Our Dermatology Online

Review Article

Spironolactone, bicalutamide, and dutasteride as a treatment option for androgenetic alopecia

Sheila Collado Marmolejos[1], Victoria Palmer[2], Manuel Valdebran[3,4]

[1]Department of Dermatology, Isa Dermatology Group, Santo Domingo, Dominican Republic, [2]Department of Medicine, Richmond University Medical Center, Staten Island, NY 10310, USA, [3]Department of Dermatology and Dermatologic Surgery, Medical University of South Carolina, Charleston, SC, 29425, USA, [4]Department of Pediatrics, Medical University of South Carolina, Charleston, SC 29425, USA

Corresponding author: Sheila Collado Marmolejos, MD, E-mail: sheilacolladom@gmail.com

ABSTRACT

Androgenetic alopecia is the most common type of hair loss. Although the exact cause of this condition is not fully understood, it is known to involve excessive amounts of dihydrotestosterone. There are various treatment options available for androgenetic alopecia that aim to target these mechanisms. The FDA-approved therapies for this condition include topical minoxidil, oral finasteride, and low-level light therapy. This review will discuss the potential benefits of using spironolactone, dutasteride, and bicalutamide as alternative treatment options for androgenetic alopecia.

Key words: Spironolactone, Bicalutamide, Dutasteride, Androgenetic alopecia

INTRODUCTION

Androgenetic alopecia (AGA) or hair pattern baldness, is the most common type of hair loss. It affects at least 80% of men and 50% of women by age 70, with the incidence increasing with age due to the changes in androgen metabolism [1,2]. Although the exact cause is not fully known, hereditary factors, environmental elements, nutritional aspects, and the presence of androgens are among the factors that contribute to it [3]; (Fig. 1); [4–7].

Testosterone is converted into dihydrotestosterone (DHT) by type I, 5-alpha reductase. Excessive amounts of DHT can cause hair follicles to shrink, leading to the replacement of terminal hairs with vellus hairs, which ultimately results in Androgenetic Alopecia (AGA) [6]. Scalp DHT can inhibit the expression of Wnt/B-catenin and generate passive feedback in notch signaling, which then, results in miniaturization of the hair follicle. This is the reason why lowering levels of DHT is useful in the treatment of AGA [8].

The primary cause of baldness is related to hair cycle dynamics. In AGA, the anagen phase gradually becomes shorter, while the telogen phase lengthens, resulting in a bald appearance [7].

Medical treatment for hair loss is most effective when initiated during the early stages. This is because as androgen receptors get activated in AGA, the hair follicles progressively shorten until they are no longer able to penetrate through the epidermis [2]. Therefore, early intervention can help in preventing further hair loss. The effectiveness of the treatment may depend on various factors such as the duration and location of hair loss, whether there is shedding or thinning of hair, the patient's age, and any other medical conditions. It is important to note that early-onset AGA is strongly associated with severe coronary artery disease and metabolic syndrome. Patients with a high body mass index are also more likely to have severe AGA [9].

Current FDA-approved therapies for AGA include topical minoxidil, oral finasteride, and low-level light therapy. This review will outline the uses of

How to cite this article: Collado Marmolejos S, Palmer V, Valdebran M. Spironolactone, bicalutamide, and dutasteride as a treatment option for androgenetic alopecia. Our Dermatol Online. 2024;15(3):304-309.

Submission: 22.02.2024; **Acceptance:** 01.04.2024

DOI: 10.7241/ourd.20243.20

Figure 1: AGA etiology.

spironolactone, dutasteride, and bicalutamide as alternative treatment options in this entity.

Spironolactone

Spironolactone is traditionally used as a potassium-sparing diuretic and antihypertensive agent due to its competitive antagonism against the aldosterone receptor [10]. It also has properties blocking the androgen nuclear receptors (NR3C4) [3] and decreasing testosterone production in the adrenal gland by affecting the 17a- hydroxylase and desmolase [1].

Spironolactone is used as an anti-androgen for female AGA. The oral doses can range from 25-200 mg/day [1,11]. This medication can be used combined with other therapies, such as oral minoxidil.

