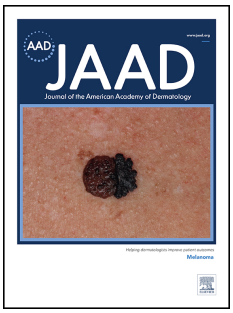

# EFFECTIVENESS OF DUTASTERIDE IN A LARGE SERIES OF PATIENTS WITH FRONTAL FIBROSING ALOPECIA IN REAL CLINICAL PRACTICE

Cristina Pindado-Ortega, MD, David Saceda-Corralo, MD, PhD, Oscar M. Moreno-Arrones, MD, PhD, Ana R. Rodrigues-Barata, A. Hermosa-Gelbard, MD, Pedro Jaén-Olasolo, MD, PhD, Sergio Vañó-Galván, MD, PhD.

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# EFFECTIVENESS OF DUTASTERIDE IN A LARGE SERIES OF PATIENTS WITH FRONTAL FIBROSING ALOPECIA IN REAL CLINICAL PRACTICE

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## ABSTRACT

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

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

**Methods:** 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) 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*=0.000, 0.006 and 0.006, 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*<0.005). Dutasteride was well tolerated in all patients.

**Limitations:** 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 to other systemic therapies or no systemic treatment.

## CAPSULE SUMMARY

Oral dutasteride was the most effective therapy frontal fibrosing alopecia in real clinical practice compared to other systemic therapies or no systemic treatment.

The response was associated with an increasing dose of dutasteride, being the most effective dose 5 to 7 capsules of dutasteride 0.5mg per week.

## INTRODUCTION

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 (LPP),[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]

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, minoxidil), and systemic therapies with different targets (hydroxychloroquine, oral corticosteroid therapy, oral retinoids, etc.).[5] Results from retrospective studies reveal that 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 three isoforms of the 5α-reductase enzyme. Compared to finasteride, dutasteride inhibits 5α-reductase type 1with an affinity 50 times higher and type 2 with an affinity 11 times higher.[7] Thus, dutasteride achieves a greater suppression of serum DHT 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 to other therapeutic modalities or no systemic treatment. The secondary objective was to assess the most effective dose of dutasteride. Additionally, prognostic factors associated with a better therapeutic response were analyzed.

## MATERIALS AND METHODS

**Study design**

A retrospective study including all patients with a confirmed diagnosis of FFA at a specialized Trichology consultation from 2010-2018 was designed. Diagnosis of FFA was made by a dermatologist specialized in Trichology fulfilling the updated diagnostic criteria for FFA.[8,9] Skin biopsies were performed in routine clinical practice in patients with a doubtful diagnosis. The selection of treatment in our patients was done in 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 to 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 (SVG). 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 "responder" when measures kept equal to the initial one after at least 6 months of follow-up. FFA patterns were classified according to the Moreno-Arrones et al. prognostic classification, since it was described.[10] Prior to the beginning of the study, an Institutional Review Board approval was obtained (289/17). Several clinical, diagnostic, and therapeutic variables were recorded.

**Statistical analysis**

Data are presented as mean ± standard deviation, median ($25^{th}$ percentile-$75^{th}$ percentile) or crude numbers (percentage). A comparison was made between the different treatment groups using the Chi-Square test, Fisher's exact test, Mann-Whitney U test or Kruskal-Wallis test. Statistical significance was considered with $P<0.05$. A 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) were included in the study. The median follow-up was 24 months (range 12-108).

The dutasteride dose ranged from 1 to 7 capsules per week (Avidart® capsules 0.5 mg). 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 or 6 capsules/week). No systemic treatment was prescribed to 56 (25%) patients, finasteride 2.5-5 mg/day was prescribed to 9 (4%) patients, hydroxychloroquine 200-400 mg/day to 6 patients (2.7%), doxycycline 100 mg/day to 2 (1.3%) patients and isotretinoin 5-20 mg/day to 2 (0.9%) patients. All patients including those without systemic treatment received the same topical treatment consisting on topical minoxidil 5% five nights a week and clobetasol propionate 0.05% solution twice weekly. Significant differences ($P$=0.001, 0.008 and 0.004) 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 1 shows 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 those who received 1 or 2 capsules of 0.5 mg of dutasteride/week, Group 2 patients who received 3 capsules/week, and Group 3 patients who received 5 or 7 capsules/week. Table 1 shows clinical characteristics and response to the three 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 frontal region, 90.6% in right lateral region and 84.4% in left lateral region, *P*=0.001, 0.001 and 0.005). 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*<0.05) between Group 1 versus Group 2, Group 2 versus Group 3, and Group 1 versus Group 3.

In order 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 at least 24 months (n=78, Table 2). After 24 months, the percentage of stabilized patients with dutasteride (n=42) was 57.1% compared to 21.7% without systemic treatment (n=23) and 50.0% with finasteride (n=6) (*P*=0.016). Statistically significant differences (*P*=0.014) 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 non-stabilized patients (n=104, Table 3), the rate of disease progression calculated in millimeters per year was lower with dutasteride (n=57, 3.9 mm/yr) compared to other systemic treatments (n= 8, 4.8 mm/yr) and no systemic treatment (n=39, 7.5 mm/yr, *P*=0.006).

Baseline characteristics of responder and non-responder patients to dutasteride were analyzed (Table 4). 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*=0.006).

Regarding adverse effects, one 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, two experienced diarrhoea at the beginning of treatment.

