, n = 148 (66.1%)	Total, N = 224	*P* value	Group 1, n = 46	Group 2, n = 70	Group 3, n = 32	*P* value
Age at FFA diagnosis, years, median (P_{25}-P_{75})	65.0 (58.3-73.0)	58.5 (46.3-68)	60.0 (54.0-67.0)	61.0 (54.0-68.0)	.023	65.0 (55.0-70.3)	60.0 (53.8-66.3)	57.0 (48.5-62.8)	.005
Age of onset of FFA symptoms, years, median (P_{25}-P_{75})	60.0 (53.5-68.5)	53.0 (37.0-61.0)	55.0 (47.0-60.0)	56.0 (47.0-61.0)	>.05	57.0 (49.0-61.0)	55.0 (47.0-60.0)	52.0 (42.0-58.0)	>.05
Years of diagnostic delay, median (P_{25}-P_{75})	5.0 (3.0-7.0)	7.0 (4.0-8.0)	5.0 (4.0-7.0)	5.0 (4.0-7.0)	>.05	7.0 (4.0-8.0)	5.0 (4.0-7.0)	5.0 (3-0-7.0)	>.05
Follow-up, months, median (P_{25}-P_{75})	19.5 (12.0-39.8)	26.0 (13.5-42.5)	24.0 (14.0-37.0)	24.0 (13.0-38.3)	>.05	31.0 (18.5-44.5)	19 (12.5-30.5)	24 (12.0-32.0)	.018
Rosacea, n (%)	8 (14.3)	5 (25.0)	27/77 (35.1)	40/114 (35.1)	>.05	6/25 (24.0)	19/45 (42.2)	2/7 (28.6)	>.05
Hypothyroidism, n (%)	9 (16.1)	3 (15.0)	26 (17.6)	38 (16.9)	>.05	7/46 (15.2)	16/70 (22.9)	3/32 (9.4)	>.05
Pattern, n/N (%)									
1	25/44 (56.8)	9/17 (52.9)	56/106 (52.8)	91/168 (54.2)	>.05	15/38 (39.5)	34/54 (63.0)	7/14 (50.0)	.02
2	17/44 (38.6)	7/17 (41.2)	40/106 (37.7)	64/168 (38.1)		20/38 (52.6)	17/54 (31.5)	3/14 (21.4)	
3	2/44 (4.5)	1/17 (5.9)	10/106 (9.4)	13/168 (7.7)		3/38 (7.9)	3/54 (5.6)	4/14 (28.6)	
Beginning of FFA on eyebrows, n (%)	19 (33.9)	8/20 (40.0)	54/143 (36.5)	82/118 (68.6)	>.05	16/46 (34.8)	24/70 (34.3)	14/32 (43.8)	>.05
Eyebrow alopecia, n (%)									
Partial	27 (51.9)	8 (40.0)	44 (29.7)	81 (36.2)	>.05	16/46 (34.8)	20/70 (28.6)	8/32 (25.0)	>.05
Total	15 (28.8)	7 (35.0)	52 (35.1)	74 (33.0)		20/46 (43.5)	28/70 (40.0)	4/32 (12.5)	>.05
Eyelash alopecia, n/N (%)	10/28 (35.7)	3/19 (30.0)	18/106 (17.0)	31/145 (21.4)	.011	6/24 (25.0)	8/50 (16.0)	4/32 (12.5)	>.05
Occipital involvement, n/N (%)	2/26 (7.7)	1/9 (11.1)	17/101 (16.8)	21/137 (15.3)	.015	5/24 (20.8)	9/46 (19.6)	3/31 (9.7)	>.05
Axillary hair, n/N (%)	17/28 (60.7)	3/9 (33.3)	54/110 (49.1)	74/148 (50.0)	>.05	18/27 (66.7)	28/52 (53.8)	8/31 (25.8)	.04
Pudendal hair, n/N (%)	16/28 (57.1)	5/10 (50y)	51/109 (46.8)	72/148 (48.6)	>.05	16/26 (62.5)	26/52 (50.0)	9/31 (29.0)	>.05
Facial papules, n/N (%)	8/40 (20.0)	9/15 (60.0)	39/96 (40.6)	57/153 (37.3)	>.05	10/36 (27.8)	24/50 (48.0)	5/10 (50.0)	>.05
Upper and lower extremities, n/N (%)	22/30 (73.3)	8/12 (66.7)	71/107 (66.4)	101/150 (67.3)	>.05	20/27 (74.1)	37/48 (77.1)	14/32 (43.8)	.016

