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Conflicts of interest

None disclosed.

REFERENCES

1. Clarke LE, Flake DD II, Busam K, et al. An independent validation of a gene expression signature to differentiate malignant melanoma from benign melanocytic nevi. *Cancer*. 2017;123(4):617-628. https://doi.org/10.1002/cncr.30385
2. Lezcano C, Jungbluth AA, Nehal KS, Hollmann TJ, Busam KJ. PRAME expression in melanocytic tumors. *Am J Surg Pathol*. 2018;42(11):1456-1465. https://doi.org/10.1097/PAS.0000000000001134
3. Lezcano C, Jungbluth AA, Busam KJ. Comparison of immunohistochemistry for PRAME with cytogenetic test results in the evaluation of challenging melanocytic tumors. *Am J Surg Pathol*. 2020;44(7):893-900. https://doi.org/10.1097/PAS.0000000000001492
4. Raghavan SS, Wang JY, Kwok S, Rieger KE, Novoa RA, Brown RA. PRAME expression in melanocytic proliferations with intermediate histopathologic or spitzoid features. *J Cutan Pathol*. 2020;47:1123-1131. https://doi.org/10.1111/cup.13818
5. Lohman ME, Steen AJ, Grekin RC, North JP. The utility of PRAME staining in identifying malignant transformation of melanocytic nevi. *J Cutan Pathol*. 2021;48(7):856-862. https://doi.org/10.1111/cup.13958

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Bicalutamide improves minoxidil-induced hypertrichosis in female pattern hair loss: A retrospective review of 35 patients

To the Editor: Low-dose systemic minoxidil in combination with antiandrogen therapy has been successfully used to treat female pattern hair loss (FPHL).[1] Although minoxidil has a favorable safety profile, hypertrichosis occurs in up to 24% of patients.[2]

Table I. Patient demographics, drug doses, and follow up in female pattern hair loss patients with minoxidil-induced hypertrichosis treated with oral bicalutamide (n = 35)

Feature	Results
Age in y; mean (SD)	53.5 (16.82)
Sex	
Female; n (%)	35 (100)
Fitzpatrick skin phototype	
Type I; n (%)	7 (20)
Type II; n (%)	17 (49)
Type III; n (%)	6 (17)
Type IV; n (%)	2 (6)
Type V; n (%)	3 (9)
Type VI; n (%)	0 (0)
Duration of follow up (mo); mean (SD)	28.9 (25.92)
Dose (mg) of minoxidil causing hypertrichosis; mean (SD)	1.5 (1.07)
Dose (mg) of bicalutamide improving hypertrichosis; mean (SD)	14.4 (5.25)
10 mg; n (%)	20 (57)
20 mg; n (%)	14 (40)
25 mg; n (%)	1 (3)
Dose (mg) of minoxidil at latest review; mean (SD)	2.2 (1.67)
Dose (mg) of bicalutamide at latest review; mean (SD)	14.7 (6.30)
10 mg; n (%)	18 (56)
20 mg; n (%)	11 (34)
25 mg; n (%)	1 (3)
30 mg; n (%)	2 (6)
Time (mo) to improvement of hypertrichosis after commencement of bicalutamide; mean (SD)	3.4 (1.27)
Areas of hypertrichosis improvement	
Face; n (%)	35 (100)
Limbs; n (%)	4 (11)
Body; n (%)	4 (11)

Bicalutamide is a pure, nonsteroidal androgen receptor inhibitor that has been successfully used in the treatment of FPHL.[3] Low-dose bicalutamide (25 mg/daily) has also been used to treat moderate-to-severe hirsutism with significant efficacy.[4] Our aim was to determine whether oral bicalutamide decreases the risk of minoxidil-induced hypertrichosis.

We retrospectively reviewed the records of all FPHL patients at our institution with minoxidil-induced hypertrichosis that were concurrently treated with oral bicalutamide between May 2016 and May 2021. Those treated with laser hair removal, electrolysis, depilatory creams, or concomitant drugs

Table II. Bicalutamide-related adverse effects and discontinuation of therapy

Adverse effects	Patients, No. (%)	Discontinuation, No. (%)	Dose reduction, No. (%)
Scalp dysesthesia	1 (3)	1 (3)	0 (0)
Headaches	1 (3)	0 (0)	1 (3)
Peri-orbital edema	1 (3)	0 (0)	1 (3)
Transaminitis	2 (6)	1 (3)	1 (3)

with antiandrogen potential (eg, drospirenone, spironolactone, finasteride, or dutasteride) were excluded from the review. Improvement in hypertrichosis was determined via a combination of clinician assessment, review of photography, and subjective reporting by patients.