## DISCUSSION

Scientific evidence places 5ARIs, especially dutasteride, as the first therapeutic option for FFA.[6] In literature, more than 160 cases of FFA patients treated with dutasteride have been reported to date,[10–16] with an improvement rate of 15.3-44.4% and a stabilization rate of 29.2-80%, 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/week to 0.5 mg/day. Improvement in hair density (even without coexistence with androgenetic alopecia (AGA)) and eyebrows has been documented.[2] Possibly, 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 of 61.5%-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 FFA. The study with the biggest number of patients by Vañó-Galván et al.[2] reported a stabilization rate of 52.9%. at doses of 2.5-5 mg/day of finasteride.

Hydroxychloroquine obtained stabilization in 2 (33.3%) out of the 6 patients treated at 12 months. Large series of patients described a wide variability response to hydroxychloroquine from 25% -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, from 25% - 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 one study reported stabilization of FFA with oral retinoids.[23] Rakowska et al. reported a stabilization in 76% patients treated with isotretinoin and 73% patients treated with

acitretin versus 43% patients treated with finasteride.[23] In our study, isotretinoin treatment 5-20 mg/day in 2 patients failed to stabilize the disease.

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 AGA patients.[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 the lichenoid inflammation.[27] Our study shows clinical evidence supporting the effectiveness of dutasteride in FFA but further 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/yr (2-21) in untreated patients.[11] The progression rate in patients without antiandrogen treatment although with other systemic and topical therapies ranges from 9.5 mm/yr (range 1-25)[28] to 10.8 mm/yr (range 3.6-20.4).[29] Regarding dutasteride, It has been reported a hairline recession of 7.2mm/yr in patients treated with dutasteride 0.5mg three times a week,[10] and 2.4 mm/yr in patients treated with 0.5 mg/day.[13] In our series of patients, the progression rate in non-responders patients treated with dutasteride was 3.9 mm/yr (2.4-6.5) versus 7.5 mm/yr (3.0-15.0) in patients without systemic treatment, with statistical significance in slowing progression with 3 doses or more 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 two patients of our study reported mild adverse effects during the follow-up, not requiring discontinuation of the drug. In the literature, only one patient who experienced hyperpigmentation on the face and hands during treatment with dutasteride 0.5 mg/day and pimecrolimus 1% b.i.d has been reported.[30] However, adverse effects reported in women with AGA 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 due to 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 even they 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, age of the patient,[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. Secondly, all patients received topical treatment, so the

effectiveness reported in both dutasteride and non-dutasteride 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]

## CONCLUSIONS

Dutasteride treatment was the most effective therapy for FFA compared to 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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## FIGURE LEGENDS

**Figure 1.** Representation of stabilization at the frontal level after 12 months of therapy according to the group of dutasteride treatment. *Group 1: 1-2 capsules of dutasteride 0.5 mg a week; Group 2: 3 capsules of dutasteride 0.5 mg a week; Group 3: 5-7 dutasteride 0.5 mg capsules a week.*

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431 **Table 1**. Clinical characteristics of the 224 patients with FFA.