Continued

Table I. Cont'd

Variable	No systemic therapy, n = 56 (25.0%)	Other systemic therapies, n = 20 (8.9%)	Dutasteride, n = 148 (66.1%)	Total, N = 224	*P* value	Group 1, n = 46	Group 2, n = 70	Group 3, n = 32	*P* value
Pruritus, n/N (%)									
Mild	4/9 (44.4)	1/4 (25%)	16/37 (43.2)	21/50 (42.0)	>.05	5/8 (62.5)	14/21 (66.7)	3/6 (50.0)	>.05
Medium	1/9 (11.1)	0/4 (0.0)	2/37 (5.4)	3/50 (6.0)		1/8 (12.5)	7/21 (33.3)	0/6 (0.0)	
Trichodynia, n/N (%)									
Mild	1/9 (11.1)	1/4 (25.0)	6/31 (19.4)	8/44 (18.2)	>.05	1/6 (16.7)	3/18 (16.7)	2/7 (28.6)	>.05
Medium	1/9 (11.1)	0/4 (0.0)	1/31 (3.2)	2/18 (4.5)		0/6 (0.0)	0/17 (0.0)	1/7 (14.3)	
Perifollicular erythema, n/N (%)									
Mild	6/10 (60.0)	1/4 (25%)	14/35 (40.0)	21/49 (42.9)	>.05	0/6 (0.0)	4/13 (30.8)	1/5 (20.0)	>.05
Medium	2/10 (20.0)	3/4 (75.0)	11/35 (31.4)	16/49 (32.7)		5/6 (83.3)	6/13 (46.2)	3/5 (60.0)	
Intense	2/10 (20.0)	0/4 (0.0)	10/35 (28.6)	12/49 (24.5)		1/6 (16.7)	3/13 (23.1)	1/5 (20.0)	
Perifollicular hyperkeratosis, n/N (%)									
Mild	7/9 (77.8)	1/4 (25%)	34/53 (64.2)	42/66 (63.3)	>.05	2/6 (33.3)	3/13 (23.1)	3/5 (60.0)	>.05
Medium	0/9 (0.0)	3/4 (75.0)	12/53 (22.6)	15/66 (22.7)		4/6 (66.7)	6/13 (46.2)	1/5 (20.0)	
Intense	2/9 (22.2)	0/4 (0.0)	7/53 (13.2)	9/66 (13.6)		0/6 (0.0)	4/13 (30.8)	1/5 (20.0)	
Initial measurement, cm (median [P_{25}-P_{75}])									
Frontal	7.5 (6.5-8.5)	7.3 (7.0-9.1)	7.5 (7.0-8.5)	7.5 (7.0-8.5)	>.05	8.0 (7.0-8.5)	7.5 (6.5-8.5)	7.5 (7.0-8.4)	>.05
Right side	5.5 (4.5-7.0)	5.0 (4.1-6.9)	6.0 (4.5-7.0)	6.0 (4.5-7.0)	>.05	6.3 (4.5-7.1	6.0 (4.0-7.5)	6.0 (5.0-7.0)	>.05
Left side	5.5 (4.5-6.5)	5.0 (4.0-6.4)	6.0 (4.5-7.0)	6.0 (4.5-7.0)	>.05	6.3 (4.9-7.1)	6.0 (4.5-7.5)	6.0 (4.5-7.0)	>.05
Final measurement, cm (median [P_{25}-P_{75}])									
Frontal	8.25 (7.0-9.5)	8.0 (7.0-9.9)	8.0 (7.0-9.0)	8.0 (7.0-9.0)	>.05	8.2 (7.5-9.5)	8.0 (7.0-9.0)	7.5 (7.0-8.4)	.031
Right side	6.0 (5.0-8.0)	5.5 (4.5-8.0)	6.5 (5.0-8.0)	6.0 (5.0-8.0)	>.05	7.0 (5.4-8.5)	7.0 (5.0-7.7)	6.0 (4.5-7.0)	>.05
Left side	6.0 (5.0-7.9)	6.0 (4.5-8.0)	7.0 (5.0-8.0)	6.5 (5.0-8.0)	>.05	7.0 (5.0-8.5)	7.0 (5.0-7.7)	6.0 (4.5-7.0)	>.05