One prospective, uncontrolled, open-label observational study analyzed 100 women using a combination of minoxidil 0.25mg and spironolactone 25mg, showing it to be effective and safe in the treatment of female pattern hair loss [11,12]. A retrospective, observational study analyzed the effectiveness of oral spironolactone in 79 women as a monotherapy or adjunct therapy. The average dose was 100 mg twice daily (range 25-200 mg/day) for a minimum of 6 months. They found that all patients maintained or improved their initial Sinclair score (SS) with an average overall change of 0.65. The absolute change was linearly correlated with the presenting severity, and patients who used it for longer than 6 months had the best recorded SS at 1 year of use [1].

One of the most common side effects of this medication is menstrual irregularities, which can affect 15-30% of women[10]. Other less frequent side effects are fatigue, mastalgia, and hypotension, which affect less than 5% of patients.

It is essential to be aware that spironolactone might cause hyperkalemia in patients who have a history of kidney dysfunction, heart failure, or those taking other medications. Medications such as trimethoprim increase the risk of life-threatening hyperkalemia due to its pharmacological similarities to the potassium-sparing diuretic amiloride [10,13,14]. Although high potassium levels are a rare side effect of low-dose therapy (25-100mg/day) for women under 45 years old without underlying health conditions, higher doses (>100mg/day) could cause hyperkalemia in patients with underlying cardiac or renal issues [15]. Such patients, along with women over 45 years old, may

benefit from close monitoring of serum potassium, creatinine, and blood urea nitrogen (BUN).

It is important to exercise caution while using spironolactone during pregnancy since it is classified as a category C medication. Murine studies have shown a theoretical risk of teratogenicity, especially in male fetuses. High doses of spironolactone have been linked with the development of hypospadias and feminization of male fetuses. This risk is more significant between weeks 6-14 of pregnancy when the urogenital tract is being differentiated, therefore, avoiding the drug 1 month pre-conception and during pregnancy can prevent these adverse effects [10,15]. It's not generally prescribed to men due to the risk of gynecomastia and reduced libido [10].

Topical spironolactone can be an option that offers the same effects as the oral form without the systemic side effects [2]. Soliman et al reported the use of topical 1% spironolactone in 26 patients (16 males and 10 women) used once a day for 6 months, showing an increase in total terminal (p-value 0.006), thick terminal (p-value 0.021), and total hair count (p-value 0.009) in females, while in men there was a significant increase in total terminal (p: 0.019), thin terminal (p-value 0.006), vellus hair (p-value 0.0195) and total hair count (p-value 0.004) [16]. Ammar et al studied the use of topical spironolactone 5% vs minoxidil 5% vs a combination of the two, showing regrowth of hair in all groups but being more significant when used combined [17]. After the completion of the study, it was found that all patients experienced a significant reduction in vellus hair (with a p-value < 0.001). The study also revealed a correlation between the diversity of hair shaft, vellus hair, and uptight regrowing hair at the beginning, midpoint, and end of the study (p-value of 0.011) in all groups.