We identified 35 patients who demonstrated clear improvement of minoxidil-induced hypertrichosis after commencement or up-titration of oral bicalutamide (Table I). The mean age of patients was 53.5 years (SD, 16.82; range, 20-84 years). Daily minoxidil dose ranged from 0.25 mg to 10 mg and included oral and sublingual preparations; hypertrichosis occurred in patients taking a mean dose of 1.5 mg/day (SD, 1.07; range, 0.25-5 mg).

All patients commenced bicalutamide at a dose of 10 mg. The mean dose of bicalutamide that reduced hypertrichosis was 14.4 mg (SD, 5.25 mg). The use of concurrent bicalutamide permitted an increase in the mean daily dose of minoxidil to 2.2 mg (SD, 1.67 mg) without development of hypertrichosis.

Fifteen (43%) patients were started on bicalutamide after developing hypertrichosis from minoxidil. Twenty patients (57%) were started on bicalutamide with minoxidil concurrently, and improvement of hypertrichosis was observed in this group on up-titration of the bicalutamide dose. Patients were followed up for a mean duration of 28.9 months (SD, 25.92 months). The mean time to documented improvement of hypertrichosis was 3.4 months (SD, 1.27 months) after commencing a stable dose of bicalutamide.

Safety and efficacy of systemic minoxidil and oral bicalutamide were evaluated as secondary objectives. The mean Sinclair stage at baseline was 2.82. The mean reduction in Sinclair stage was 0.54 (19.1%) at 6 months and 0.66 (23.4%) at 12 months. Bicalutamide and minoxidil were well tolerated overall. Bicalutamide-related adverse effects occurred in 5 patients (14%) and are outlined in Table II; adverse effects led to a dose reduction in 3 patients and discontinuation of therapy in 2 patients (due to transaminitis and scalp dysesthesia). Systemic minoxidil had a favorable safety profile; adverse effects included dizziness (n = 1, 3%) and palpitations (n = 1, 3%) leading to dose reductions. One patient discontinued both minoxidil and bicalutamide due to a perceived lack of efficacy.

Oral bicalutamide appears to be beneficial in mitigating hypertrichosis caused by minoxidil in FPHL patients. Daily bicalutamide (mean dose, 14.4 mg) both reduced hypertrichosis and permitted an increase in the mean dosing of minoxidil by 0.7 mg/day without further hypertrichosis. This observation calls into question the suggestion that minoxidil-induced hypertrichosis is androgen independent and indeed the distinction between hypertrichosis and hirsutism. Although unclear, minoxidil may in fact influence the androgen receptor or its downstream signaling.[5] This study is limited by small patient numbers, the lack of a control arm, its retrospective design, and the absence of formal hypertrichosis scoring. Prospective placebo-controlled studies are required to support this conclusion.

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Conflicts of interest

Prof Sinclair, Director and Founder of Samson Medical Pty Ltd, participates on the pharmaceutical advisory board for Eli Lilly, Pfizer, and Leo Pharmaceutical; is on the speakers bureau for Abbvie and Novartis; and is principal investigator in clinical trials for Amgen, Novartis, Arcutis Biotherapeutics, Aerotech, Merck & Co, Celgene, Coherus BioSciences, Jannsen, Regeneron, MedImmune, Glaxo Smith Kline, Samson Clinical, Boehringer Ingelheim, Oncobiologics, Roche, Ascend, Dermira, AstraZeneca, Akesobio, Reistone Biopharma, UCB, Sanofi, Connect, Arena, Sun Pharma, Bristol Myer Squibb, and Galderma. Drs Moussa and Kazmi and author Bokhari have no conflicts of interest to disclose.