| 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) | 0.023 | 65.0 (55.0-70.3) | 60.0 (53.8-66.3) | 57.0 (48.5-62.8) | 0.005 |
| **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) | >0.05 | 57.0 (49.0-61.0) | 55.0 (47.0-60.0) | 52.0 (42.0-58.0) | >0.05 |
| **Years of diagnostic delay (median** | 5.0 (3.0- | 7.0 (4.0-8.0) | 5.0 (4.0-7.0) | 5.0 (4.0-7.0) | >0.05 | 7.0 (4.0-8.0) | 5.0 (4.0-7.0) | 5.0 (3-0-7.0) | >0.05 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **[$P_{25}$-$P_{75}$])** | | 7.0) | | | | | | | | |
| **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) | >0.05 | 31.0 (18.5-44.5) | 19 (12.5-30.5) | 24 (12.0-32-0) | 0.018 |
| **Rosacea (%)** | | 8 (14.3) | 5 (25.0) | 27/77 (35.1) | 40/114 (35.1) | >0.05 | 6/25 (24.0) | 19/45 (42.2) | 2/7 (28.6) | >0.05 |
| **Hypothyroidism (%)** | | 9 (16.1) | 3 (15.0) | 26 (17.6) | 38 (16.9) | >0.05 | 7/46 (15.2) | 16/70 (22.9) | 3/32 (9.4) | >0.05 |
| **Pattern (%)** | **1** | 25/44 (56.8) | 9/17 (52.9) | 56/106 (52.8) | 91/168 (54.2) | >0.05 | 15/38 (39.5) | 34/54 (63.0) | 7/14 (50.0) | 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** | | 19 | 8/20 (40.0) | 54/143 | 82/118 | >0.0 | 16/46 | 24/70 | 14/32 | >0.05 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **eyebrows (%)** | | (33.9) | | (36.5) | (68.6) | 5 | (34.8) | (34.3) | (43.8) | |
| **Eyebrow alopecia (%)** | **Partial** | 27 (51.9) | 8 (40.0) | 44 (29.7) | 81 (36.2) | >0.05 | 16/46 (34.8) | 20/70 (28.6) | 8/32 (25.0) | >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) | >0.05 |
| **Eyelash alopecia (%)** | | 10/28 (35.7) | 3/19 (30.0) | 18/106 (17.0) | 31/145 (21.4) | 0.011 | 6/24 (25.0) | 8/50 (16.0) | 4/32 (12.5) | >0.05 |
| **Occipital involvement (%)** | | 2/26 (7.7) | 1/9 (11.1) | 17/101 (16.8) | 21/137 (15.3) | 0.015 | 5/24 (20.8) | 9/46 (19.6) | 3/31 (9.7) | >0.05 |
| **Axillary hair (%)** | | 17/28 (60.7) | 3/9 (33.3) | 54/110 (49.1) | 74/148 (50.0) | >0.05 | 18/27 (66.7) | 28/52 (53.8) | 8/31 (25.8) | 0.04 |
| **Pudendal hair (%)** | | 16/28 (57.1) | 5/10 (50y) | 51/109 (46.8) | 72/148 (48.6) | >0.05 | 16/26 (62.5) | 26/52 (50.0) | 9/31 (29.0) | >0.05 |
| **Facial papules** | | 8/40 | 9/15 | 39/96 | 57/1 | >0.0 | 10/3 | 24/5 | 5/10 | >0.0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **(%)** | | (20.0) | (60.0) | (40.6) | 53 (37.3) | 5 | 6 (27.8) | 0 (48.0) | (50.0) | 5 |
| **Upper and lower extremities (%)** | | 22/30 (73.3) | 8/12 (66.7) | 71/107 (66.4) | 101/150 (67.3) | >0.05 | 20/27 (74.1) | 37/48 (77.1) | 14/32 (43.8) | 0.016 |
| **Pruritus (%)** | **Mild** | 4/9 (44.4) | 1/ 4 (25%) | 16/37 (43.2) | 21/50 (42.0) | >0.05 | 5/8 (62.5) | 14/21 (66.7) | 3/6 (50.0) | >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 (%)** | **Mild** | 1/9 (11.1) | 1/ 4 (25.0) | 6/31 (19.4) | 8/44 (18.2) | >0.05 | 1/6 (16.7) | 3/18 (16.7) | 2/7 (28.6) | >0.05 |
| | **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 (%)** | **Mild** | 6/10 (60.0) | 1/ 4 (25%) | 14/35 (40.0) | 21/49 (42.9) | >0.05 | 0/6 (0.0) | 4/13 (30.8) | 1/5 (20.0) | >0.05 |
| | **Medium** | 2/10 (20.0) | 3/ 4 (75.0) | 11/35 (31.4) | 16/49 (32. | | 5/6 (83.3) | 6/13 (46.2) | 3/5 (60.0) | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 7) | | | | | |
| | **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 (%)** | **Mild** | 7/9 (77.8) | 1/ 4 (25%) | 34/53 (64.2) | 42/66 (63.3) | >0.05 | 2/6 (33.3) | 3/13 (23.1) | 3/5 (60.0) | >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) | >0.05 | 8.0 (7.0-8.5) | 7.5 (6.5-8.5) | 7.5 (7.0-8.4) | >0.05 |
| | **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) | >0.05 | 6.3 (4.5-7.1 | 6.0 (4.0-7.5) | 6.0 (5.0-7.0) | >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) | >0.05 | 6.3 (4.9-7.1) | 6.0 (4.5-7.5) | 6.0 (4.5-7.0) | >0.05 |
| **Final** | **Fro** | 8.25 | 8.0 | 8.0 (7.0- | 8.0 | >0.0 | 8.2 | 8.0 | 7.5 | 0.03 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **measurement (cm) (median [$P_{25}$-$P_{75}$])** | **ntal** | (7.0-9.5) | (7.0-9.9) | 9.0) | (7.0-9.0) | 5 | (7.5-9.5) | (7.0-9.0) | (7.0-8.4) | 1 |
| | **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) | >0.05 | 7.0 (5.4-8.5) | 7.0 (5.0-7.7) | 6.0 (4.5-7.0) | >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) | >0.05 | 7.0 (5.0-8.5) | 7.0 (5.0-7.7) | 6.0 (4.5-7.0) | >0.05 |

*$P_{25}$: 25$^{th}$ percentile; $P_{75}$: 75$^{th}$ percentile. Group 1: 1-2 capsules of dutasteride 0.5 mg a week; Group 2: 3 capsules of dutasteride 0.5 mg a week; Group 3: 5-7 dutasteride 0.5 mg capsules a week*

**Table 2.** Percentage of stabilized patients in the frontal region at 12 months and 24 months.

| | | **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 months** | **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) | 0.000 | 21/46 (45.7) | 42/70 (60.0) | 28/32 (87.5) | 0.000 |
| | **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) | 0.006 | 22/46 (47.8) | 44/70 (62.9) | 29/32 (90.6) | 0.000 |
| | **Left lat** | 21/56 (37.5) | 5/9 (55.6) | 2/6 (33.3) | 0/3 (0.0) | 0/2 (0.0) | 91/148 (61.5) | 0.006 | 22/46 (4 | 42/70 (6 | 27/32 (8 | 0.004 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **eral** | | | | | | | | 7.8) | 0.0) | 4.4) | |
| **24 months** | **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) | 0.016 | 10/21 (47.6) | 9/16 (56.3) | 5/5 (100.0) | 0.014 |
| | **Right lateral** | 6/23 (26.1) | 1/6 (26.3) | 1/4(25.0) | 0/2 (0.0) | - | 27/42 (64.3) | 0.274 | 12/21 (57.1) | 10/16 (62.5) | 5/5 (100.0) | 0.043 |
| | **Left lateral** | 6/23 (26.1) | 2/6 (33.3) | 0/4 (0.0) | 0/2 (0.0) | - | 26/42 (61.9) | 0.28 | 13/21 (61.9) | 9/16 (56.3) | 4/5 (80.0) | 0.239 |

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447 **Table 3.** Rate of disease progression in non-stabilized patients.