Bicalutamide

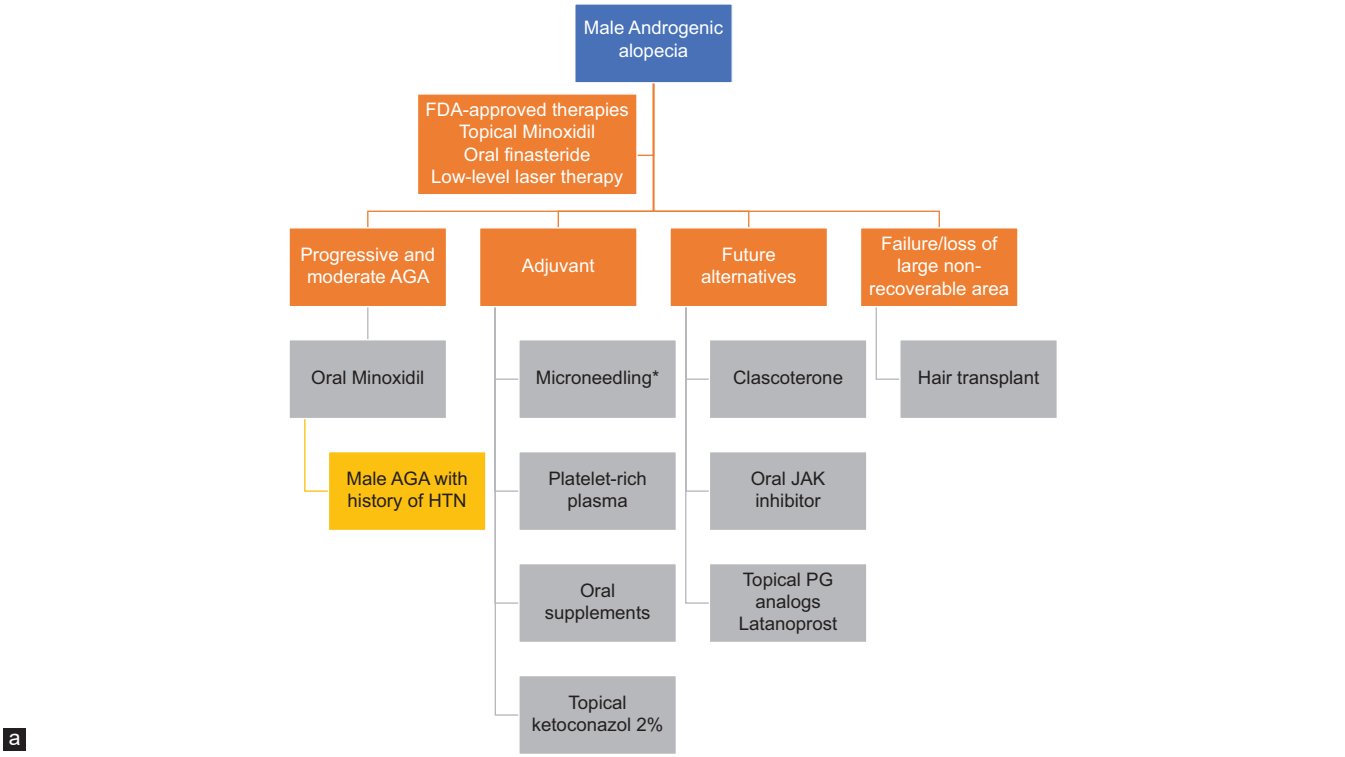
Bicalutamide is a non-steroidal antiandrogen medication used to treat prostate cancer. It selectively and competitively inhibits the androgen nuclear receptor (NR3C4) with a stronger effect than spironolactone. This drug is an option for treating female pattern baldness, particularly in patients with polycystic ovarian syndrome or signs of hyperandrogenism like acne, hirsutism, or seborrhea [18,19]. Two studies assessed bicalutamide for AGA, with a reduction in the SS ranging from 20.2%-27.5% (SS: 2.14 – 2.21) after at least 6 months of use [18,20].

The recommended daily dose of this medication is not standardized and can range from 10 to 50 mg per day [1], however, it is considered safe. Carvalho et al have suggested a method for prescribing and monitoring this medication. Before starting, they recommend conducting blood work which should include a complete blood count, AST, ALT, AP, total bilirubin and fractions, prothrombin time, creatinine, urea, sodium, potassium, and lipid profile. After the results are analyzed, an initial dose of 12.5 mg per day should be taken for four weeks. If there are no changes in the test results, the dosage can be increased to 25 mg per day. The next set of tests should be conducted at 12 and 24 weeks. If there is no response or a better response can be achieved, the dosage can be increased to 50 mg per day after 24 weeks. In the maintenance phase, it is recommended to conduct blood work and follow-ups every six months[19].

Bicalutamide is usually used in combination therapies such as oral spironolactone or minoxidil (oral 0.5-1mg or topical 5%) [18]. This medication does not possess diuretic or antihypertensive properties, which makes it a convenient option to use when oral minoxidil is required. Studies have demonstrated that taking oral bicalutamide at a dosage of 14.4mg/day for at least three months can reduce minoxidil-induced hypertrichosis. This can enable patients who need a higher dose of minoxidil to increase it without experiencing unwanted hair growth [21].