Group 1: 1-2 capsules of dutasteride 0.5 mg per week; group 2: 3 capsules of dutasteride 0.5 mg per week; group 3: 5-7 dutasteride 0.5 mg capsules per week.
FFA, Frontal fibrosing alopecia; P_{25}, 25th percentile; P_{75}, 75th percentile.

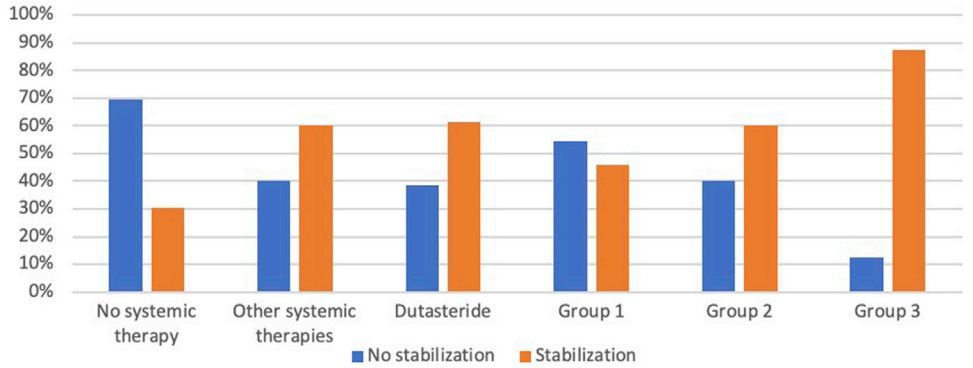

Fig 1. Representation of stabilization at the frontal level after 12 months of therapy according to the group of dutasteride treatment. Group 1 received 1 to 2 capsules of dutasteride 0.5 mg per week; group 2 received 3 capsules of dutasteride 0.5 mg per week; and group 3 received 5 to 7 dutasteride 0.5 mg capsules per week.

200 to 400 mg per day to 6 patients (2.7%), doxycycline 100 mg per day to 2 (1.3%) patients, and isotretinoin 5 to 20 mg per day to 2 (0.9%) patients. All patients including those without systemic treatment received the same topical treatment consisting of topical minoxidil 5% 5 nights a week and clobetasol propionate 0.05% solution twice weekly. Significant differences (P = .001, .008, and .004) were observed in the percentage of stabilized patients after 12 months of therapy for the frontal, right lateral, and left lateral regions between patients treated with dutasteride (61.5%, 64.2%, and 61.5%, respectively) versus other systemic treatments (60.0%, 35%, and 35.0%, respectively) and no systemic treatment (38.2%, 43.4%, and 38.2%, respectively). Table I shows the clinical characteristics of patients and response to dutasteride, other systemic therapies, and no systemic therapy.

To assess the effectiveness of the weekly dose of dutasteride, patients were grouped into 3 groups: group 1 patients received 1 or 2 capsules of 0.5 mg of dutasteride per week, group 2 patients received 3 capsules per week, and group 3 patients received 5 or 7 capsules per week. Table I shows the clinical characteristics and response to the 3 dutasteride treatment groups. Stabilization showed a significant association with an increasing dose of dutasteride, showing a higher response rate with a weekly treatment of 5 or 7 doses of 0.5 mg (87.5% in the frontal region, 90.6% in the right lateral region, and 84.4% in the left lateral region [P = .001, .001, and .005, respectively). Figure 1 represents the stabilization at the frontal level according to the dutasteride treatment group. Pairwise comparisons for the percentage of stabilized patients showed statistically significant differences ($P < .05$) between group 1 versus group 2, group 2 versus group 3, and group 1 versus group 3.