| | **NO** | **OTHER** | **DUTASTER** | **TOT** | **P-** | **Gro** | **Gro** | **Gro** | **P-** |
|---|---|---|---|---|---|---|---|---|---|

| | **SYSTEMIC THERAPY N=39 (37.5%)** | **SYSTEMIC THERAPIES N=8 (7.7%)** | **IDE N=57 (54.8%)** | **AL N=104** | **value** | **up 1 N=25** | **up 2 N=28** | **up 3 N=4** | **value** |
|---|---|---|---|---|---|---|---|---|---|
| **Frontal (mm/yr) (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) | 0.006 | 4.29 (2.27-7.28) | 3.25 (2.32-5.34) | 5.00 (4.25-5.00) | 0.018 |
| **Right side (mm/yr) (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) | >0.05 | 5.86 (2.79-6.96) | 6.19 (3.06-12.47) | 5.00 (5.00-5.00) | >0.05 |
| **Left side (mm/yr) (median** | 2.67 (0.00-8.78) | 6.32 (3.87-8.28) | 2.61 (0.00-6.33) | 6.00 (3.33-10.00) | >0.05 | 4.79 (2.88-6.90) | 6.16 (4.07-11.81) | 7.50 (4.46-10.00) | >0.05 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **[$P_{25}$-$P_{75}$])** | | | | | | | | | |

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449 **Table 4**. Baseline characteristics of patients treated with dutasteride.

| **VARIABLE** | | **NON-RESPONDERS 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) | 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) | >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) | >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) | 0.000 |
| **Rosacea (%)** | | 15 (55.5) | 12 (44.4) | 27 | >0.05 |
| **Hypothyroidism (%)** | | 8 (30.8) | 18 (69.2) | 26 | >0.05 |
| **Pattern (%)** | **1** | 21/45 (48.9) | 35/61 (57.4) | 56/106 (52.8) | >0.05 |
| | **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** | | 21 (38.9) | 33 (61.1) | 54 | >0.05 |

| | | | | | |
|---|---|---|---|---|---|
| **(%)** | | | | | |
| **Eyebrow alopecia (%)** | **Partial** | 19 (43.2) | 25 (56.8) | 44 | 0.040 |
| | **Total** | 25 (48.1) | 27 (51.9) | 52 | |
| **Facial papules (%)** | | 17 (43.6) | 22 (56.4) | 39 | >0.05 |
| **Upper and lower extremities (%)** | | 28 (39.4) | 43 (60.5) | 71 | >0.05 |
| **Pruritus (%)** | **Mild** | 14 (56.0) | 11 (44.0) | 25 | >0.05 |
| | **Medium** | 2 (50.0) | 2 (50.0) | 4 | |
| **Trichodynia (%)** | **Mild** | 1 (16.7) | 5 (83.3) | 6 | >0.05 |
| | **Medium** | 0 (0.0) | 1 (100.0) | 1 | |
| **Perifollicular erythema (%)** | **Mild** | 4 (28.6) | 10 (71.4) | 14 | >0.05 |
| | **Medium** | 0 (0.0) | 5 (100.0) | 5 | |
| **Perifollicular hyperkeratosis (%)** | **Mild** | 4 (33.3) | 8 (66.6) | 12 | >0.05 |
| | **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) | >0.05 |
| | **Right side** | 6.5 (5.3-7.5) | 6.0 (4.4-7.0) | 6.0 (4.5-7.0) | >0.05 |
| | **Left side** | 6.5 (5.5-7.0) | 5.5 (4.5-7.1) | 6.0 (4.5-7.0) | >0.05 |
| **Weekly dose of dutasteride (group of treament) (%)** | **Group 1** | 25 (54.3) | 21 (45.7) | 46 | 0.001 |
| | **Group 2** | 28 (40.0) | 42 (60.0) | 70 | |
| | **Group 3** | 4 (12.5) | 28 (87.5) | 32 | |

*$P_{25}$: 25$^{th}$ percentile; $P_{75}$: 75$^{th}$ percentile***.** *Group 1: 1-2 capsules of dutasteride 0.5 mg a wee; Group 2: 3 capsules of dutasteride 0.5 mg a week; Group 3: 5-7 dutasteride 0.5 mg capsules a week.*

# EFFECTIVENESS OF DUTASTERIDE IN A LARGE SERIES OF PATIENTS WITH FRONTAL FIBROSING ALOPECIA IN REAL CLINICAL PRACTICE

**Article type:** Original article

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## ABSTRACT

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

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

**Methods:** 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) 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*=0.000, 0.006 and 0.006, 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*<0.005). Dutasteride was well tolerated in all patients.

**Limitations:** 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 to other systemic therapies or no systemic treatment.

## CAPSULE SUMMARY

Oral dutasteride was the most effective therapy frontal fibrosing alopecia in real clinical practice compared to other systemic therapies or no systemic treatment.

The response was associated with an increasing dose of dutasteride, being the most effective dose 5 to 7 capsules of dutasteride 0.5mg per week.

## INTRODUCTION

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 (LPP),[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]

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, minoxidil), and systemic therapies with different targets (hydroxychloroquine, oral corticosteroid therapy, oral retinoids, etc.).[5] Results from retrospective studies reveal that 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 three isoforms of the 5α-reductase enzyme. Compared to finasteride, dutasteride inhibits 5α-reductase type 1with an affinity 50 times higher and type 2 with an affinity 11 times higher.[7] Thus, dutasteride achieves a greater suppression of serum DHT 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 to other therapeutic modalities or no systemic treatment. The secondary objective was to assess the most effective dose of dutasteride. Additionally, prognostic factors associated with a better therapeutic response were analyzed.

## MATERIALS AND METHODS

### Study design

A retrospective study including all patients with a confirmed diagnosis of FFA at a specialized Trichology consultation from 2010-2018 was designed. Diagnosis of FFA was made by a dermatologist specialized in Trichology fulfilling the updated diagnostic criteria for FFA.[8,9] Skin biopsies were performed in routine clinical practice in patients with a doubtful diagnosis.

The selection of treatment in our patients was done in 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 to 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 (SVG). 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 "responder" when measures kept equal to the initial one after at least 6 months of follow-up. FFA patterns were classified according to the Moreno-Arrones et al. prognostic classification, since it was described.[10] Prior to the beginning of the study, an Institutional Review Board approval was obtained (289/17). Several clinical, diagnostic, and therapeutic variables were recorded.