The side effects include mild elevation of transaminases, mastalgia, amenorrhea, and peripheral edema [19]. Bicalutamide is a medication that is peripherally selective and does not cross the blood-brain barrier. As a result, it does not have any effect on serum LH and testosterone levels. Prescribing oral hormonal contraceptives is important in premenopausal women due to its anti-androgenic effect, which may cause the feminization of a male fetus [19,22].

Intralesional bicalutamide may be considered when adverse outcomes are a concern, but there is limited literature on its use. One study evaluated six premenopausal women with AGA and seborrheic dermatitis and treated them with 1 ml bicalutamide 0.5% mixed with 1 ml lidocaine 2%. They held monthly sessions for three months, followed by a follow-up session three months later. This study found



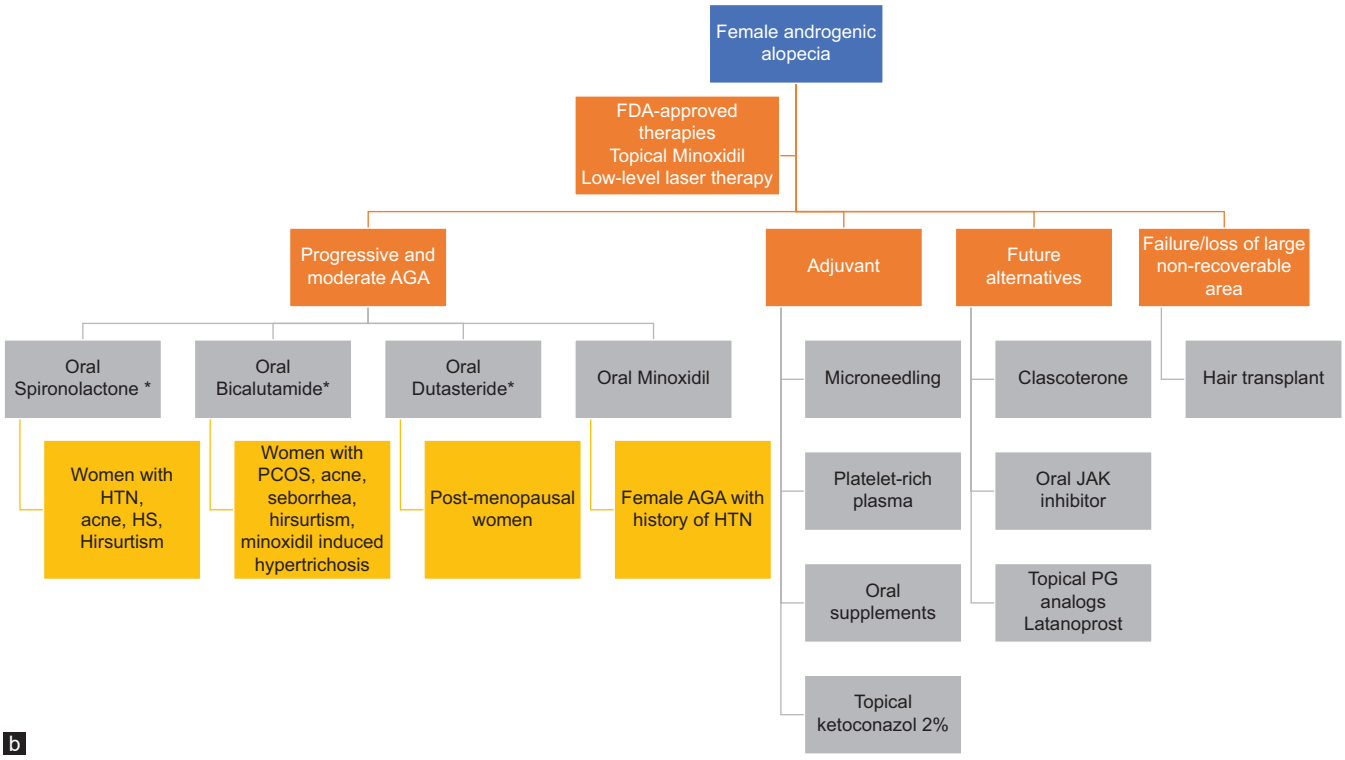


Figure 2: (a) Male Androgenic Alopecia. Treatment approach. **Microneedling with dutasteride and bicalutamide can be considered in male AGA. HTN: hypertension. Some of the therapies included were adapted from the guideline of the European Academy of Dermatology and Venereology [31].* (b) Female Androgenic Alopecia. Treatment approach. **Antiandrogens. HS: hidradenitis suppurativa; HTN: hypertension; PG: prostaglandin. Some of the therapies included were adapted from the guideline of the European Academy of Dermatology and Venereology [31].*

bicalutamide mesotherapy as a positive approach, with a subtle improvement in hair density in all patients [23]. More studies are needed to evaluate the effectiveness of this modality.