To evaluate the stabilization rates of dutasteride versus other treatments or no treatment in patients with a longer follow-up, we analyzed the percentage of stabilized patients in the cohort of patients with a follow-up of ≥24 months (n = 78; Table II). After 24 months, the percentage of stabilized patients with dutasteride (n = 42) was 57.1% compared with 21.7% without systemic treatment (n = 23) and 50.0% with finasteride (n = 6; P = .016). Statistically significant differences (P = .014) were also observed in the stabilization of the dutasteride treatment groups: 47.6% for group 1 (n = 21), 56.3% for group 2 (n = 16), and 100% for group 3 (n = 5).

In nonstabilized patients (n = 104; Table III), the rate of disease progression calculated in millimeters per year was lower with dutasteride (n = 57, 3.9 mm/year) compared with other systemic treatments (n = 8, 4.8 mm/year), and no systemic treatment (n = 39, 7.5 mm/year; P = .006).

Baseline characteristics of responders and nonresponders to dutasteride were analyzed (Table IV). A logistic regression model was considered with the age of consultation, eyebrow alopecia, and weekly dose of dutasteride. The only statistically significant variable for response to dutasteride was the weekly dose of treatment (P = .006).

Regarding adverse effects, 1 patient reported ankle swelling and another patient an acute urticaria during treatment with dutasteride. Both conditions resolved without withdrawing dutasteride. Among patients who received hydroxychloroquine, 2 experienced diarrhea at the beginning of treatment.

Table II. Percentage of stabilized patients in the frontal region at 12 months and 24 months

Months	Region	No systemic treatment, n = 56 (25%)	Finasteride, n = 9 (4.0%)	Hydroxychloroquine, n = 6 (2.7%)	Doxycycline, n = 3 (1.3%)	Isotretinoin, n = 2 (0.9%)	Dutasteride, n = 148 (66.1%)	*P* value	Group 1	Group 2	Group 3	*P* value
12	Frontal	17/56 (30.4)	7/9 (77.8)	2/6 (33.3)	3/3 (100.0)	0/2 (0.0)	91/148 (61.5)	.000	21/46 (45.7)	42/70 (60.0)	28/32 (87.5)	.000
	Right lateral	23/56 (41.1)	4/9 (44.4)	3/6 (50.0)	0/3 (0.0)	0/2 (0.0)	95/148 (64.2)	.006	22/46 (47.8)	44/70 (62.9)	29/32 (90.6)	.000
	Left lateral	21/56 (37.5)	5/9 (55.6)	2/6 (33.3)	0/3 (0.0)	0/2 (0.0)	91/148 (61.5)	.006	22/46 (47.8)	42/70 (60.0)	27/32 (84.4)	.004
24	Frontal	5/23 (21.7)	3/6 (50.0)	0/4 (0.0)	0/2 (0.0)	0/1 (0.0)	24/42 (57.1)	.016	10/21 (47.6)	9/16 (56.3)	5/5 (100.0)	.014
	Right lateral	6/23 (26.1)	1/6 (26.3)	1/4 (25.0)	0/2 (0.0)	—	27/42 (64.3)	.274	12/21 (57.1)	10/16 (62.5)	5/5 (100.0)	.043
	Left lateral	6/23 (26.1)	2/6 (33.3)	0/4 (0.0)	0/2 (0.0)		26/42 (61.9)	.28	13/21 (61.9)	9/16 (56.3)	4/5 (80.0)	.239

Group 1: 1-2 capsules of dutasteride 0.5 mg per week; group 2: 3 capsules of dutasteride 0.5 mg per week; group 3: 5-7 dutasteride 0.5 mg capsules per week.