**Statistical analysis**

Data are presented as mean ± standard deviation, median ($25^{th}$ percentile-$75^{th}$ percentile) or crude numbers (percentage). A comparison was made between the different treatment groups using the Chi-Square test, Fisher's exact test, Mann-Whitney U test or Kruskal-Wallis test. Statistical significance was considered with $P<0.05$. A 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) were included in the study. The median follow-up was 24 months (range 12-108).

The dutasteride dose ranged from 1 to 7 capsules per week (Avidart® capsules 0.5 mg). 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 or 6 capsules/week). No systemic treatment was prescribed to 56 (25%) patients, finasteride 2.5-5 mg/day was prescribed to 9 (4%) patients, hydroxychloroquine 200-400 mg/day to 6 patients (2.7%), doxycycline 100 mg/day to 2 (1.3%) patients and isotretinoin 5-20 mg/day to 2 (0.9%) patients. All patients including those without systemic treatment received the same topical treatment consisting on topical minoxidil 5% five nights a week and clobetasol propionate 0.05% solution twice weekly. Significant differences ($P$=0.001, 0.008 and 0.004) 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 1 shows 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 those who received 1 or 2 capsules of 0.5 mg of dutasteride/week, Group 2 patients who received 3 capsules/week, and Group 3 patients who received 5 or 7 capsules/week. Table 1 shows clinical characteristics and response to the three 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 frontal region, 90.6% in right lateral region and 84.4% in left lateral region, $P$=0.001, 0.001 and 0.005). 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 ($P$<0.05) between Group 1 versus Group 2, Group 2 versus Group 3, and Group 1 versus Group 3.

In order 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 at least 24 months (n=78, Table 2). After 24 months, the percentage of stabilized patients with dutasteride (n=42) was 57.1% compared to 21.7% without systemic treatment (n=23) and 50.0% with finasteride (n=6) (*P*=0.016). Statistically significant differences (*P*=0.014) 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 non-stabilized patients (n=104, Table 3), the rate of disease progression calculated in millimeters per year was lower with dutasteride (n=57, 3.9 mm/yr) compared to other systemic treatments (n= 8, 4.8 mm/yr) and no systemic treatment (n=39, 7.5 mm/yr, *P*=0.006).

Baseline characteristics of responder and non-responder patients to dutasteride were analyzed (Table 4). 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*=0.006).

Regarding adverse effects, one 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, two experienced diarrhoea at the beginning of treatment.

## DISCUSSION

Scientific evidence places 5ARIs, especially dutasteride, as the first therapeutic option for FFA.[6] In literature, more than 160 cases of FFA patients treated with dutasteride have been reported to date,[10–16] with an improvement rate of 15.3-44.4% and a stabilization rate of 29.2-80%, 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/week to 0.5 mg/day. Improvement in hair density (even without coexistence with androgenetic alopecia (AGA)) and

665 eyebrows has been documented.[2] Possibly, patients who experienced hair regrowth received
666 treatment with dutasteride before establishing a cicatricial alopecia. Therefore, early treatment
667 of these patients is advisable.[15]
668 In the present study, all patients received the same topical treatment and only those receiving a
669 systemic monotherapy were included. Dutasteride was the most effective therapeutic modality
670 with a stabilization rate of 61.5%-64.2% after 12 months of treatment in a total of 148 patients.
671 The rest of the therapies are far behind in terms of the number of patients treated. Finasteride
672 was prescribed in 9 patients, with a response rate at the frontal level of 77.8% at 12 months, but
673 50% at 24 months. Previous studies show a variable response rate of finasteride in FFA. The
674 study with the biggest number of patients by Vañó-Galván et al.[2] reported a stabilization rate of
675 52.9%. at doses of 2.5-5 mg/day of finasteride.
676 Hydroxychloroquine obtained stabilization in 2 (33.3%) out of the 6 patients treated at 12
677 months. Large series of patients described a wide variability response to hydroxychloroquine
678 from 25% -100%.[11,12,17–22] Doxycycline was used in 3 patients, with a good response to
679 treatment in all of them at 12 months, but lost of stabilization at 24 months. The stabilization
680 response rates described are also variable, from 25% - 100%.[12,17,20] However, the low number of
681 patients in the literature treated with this therapy do not support its use as a first-line therapy for
682 FFA.
683 Finally, only one study reported stabilization of FFA with oral retinoids.[23] Rakowska et al.
684 reported a stabilization in 76% patients treated with isotretinoin and 73% patients treated with
685 acitretin versus 43% patients treated with finasteride.[23] In our study, isotretinoin treatment 5-20
686 mg/day in 2 patients failed to stabilize the disease.
687 The mechanism of action of 5ARIs in FFA remains unclear. Considering the preferential
688 involvement of the frontotemporal hairline implantation, the high prevalence of FFA in
689 postmenopausal women,[11,24] and the increased incidence of early menopause,[4,25] an androgen-
690 related stimulus has been proposed as a trigger for the onset of FFA.[4] It has been hypothesized
691 that a currently unknown antigenic stimulus would trigger a lichenoid reaction in genetically
692 susceptible individuals.[4] Dutasteride might interfere with the pathogenic pathway of FFA by

693 acting against androgenic influence on androgen-dependent hair follicles of the frontal scalp.[4]
694 Furthermore, there is evidence that 5ARIs have an inhibitory effect on androgen-induced
695 peripheral fibrosis in AGA patients.[26] Finally, a preferential involvement of vellus and
696 intermediate hairs has been described in FFA.[27] 5ARIs reverse the miniaturization of terminal
697 hairs into vellus and terminal hairs, which can prevent the lichenoid inflammation.[27] Our study
698 shows clinical evidence supporting the effectiveness of dutasteride in FFA but further research
699 is required to elucidate the exact mechanism of action of dutasteride in FFA.