REFERENCES

1. Sinclair RD. Female pattern hair loss: a pilot study investigating combination therapy with low-dose oral minoxidil and

spironolactone. *Int J Dermatol*. 2018;57(1):104-109. https://doi.org/10.1111/ijd.13838
2. Jimenez-Cauhe J, Saceda-Corralo D, Rodrigues-Barata R, et al. Safety of low-dose oral minoxidil treatment for hair loss. A systematic review and pooled-analysis of individual patient data. *Dermatol Ther*. 2020;33(6):e14106. https://doi.org/10.1111/dth.14106
3. Fernandez-Nieto D, Saceda-Corralo D, Jimenez-Cauhe J, et al. Bicalutamide: a potential new oral antiandrogenic drug for female pattern hair loss. *J Am Acad Dermatol*. 2020;83(5):e355-e356. https://doi.org/10.1016/j.jaad.2020.04.054
4. Müderris II, Bayram F, Ozçelik B, Güven M. New alternative treatment in hirsutism: bicalutamide 25 mg/day. *Gynecol Endocrinol*. 2002;16(1):63-66.
5. Hsu CL, Liu JS, Lin AC, Yang CH, Chung WH, Wu WG. Minoxidil may suppress androgen receptor-related functions. *Oncotarget*. 2014;5(8):2187-2197. https://doi.org/10.18632/oncotarget.1886

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Propranolol response in patients with segmental versus focal facial hemangiomas: A retrospective case-control study

To the Editor: About 10% of infantile hemangiomas (IHs) are located on the face. They can be subdivided into focal facial hemangiomas (FFHs) and segmental facial hemangiomas (SFHs). SFHs are confined to anatomically defined segments and are frequently associated with cerebrovascular and other anomalies[1]; patients with definite or possible PHACE (posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities) syndrome have SFH diameters >5 cm.[2] Because their proliferative phase is longer, SFHs frequently require extended periods of treatment.[3] The length of oral propranolol therapy (OPT) required by patients with SFH versus that required by patients with FFH and their respective relapse rates (RRs) have not been previously studied systematically.

In a retrospective case-control study, we analyzed 52 patients with SFH and 108 age-matched patients with FFH (Table I) who had received OPT and were followed up at 3-month intervals until final remission. IHs were classified as superficial (no subcutaneous involvement; SFH: 48%, FFH: 31%), mixed (42%, 40%), or deep (predominant subcutaneous component; 10%, 29%) independently by both the authors (Drs Schmid and Hoeger); discrepant results (<10%) were reevaluated by a third expert. Fifty-two patients with SFH were categorized as those with definite (15, 29%) or possible (2, 4%) PHACE syndrome and those not fulfilling the current PHACE criteria (35, 67%).[1] All the patients received 2.0-2.5 mg of propranolol per kilogram body weight per day during an initial course of 6 months, with monthly dose adjustments. The treatment was continued as long as there was objective evidence of growth or relapse, as assessed using standardized photographs, and permanently discontinued

Table I. Patient characteristics and details of oral propranolol therapy in children with focal versus segmental facial hemangiomas

Parameters	FFH	SFH	*P*
	n = 108	n = 52	
Female sex, n (%)	76 (70.4)	32 (61.5)	.264*
Preterm, n (%)	17 (15.7)	4 (7.7)	.170*
Median diameter of IH, mm (range)†	14 (3-60)	40 (15-125)	<.001‡
Ulceration, n (%)	3 (2.8)	12 (23.1)	<.001*
Oral propranolol therapy, d (range)			
Median age at initiation	94 (30-392)	54 (21-1389)	<.001‡
Mean total duration of OPT	190 (140-539)	382 (174-1988)§	
Mean age at the last dose of OPT	296 (207-778)	525 (206-3955)§	
Median follow-up period after the initiation of OPT	348 (260-1771)	1098 (278-3675)	
Relapse rate‖			
Patients with relapses, n (%)	10 (9.3)	28 (53.8)	<.001*

If more than 1 course of OPT was required, all days on therapy were added up. In case of ongoing therapy, January 31, 2021, was defined as the last countable date.

FFH, Focal facial hemangioma; *IH*, infantile hemangioma; *OPT*, oral propranolol therapy; *SFH*, segmental facial hemangioma.

*χ^2 test.

†Patients with SFH partially overlapped with those previously reported in a study on cerebrovascular anomalies (reference 1)

‡Mann-Whitney U test.

§Includes 5 patients with ongoing OPT after the completion of the first course of OPT.

‖Relapse was defined as regrowth ≥4 weeks after the completion of the last OPT course, requiring the restart of OPT.