DISCUSSION

Scientific evidence places 5ARIs, especially dutasteride, as the first therapeutic options for FFA.[6] In the published literature, >160 patients with FFA treated with dutasteride have been reported to date,[10-16] with an improvement rate ranging from 15.3% to 44.4% and a stabilization rate ranging from 29.2% to 80% without a regrowth effect in the cicatricial area. In all studies, patients received adjuvant therapies along with dutasteride, mainly topical or intralesional corticosteroids and topical calcineurin inhibitors. The weekly dose of dutasteride ranged from 0.5 mg per week to 0.5 mg per day. Improvement in hair density (even without coexistence with androgenetic alopecia) and eyebrows has been documented.[2] It is possible that patients who experienced hair regrowth received treatment with dutasteride before establishing a cicatricial alopecia. Therefore, early treatment of these patients is advisable.[15]

In the present study, all patients received the same topical treatment and only those receiving a systemic monotherapy were included. Dutasteride was the most effective therapeutic modality, with a stabilization rate ranging from 61.5% to 64.2% after 12 months of treatment in a total of 148 patients.

The rest of the therapies are far behind in terms of the number of patients treated. Finasteride was prescribed in 9 patients, with a response rate at the frontal level of 77.8% at 12 months but 50% at 24 months. Previous studies show a variable response rate of finasteride in the treatment of FFA. The study with the largest number of patients, that by Vañó-Galván et al,[2] reported a stabilization rate of 52.9% at doses of 2.5 to 5 mg per day of finasteride.

Hydroxychloroquine obtained stabilization in 2 (33.3%) of the 6 patients treated at 12 months. Large series of patients described a wide variability of response to hydroxychloroquine, ranging from 25% to 100%.[11,12,17-22] Doxycycline was used in 3 patients, with a good response to treatment in all of them at 12 months, but lost of stabilization at 24 months. The stabilization response rates described are also variable, ranging from 25% to 100%.[12,17,20] However, the low number of patients in the literature treated with this therapy do not support its use as a first-line therapy for FFA.

Finally, only 1 study reported stabilization of FFA with oral retinoids.[23] Rakowska et al[23] reported a stabilization in 76% of patients treated with isotretinoin and 73% of patients treated with acitretin versus 43% patients treated with finasteride.[23] In our study, isotretinoin treatment 5 to 20 mg per day in 2 patients failed to stabilize the disease.

Table III. Rate of disease progression in nonstabilized patients

	No systemic therapy, n = 39 (37.5%)	Other systemic therapies, n = 8 (7.7%)	Dutasteride, n = 57 (54.8%)	Total, n = 104	*P* value	Group 1, n = 25	Group 2, n = 28	Group 3, n = 4	*P* value
Frontal, mm/year, median (P_{25}-P_{75})	7.50 (3.00-15.00)	4.81 (1.70-17.09)	3.87 (2.40-6.48)	4.80 (2.4-8.2)	.006	4.29 (2.27-7.28)	3.25 (2.32-5.34)	5.00 (4.25-5.00)	.018
Right side, mm/year, median (P_{25}-P_{75})	3.00 (0.00-10.00)	4.07 (3.37-7.89)	2.31 (0.00-6.00)	6.00 (3.33-10.00)	>.05	5.86 (2.79-6.96)	6.19 (3.06-12.47)	5.00 (5.00-5.00)	>.05
Left side, mm/year, median (P_{25}-P_{75})	2.67 (0.00-8.78)	6.32 (3.87-8.28)	2.61 (0.00-6.33)	6.00 (3.33-10.00)	>.05	4.79 (2.88-6.90)	6.16 (4.07-11.81)	7.50 (4.46-10.00)	>.05

Group 1: 1-2 capsules of dutasteride 0.5 mg per week; group 2: 3 capsules of dutasteride 0.5 mg per week; group 3: 5-7 dutasteride 0.5 mg capsules per week.
P_{25}, 25th percentile; P_{75}, 75th percentile.