700 Natural history of FFA without treatment is only known in a small number of patients. It has
701 been described that the recession of the hairline implantation is progressive, with a medium
702 progression rate of 10.5 mm/yr (2-21) in untreated patients.[11] The progression rate in patients
703 without antiandrogen treatment although with other systemic and topical therapies ranges from
704 9.5 mm/yr (range 1-25)[28] to 10.8 mm/yr (range 3.6-20.4).[29] Regarding dutasteride, It has been
705 reported a hairline recession of 7.2mm/yr in patients treated with dutasteride 0.5mg three times
706 a week,[10] and 2.4 mm/yr in patients treated with 0.5 mg/day.[13] In our series of patients, the
707 progression rate in non-responders patients treated with dutasteride was 3.9 mm/yr (2.4-6.5)
708 versus 7.5 mm/yr (3.0-15.0) in patients without systemic treatment, with statistical significance
709 in slowing progression with 3 doses or more of dutasteride 0.5 mg per week. All these data
710 support the effectiveness of dutasteride in patients with FFA, with a dose dependent response.

711 Regarding the safety profile of dutasteride in patients with FFA, only two patients of our study
712 reported mild adverse effects during the follow-up, not requiring discontinuation of the drug. In
713 the literature, only one patient who experienced hyperpigmentation on the face and hands
714 during treatment with dutasteride 0.5 mg/day and pimecrolimus 1% b.i.d has been reported.[30]
715 However, adverse effects reported in women with AGA and hirsutism treated with dutasteride
716 include birth defects in male fetuses, headache, gastrointestinal discomfort, menstrual disorders,
717 or dizziness.[31] The main limitation to dutasteride treatment in our patients was a personal or
718 family history of breast cancer due to a potential increased risk of relapse in women with breast
719 cancer treated with 5ARIs.[32–35] However, no studies on female breast cancer patients exposed to

5ARIS have been conducted to date[35] and even they 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, age of the patient,[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. Secondly, all patients received topical treatment, so the effectiveness reported in both dutasteride and non-dutasteride 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]

## CONCLUSIONS

Dutasteride treatment was the most effective therapy for FFA compared to 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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## FIGURE LEGENDS

**Figure 1.** Representation of stabilization at the frontal level after 12 months of therapy according to the group of dutasteride treatment. *Group 1: 1-2 capsules of dutasteride 0.5 mg a*

*week; Group 2: 3 capsules of dutasteride 0.5 mg a week; Group 3: 5-7 dutasteride 0.5 mg capsules a week.*