Table 1: Therapeutic recommendations of anti-androgen therapy in AGA

	Spironolactone	Bicalutamide	Dutasteride
Oral	25-200mg/day Used in women.	10-50mg/day Preferred in women with PCOS and signs of hyperandrogenism such as acne and seborrhea.	0.5 mg/day
Topical	1 – 5% Can be used in men.	Mesotherapy with bicalutamide 0.5%	Mesotherapy with dutasteride 0.01%
Benefits	Safe and effective	Improve hypertrichosis induced by minoxidil, no diuretic or antihypertensive effect.	Higher efficacy and a safer side-effect profile in comparison to finasteride. Alternative treatment in men with AGA.
Side effects	Menstrual irregularities, fatigue, mastalgia, and hypotension. Risk of life-threatening hyperkalemia in predisposed patients	Mild elevation of transaminases, mastalgia, amenorrhea, and peripheral edema	Decreased libido, impotence, ejaculatory dysfunction, and gynecomastia
Special considerations	Better if used in combination therapy with oral or topical minoxidil. Risk of feminization of male fetus.	More effective if used in combination with oral spironolactone or minoxidil (topical or oral). Important to conduct periodical blood work. Risk of feminization of male fetus.	Could be considered in postmenopausal women. Controversy surrounding the duration and severity of the sexual side effects in men.

*(PCOS) Polycystic Ovarian Syndrome

Dutasteride

Dutasteride is a second-generation 5 alpha-reductase (5aR) inhibitor. It competitively blocks the type I and type II isoenzyme. Dutasteride is three times more potent than finasteride in blocking the type II and 100 times more potent at blocking the type I isotype[24]. This leads to a 98% suppression of the dihydrotestosterone (DHT) levels compared with 71% for finasteride [8,25]

Dutasteride is used to treat male pattern baldness by improving hair growth. The recommended oral dose is 0.5mg/day, which has a good therapeutic effect [26].

Dutasteride is known to cause sexual side effects, including reduced libido, erectile dysfunction, ejaculation problems, and breast enlargement [8]. However, there are differing opinions on the duration and severity of these adverse effects. Due to these concerns, the drug should be used on a case-by-case basis after discussing potential side effects with patients.

The side effect profile has led to the refusal of oral use by some patients and the search for alternatives to avoid unwanted adverse outcomes. In this sense, the use of an intralesional route could be a feasible alternative. Even though there is no standardized intervention protocol for this, a group did a prospective clinical study with 6 patients diagnosed with AGA. They used 1mL of intradermal dutasteride 0.01% injections, with one session treatment every three months for 9 months. They saw a subjective increase in hair density and hair diameter in trichoscopy, with no incidence of side effects [27]. Sobhy et al. conducted an open, randomized, placebo-controlled trial to compare the effects of injections containing dutasteride 0.05% with two other groups. The second group received a dutasteride solution that also contained D-panthenol, biotin, and pyridoxines, while the third group was given a saline solution. The study found a statistically significant increase in anagen hair percentage and a decrease in telogen hair percentage after treatment ($p=0.005$) in the second group [28]. Moftah et al conducted a study to assess the effectiveness and safety of mesotherapy with a dutasteride-containing preparation for treating FPHL. The results demonstrated a significant improvement in hair growth in 62.8% of patients compared to those who received a placebo ($p<0.05$). Moreover, the group that received the treatment exhibited a significant increase in the mean hair diameter ($p<0.05$), and patients reported higher satisfaction with the treatment ($p<0.05$) [29].

A systematic review evaluated the use of oral vs intralesional dutasteride, and they found a mean change in hair growth of 15.92 hairs per cm^2 with the oral formulation compared to a mean change of 7.9 hairs per cm^2 with the intralesional formulation. As of today, due to the lack of more studies, the oral form is the preferred modality, and it appears to be more effective than the intralesional [30].