The mechanism of action of 5ARIs in FFA remains unclear. Considering the preferential involvement of the frontotemporal hairline implantation, the high prevalence of FFA in postmenopausal women,[11,24] and the increased incidence of early menopause,[4,25] an androgen-related stimulus has been proposed as a trigger for the onset of FFA.[4] It has been hypothesized that a currently unknown antigenic stimulus would trigger a lichenoid reaction in genetically susceptible individuals.[4] Dutasteride might interfere with the pathogenic pathway of FFA by acting against androgenic influence on androgen-dependent hair follicles of the frontal scalp.[4] Furthermore, there is evidence that 5ARIs have an inhibitory effect on androgen-induced peripheral fibrosis in patients with androgenetic alopecia.[26] Finally, a preferential involvement of vellus and intermediate hairs has been described in FFA.[27] 5ARIs reverse the miniaturization of terminal hairs into vellus and terminal hairs, which can prevent lichenoid inflammation.[27] Our study shows clinical evidence supporting the effectiveness of dutasteride in FFA, but additional research is required to elucidate the exact mechanism of action of dutasteride in FFA.

Natural history of FFA without treatment is only known in a small number of patients. It has been described that the recession of the hairline implantation is progressive, with a medium progression rate of 10.5 mm per year (range 2-21 mm/year) in untreated patients.[11] The progression rate in patients without antiandrogen treatment but with other systemic and topical therapies ranges from 9.5 mm per year (range 1-25 mm/years)[28] to 10.8 mm per year (range 3.6-20.4 mm/year).[29] Regarding dutasteride, researchers have found hairline recession of 7.2 mm per year in patients treated with dutasteride 0.5 mg 3 times a week[10] and 2.4 mm per year in patients treated with dutasteride 0.5 mg per day.[13] In our series of patients, the progression rate in nonresponders treated with dutasteride was 3.9 mm per year (range 2.4-6.5 mm/year) versus 7.5 mm per year (range 3.0-15.0 mm/years) in patients without systemic treatment, with statistical significance in slowing progression with ≥3 doses of dutasteride 0.5 mg per week. All these data support the effectiveness of dutasteride in patients with FFA, with a dose-dependent response.

Regarding the safety profile of dutasteride in patients with FFA, only 2 patients in our study reported mild adverse effects during the follow-up period that did not require discontinuation of the drug. In the published literature, only 1 patient who experienced hyperpigmentation on the face and

Table IV. Baseline characteristics of patients treated with dutasteride

Variable	Nonresponders, n = 57	Responders, n = 91	Total, n = 148	*P* value
Age at FFA diagnosis, years, median (P_{25}-P_{75})	65.0 (54.0-69.5)	59.0 (53.0-65.0)	60.0 (54.0-67.0)	.029
Age of onset of FFA symptoms, years, median (P_{25}-P_{75})	56.0 (47.0-62.0)	54.0 (47.0-58.5)	55.0 (47.0-60.0)	>.05
Years of diagnostic delay, median (P_{25}-P_{75})	6.0 (4.0-8.0)	5.0 (3.0-7.0)	5.0 (4.0-7.0)	>.05
Follow-up, months, median (P_{25}-P_{75})	29.0 (22.0-42.0)	19.0 (12.0-32.0)	24.0 (14.0-37.0)	.000
Rosacea, n (%)	15 (55.5)	12 (44.4)	27	>.05
Hypothyroidism, n (%)	8 (30.8)	18 (69.2)	26	>.05
Pattern, n/N (%)				
1	21/45 (48.9)	35/61 (57.4)	56/106 (52.8)	>.05
2	22/45 (50.0)	18/61 (29.5)	40/106 (37.7)	
3	2/45 (4.4)	8/61 (13.1)	10/106 (9.4)	
Beginning of FFA on eyebrows, n (%)	21 (38.9)	33 (61.1)	54	>.05
Eyebrow alopecia, n (%)				
Partial	19 (43.2)	25 (56.8)	44	.040
Total	25 (48.1)	27 (51.9)	52	
Facial papules, n (%)	17 (43.6)	22 (56.4)	39	>.05
Upper and lower extremities, n (%)	28 (39.4)	43 (60.5)	71	>.05
Pruritus, n (%)				
Mild	14 (56.0)	11 (44.0)	25	>.05
Medium	2 (50.0)	2 (50.0)	4	
Trichodynia, n (%)				
Mild	1 (16.7)	5 (83.3)	6	>.05
Medium	0 (0.0)	1 (100.0)	1	
Perifollicular erythema, n (%)				
Mild	4 (28.6)	10 (71.4)	14	>.05
Medium	0 (0.0)	5 (100.0)	5	
Perifollicular hyperkeratosis, n (%)				
Mild	4 (33.3)	8 (66.6)	12	>.05
Medium	1 (14.3)	6 (85.7)	7	
Initial measurement, cm, median (P_{25}-P_{75})				
Frontal	7.5 (7.0-8.5)	7.5 (7.0-8.5)	7.5 (7.0-8.5)	>.05
Right side	6.5 (5.3-7.5)	6.0 (4.4-7.0)	6.0 (4.5-7.0)	>.05
Left side	6.5 (5.5-7.0)	5.5 (4.5-7.1)	6.0 (4.5-7.0)	>.05
Weekly dose of dutasteride by treatment group, n (%)				
Group 1	25 (54.3)	21 (45.7)	46	.001
Group 2	28 (40.0)	42 (60.0)	70	
Group 3	4 (12.5)	28 (87.5)	32	