**Table 1**. Clinical characteristics of the 224 patients with FFA.

| VARIABLE | NO | OTHE | DUTAST | TO | P- | GR | GR | GR | P- |
|---|---|---|---|---|---|---|---|---|---|

| | **SYSTEMIC THERAPY N=56 (25.0 %)** | **R SYSTEMIC THERAPIES N=20 (8.9)** | **ERIDE N=148 (66.1%)** | **TAL N=224** | **VALUE** | **OUP 1 (N=46)** | **OUP 2 (N=70)** | **OUP 3 (N=32)** | **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) | 0.023 | 65.0 (55.0-70.3) | 60.0 (53.8-66.3) | 57.0 (48.5-62.8) | 0.005 |
| **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) | >0.05 | 57.0 (49.0-61.0) | 55.0 (47.0-60.0) | 52.0 (42.0-58.0) | >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) | >0.05 | 7.0 (4.0-8.0) | 5.0 (4.0-7.0) | 5.0 (3-0-7.0) | >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) | >0.05 | 31.0 (18.5-44.5) | 19 (12.5-30.5) | 24 (12.0-32-0) | 0.018 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Rosacea (%)** | | 8 (14.3) | 5 (25.0) | 27/77 (35.1) | 40/114 (35.1) | >0.05 | 6/25 (24.0) | 19/45 (42.2) | 2/7 (28.6) | >0.05 |
| **Hypothyroidism (%)** | | 9 (16.1) | 3 (15.0) | 26 (17.6) | 38 (16.9) | >0.05 | 7/46 (15.2) | 16/70 (22.9) | 3/32 (9.4) | >0.05 |
| **Pattern (%)** | **1** | 25/44 (56.8) | 9/17 (52.9) | 56/106 (52.8) | 91/168 (54.2) | >0.05 | 15/38 (39.5) | 34/54 (63.0) | 7/14 (50.0) | 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 (%)** | | 19 (33.9) | 8/20 (40.0) | 54/143 (36.5) | 82/118 (68.6) | >0.05 | 16/46 (34.8) | 24/70 (34.3) | 14/32 (43.8) | >0.05 |
| **Eyebrow alopecia** | **Partial** | 27 (51.9) | 8 (40.0) | 44 (29.7) | 81 (36.2) | >0.05 | 16/46 (34.8) | 20/70 (28.6) | 8/32 (25.0) | >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) | >0.05 |
| **Eyelash alopecia (%)** | | 10/28 (35.7) | 3/19 (30.0) | 18/106 (17.0) | 31/145 (21.4) | 0.011 | 6/24 (25.0) | 8/50 (16.0) | 4/32 (12.5) | >0.05 |
| **Occipital involvement (%)** | | 2/26 (7.7) | 1/9 (11.1) | 17/101 (16.8) | 21/137 (15.3) | 0.015 | 5/24 (20.8) | 9/46 (19.6) | 3/31 (9.7) | >0.05 |
| **Axillary hair (%)** | | 17/28 (60.7) | 3/9 (33.3) | 54/110 (49.1) | 74/148 (50.0) | >0.05 | 18/27 (66.7) | 28/52 (53.8) | 8/31 (25.8) | 0.04 |
| **Pudendal hair (%)** | | 16/28 (57.1) | 5/10 (50y) | 51/109 (46.8) | 72/148 (48.6) | >0.05 | 16/26 (62.5) | 26/52 (50.0) | 9/31 (29.0) | >0.05 |
| **Facial papules (%)** | | 8/40 (20.0) | 9/15 (60.0) | 39/96 (40.6) | 57/153 (37.3) | >0.05 | 10/36 (27.8) | 24/50 (48.0) | 5/10 (50.0) | >0.05 |
| **Upper and lower extremities (%)** | | 22/30 (73.3) | 8/12 (66.7) | 71/107 (66.4) | 101/150 (67. | >0.05 | 20/27 (74.1 | 37/48 (77.1 | 14/32 (43.8 | 0.016 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 3) | | ) | ) | ) | |
| **Pruritus (%)** | **Mild** | 4/9 (44.4) | 1/ 4 (25%) | 16/37 (43.2) | 21/50 (42.0) | >0.05 | 5/8 (62.5) | 14/21 (66.7) | 3/6 (50.0) | >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 (%)** | **Mild** | 1/9 (11.1) | 1/ 4 (25.0) | 6/31 (19.4) | 8/44 (18.2) | >0.05 | 1/6 (16.7) | 3/18 (16.7) | 2/7 (28.6) | >0.05 |
| | **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 (%)** | **Mild** | 6/10 (60.0) | 1/ 4 (25%) | 14/35 (40.0) | 21/49 (42.9) | >0.05 | 0/6 (0.0) | 4/13 (30.8) | 1/5 (20.0) | >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) | |
| **Perifolli** | **Mild** | 7/9 | 1/ 4 | 34/53 | 42/6 | >0.0 | 2/6 | 3/13 | 3/5 | >0.0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **cular hyperkeratosis (%)** | | (77.8) | (25%) | (64.2) | 6 (63.3) | 5 | (33.3) | (23.1) | (60.0) | 5 |
| | **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) | >0.05 | 8.0 (7.0-8.5) | 7.5 (6.5-8.5) | 7.5 (7.0-8.4) | >0.05 |
| | **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) | >0.05 | 6.3 (4.5-7.1 | 6.0 (4.0-7.5) | 6.0 (5.0-7.0) | >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) | >0.05 | 6.3 (4.9-7.1) | 6.0 (4.5-7.5) | 6.0 (4.5-7.0) | >0.05 |
| **Final measurement (cm) (median [$P_{25}$-** | **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) | >0.05 | 8.2 (7.5-9.5) | 8.0 (7.0-9.0) | 7.5 (7.0-8.4) | 0.031 |
| | **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) | >0.05 | 7.0 (5.4-8.5) | 7.0 (5.0-7.7) | 6.0 (4.5-7.0) | >0.05 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **$P_{75}$])** | **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) | >0.05 | 7.0 (5.0-8.5) | 7.0 (5.0-7.7) | 6.0 (4.5-7.0) | >0.05 |

*$P_{25}$: 25$^{th}$ percentile; $P_{75}$: 75$^{th}$ percentile. Group 1: 1-2 capsules of dutasteride 0.5 mg a week; Group 2: 3 capsules of dutasteride 0.5 mg a week; Group 3: 5-7 dutasteride 0.5 mg capsules a week*



**Table 2.** Percentage of stabilized patients in the frontal region at 12 months and 24 months.

| | | **NO SYSTEMIC TREATMENT** | **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** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **N= 56 (25%)** | | | | | | | | | | |
| **12 months** | **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) | 0.000 | 21/46 (45.7) | 42/70 (60.0) | 28/32 (87.5) | 0.000 |
| | **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) | 0.006 | 22/46 (47.8) | 44/70 (62.9) | 29/32 (90.6) | 0.000 |
| | **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) | 0.006 | 22/46 (47.8) | 42/70 (60.0) | 27/32 (84.4) | 0.004 |
| **24 month** | **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) | 0.016 | 10/21 (4 | 9/16 (56. | 5/5 (100 | 0.014 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **s** | | | | | | | | | 7.6) | 3) | .0) | |
| | **Right lateral** | 6/23 (26.1) | 1/6 (26.3) | 1/4(25.0) | 0/2 (0.0) | - | 27/42 (64.3) | 0.274 | 12/21 (57.1) | 10/16 (62.5) | 5/5 (100.0) | 0.043 |
| | **Left lateral** | 6/23 (26.1) | 2/6 (33.3) | 0/4 (0.0) | 0/2 (0.0) | - | 26/42 (61.9) | 0.28 | 13/21 (61.9) | 9/16 (56.3) | 4/5 (80.0) | 0.239 |

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916 **Table 3.** Rate of disease progression in non-stabilized 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** |
|---|---|---|---|---|---|---|---|---|---|
| **Front** | 7.50 | 4.81 (1.70- | 3.87 (2.40- | 4.80 | 0.00 | 4.29 | 3.25 | 5.00 | 0.01 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **al (mm/ yr) (medi an [$P_{25}$-$P_{75}$])** | (3.00-15.00) | 17.09) | 6.48) | (2.4-8.2) | 6 | (2.27 - 7.28) | (2.32 - 5.34) | (4.25 - 5.00) | 8 |
| **Right side (mm/ yr) (medi an [$P_{25}$-$P_{75}$])** | 3.00 (0.00-10.00) | 4.07 (3.37-7.89) | 2.31 (0.00-6.00) | 6.00 (3.33-10.00) | >0. 05 | 5.86 (2.79 - 6.96) | 6.19 (3.06 - 12.47) | 5.00 (5.00 - 5.00) | >0. 05 |
| **Left side (mm/ yr) (medi an [$P_{25}$-$P_{75}$])** | 2.67 (0.00-8.78) | 6.32 (3.87-8.28) | 2.61 (0.00-6.33) | 6.00 (3.33-10.00) | >0. 05 | 4.79 (2.88 - 6.90) | 6.16 (4.07 - 11.81) | 7.50 (4.46 - 10.00) | >0. 05 |