A summary of the different treatment approaches to male and female AGA is provided below (Table 1, Figs. 2a and 2b).

CONCLUSION

AGA it's a condition that requires in most of cases combination therapy to achieve a good therapeutic

response. FDA-approved treatments are topical minoxidil, oral finasteride, and low-level light therapy. The use of antiandrogens, such as oral spironolactone and bicalutamide are suitable options in female AGA, whereas oral dutasteride is an excellent option in male pattern baldness. The topical and intralesional forms of these therapies can be a good alternative for those who wish to avoid side effects. Further studies are needed to evaluate the effects of these modalities on a broader group of individuals.

REFERENCES

1. Nestor MS, Ablon G, Gade A, Han H, Fischer DL. Treatment options for androgenetic alopecia: Efficacy, side effects, compliance, financial considerations, and ethics. J Cosmet Dermatol. 2021;20:3759–81.
2. Kaiser M, Abdin R, Gaumond SI, Issa NT, Jimenez JJ. Treatment of Androgenetic Alopecia: Current Guidance and Unmet Needs. Clin Cosmet Investig Dermatol. 2023;16:1387–406.
3. Müller Ramos P, Melo DF, Radwanski H, de Almeida RFC, Miot HA. Female-pattern hair loss: therapeutic update. An Bras Dermatol. 2023;98:506–19.
4. Gatherwright J, Liu MT, Gliniak C, Totonchi A, Guyuron B. The contribution of endogenous and exogenous factors to female alopecia: A study of identical twins. Plast Reconstr Surg. 2012;130:1219–26.
5. Sadgrove NJ. The 'bald' phenotype (androgenetic alopecia) is caused by the high glycaemic, high cholesterol and low mineral 'western diet.' Trends Food Sci Technol. 2021;116:1170–8.
6. Ntshingila S, Oputu O, Arowolo AT, Khumalo NP. Androgenetic alopecia: An update. JAAD Int 2023;13:150–8.
7. Lolli F, Pallotti F, Rossi A, Fortuna MC, Caro G, Lenzi A, et al. Androgenetic alopecia: a review. Endocrine. 2017;57:9–17.
8. Zhou Z, Song S, Gao Z, Wu J, Ma J, Cui Y. The efficacy and safety of dutasteride compared with finasteride in treating men with androgenetic alopecia: A systematic review and meta-analysis. Clin Interv Aging. 2019;14:399–406.
9. Devjani S, Ezemma O, Kelley KJ, Stratton E, Senna M. androgenetic alopecia: therapy update. drugs. 2023;83:701–15.
10. Vargas-Mora P, Morgado-Carrasco D. Spironolactone in Dermatology: Uses in Acne, Hidradenitis Suppurativa, Female Pattern Hair Loss, and Hirsutism. Actas Dermosifiliogr. 2020;111:639-49.
11. Sinclair RD. Female pattern hair loss: a pilot study investigating combination therapy with low-dose oral minoxidil and spironolactone. Int J Dermatol. 2018;57:104–9.
12. Burns LJ, De Souza B, Flynn E, Hagigeorges D, Senna MM. Spironolactone for treatment of female pattern hair loss. J Am Acad Dermatol. 2020;83:276–8.
13. Layton AM, Eady EA, Whitehouse H, Del Rosso JQ, Fedorowicz Z, van Zuuren EJ. Oral Spironolactone for Acne Vulgaris in Adult Females: A Hybrid Systematic Review. Am J Clin Dermatol. 2017;18:169–91.
14. Antoniou T, Gomes T, Mamdani MM, Yao Z, Hellings C, Garg AX, et al. Trimethoprim-sulfamethoxazole induced hyperkalaemia in elderly patients receiving spironolactone: Nested case-control study. BMJ. 2011;343:d5228.
15. Kim GK, Del Rosso JQ. Oral Spironolactone in Post-teenage Female Patients with Acne Vulgaris Practical Considerations for the Clinician Based on Current Data and Clinical Experience. J Clin Aesthet Dermatol. 2012;5:37-50.