Group 1: 1-2 capsules of dutasteride 0.5 mg per week; group 2: 3 capsules of dutasteride 0.5 mg per week; group 3: 5-7 dutasteride 0.5 mg capsules per week.
FFA, Frontal fibrosing alopecia; *P_{25}*, 25th percentile; *P_{75}*, 75th percentile.

hands during treatment with dutasteride 0.5 mg per day and pimecrolimus 1% twice daily has been reported.[30] However, adverse effects reported in women with androgenetic alopecia and hirsutism treated with dutasteride include birth defects in male fetuses, headache, gastrointestinal discomfort, menstrual disorders, or dizziness.[31] The main limitation to dutasteride treatment in our patients was a personal or family history of breast cancer because of a potential increased risk of relapse in women with breast cancer treated with 5ARIs.[32-35] However, no studies on female breast cancer patients exposed to 5ARIs have been conducted to date,[35] and 5ARIs have been proposed to be protective against postmenopausal breast cancer.[32] This association needs to be investigated further. Regarding male patients, a large series of patients and a systematic review have found no evidence of an increased risk of breast cancer in patients exposed to 5ARIs.[33,34] Taken together, dutasteride seems to be a safe therapy in patients with FFA. Physicians should take into account that dutasteride is an off-label treatment in FFA, and an effective contraceptive method should be used by premenopausal women treated with dutasteride during treatment and 6 months after withdrawal.[36]

Although it was not the primary aim of this study, we evaluated prognostic factors associated with a better therapeutic response to dutasteride. So far, patient age,[37] age of onset of the disease,[37] low

educational level,[37] body mass index,[37] and FFA clinical pattern[10] are described prognostic factors of FFA.[37] We did not find any prognostic factor of response to dutasteride. However, data about the clinical pattern of 25% of our patients could not be recovered.[10] Future studies will need to assess whether the clinical pattern influences the response to treatment. On the other hand, it seems logical to think that prognosis is worse the more advanced the scarring is when treatment is started.[20]

The main limitation of our study is the observational and retrospective design conditioned by the slow progression of the disease. Second, all patients received topical treatment, so the effectiveness reported in both dutasteride and nondutasteride patients is the effect of systemic and topical treatment. Finally, missing data about FFA patterns may be a potential limitation since clinical pattern has been described as a prognostic factor of FFA.[10]

In conclusion, dutasteride treatment was the most effective therapy for FFA compared with other systemic therapies or no systemic treatment. The response was dose dependent and the most effective dose was 5 to 7 capsules of dutasteride 0.5 mg per week. No other prognostic factors associated with a better therapeutic response were found. Dutasteride was well tolerated in all patients.

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