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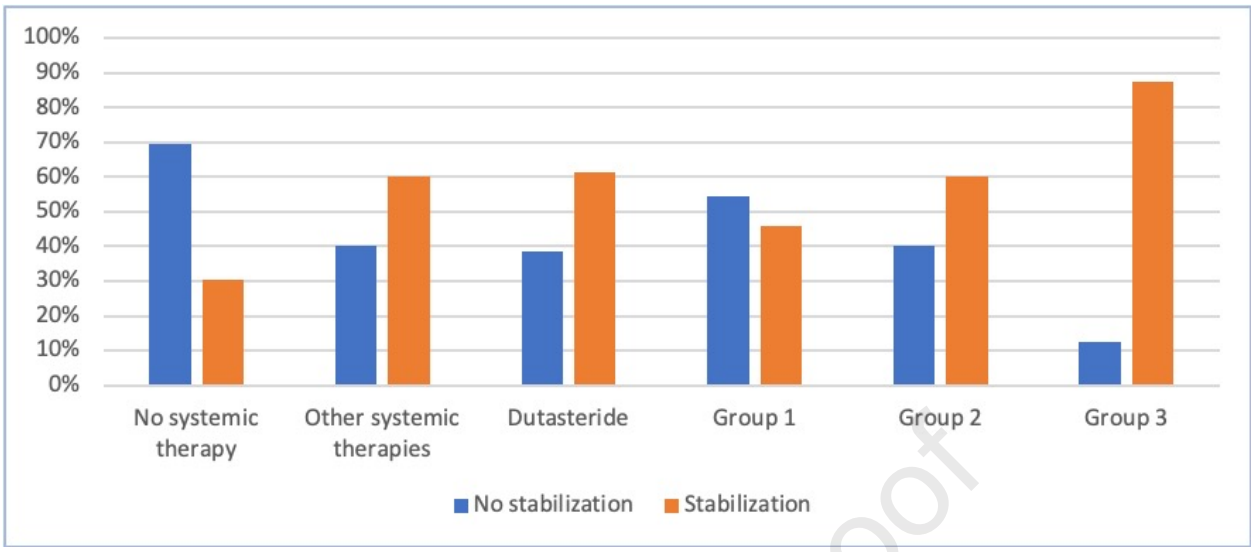
918 **Table 4**. Baseline characteristics of patients treated with dutasteride.

| VARIABLE | NON-RESPONDERS | RESPONDERS N=91 | TOTAL N=148 | P-VALUE |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| | | **N=57** | | | |
| **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) | 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) | >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) | >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) | 0.000 |
| **Rosacea (%)** | | 15 (55.5) | 12 (44.4) | 27 | >0.05 |
| **Hypothyroidism (%)** | | 8 (30.8) | 18 (69.2) | 26 | >0.05 |
| **Pattern (%)** | **1** | 21/45 (48.9) | 35/61 (57.4) | 56/106 (52.8) | >0.05 |
| | **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 (%)** | | 21 (38.9) | 33 (61.1) | 54 | >0.05 |
| **Eyebrow alopecia (%)** | **Partial** | 19 (43.2) | 25 (56.8) | 44 | 0.040 |
| | **Total** | 25 (48.1) | 27 (51.9) | 52 | |
| **Facial papules (%)** | | 17 (43.6) | 22 (56.4) | 39 | >0.05 |
| **Upper and lower extremities (%)** | | 28 (39.4) | 43 (60.5) | 71 | >0.05 |
| **Pruritus (%)** | **Mild** | 14 (56.0) | 11 (44.0) | 25 | >0.05 |

| | | | | | |
|---|---|---|---|---|---|
| | **Medium** | 2 (50.0) | 2 (50.0) | 4 | |
| **Trichodynia (%)** | **Mild** | 1 (16.7) | 5 (83.3) | 6 | >0.05 |
| | **Medium** | 0 (0.0) | 1 (100.0) | 1 | |
| **Perifollicular erythema (%)** | **Mild** | 4 (28.6) | 10 (71.4) | 14 | >0.05 |
| | **Medium** | 0 (0.0) | 5 (100.0) | 5 | |
| **Perifollicular hyperkeratosis (%)** | **Mild** | 4 (33.3) | 8 (66.6) | 12 | >0.05 |
| | **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) | >0.05 |
| | **Right side** | 6.5 (5.3-7.5) | 6.0 (4.4-7.0) | 6.0 (4.5-7.0) | >0.05 |
| | **Left side** | 6.5 (5.5-7.0) | 5.5 (4.5-7.1) | 6.0 (4.5-7.0) | >0.05 |
| **Weekly dose of dutasteride (group of treament) (%)** | **Group 1** | 25 (54.3) | 21 (45.7) | 46 | 0.001 |
| | **Group 2** | 28 (40.0) | 42 (60.0) | 70 | |
| | **Group 3** | 4 (12.5) | 28 (87.5) | 32 | |

*$P_{25}$: 25$^{th}$ percentile; $P_{75}$: 75$^{th}$ percentile***.** *Group 1: 1-2 capsules of dutasteride 0.5 mg a wee; Group 2: 3 capsules of dutasteride 0.5 mg a week; Group 3: 5-7 dutasteride 0.5 mg capsules a week.*



## CAPSULE SUMMARY

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