16. Soliman A, Hussein S, Shehata H, Aly H, Zawahry Y, Emam H, Rabie A. Assessment of the efficacy of topical antiandrogen; spironolactone in patients with androgenetic alopecia by dermoscopy. J Pak Assoc Dermatol. 2022;32:493-501.
17. Ammar AM, Elshahid AR, Abdel-Dayem HA, Mohamed AA, Elsaie ML. Dermoscopic evaluation of the efficacy of combination of topical spironolactone 5% and minoxidil 5% solutions in the treatment of androgenetic alopecia: A cross sectional-comparative study. J Cosmet Dermatol. 2022;21:5790–9.
18. Fernandez-Nieto D, Saceda-Corralo D, Jimenez-Cauhe J, Moreno-Arrones OM, Rodrigues-Barata R, Hermosa-Gelbard A, et al. Bicalutamide: A potential new oral antiandrogenic drug for female pattern hair loss. J Am Acad Dermatol. 2020;83:355–6.
19. Carvalho R de M, Santos LDN, Ramos PM, Machado CJ, Acioly P, Frattini SC, et al. Bicalutamide and the new perspectives for female pattern hair loss treatment: What dermatologists should know. J Cosmet Dermatol. 2022;21:4171–5.
20. Ismail FF, Meah N, Trindade de Carvalho L, Bhoyrul B, Wall D, Sinclair R. Safety of oral bicalutamide in female pattern hair loss: A retrospective review of 316 patients. J Am Acad Dermatol. 2020;83:1478–9.
21. Moussa A, Kazmi A, Bokhari L, Sinclair RD. Bicalutamide improves minoxidil-induced hypertrichosis in female pattern hair loss: A retrospective review of 35 patients. J Am Acad Dermatol. 2022;87:488–90.
22. Pegalajar-García MD, Gil-Villalba A, de la Torre-Gomar FJ. Bicalutamide: An Emergent Treatment Option in Trichology. Actas Dermosifiliogr. 2023;114:812–5.
23. Gomez-Zubiaur A, Andres-Lencina J, Cabezas V, Corredera C, di Brisco F, Ferrer B, et al. Mesotherapy with bicalutamide: A new treatment for androgenetic alopecia. Int J Trichology. 2023;15:39.
24. Clark R V., Hermann DJ, Cunningham GR, Wilson TH, Morrill BB, Hobbs S. Marked Suppression of Dihydrotestosterone in Men with Benign Prostatic Hyperplasia by Dutasteride, a Dual 5α-Reductase Inhibitor. J Clin Endocrinol Metab. 2004;89:2179–84.
25. Choi GS, Sim WY, Kang H, Huh CH, Lee YW, Shantakumar S, et al. Long-Term Effectiveness and Safety of Dutasteride versus Finasteride in Patients with Male Androgenic Alopecia in South Korea: A Multicentre Chart Review Study. Ann Dermatol. 2022;34:349-59.
26. Youssef M, Alzaid M. Dutasteride for Androgenetic Alopecia: Review Article. Egypt J Hosp Med. 2023;90:1098-101.
27. Saceda-Corralo D, Rodrigues-Barata A, Vano-Galvan S, Jaen-Olasolo P. Mesotherapy with dutasteride in the treatment of androgenetic alopecia. Int J Trichology. 2017;9:143.
28. Sobhy N, Aly H, El Shafee A, El Deeb M. Evaluation of the effect of injection of dutasteride as mesotherapeutic tool in treatment of androgenetic alopecia in males. Our Dermatol Online. 2013;4:40–5.
29. Moftah N, Moftah N, Abd-Elaziz G, Ahmed N, Hamed Y, Ghannam B, et al. Mesotherapy using dutasteride-containing preparation in treatment of female pattern hair loss: Photographic, morphometric and ultrastructural evaluation. J Eur Acad Dermatol Venereol. 2013;27:686–93.
30. Herz-Ruelas ME, Álvarez-Villalobos NA, Millán-Alanís JM, León-Gutiérrez H De, Ocampo-Garza SS, Gómez-Flores M, et al. Efficacy of intralesional and oral dutasteride in the treatment of androgenetic alopecia: a systematic review. Skin Appendage Disord. 2020;6:338–45.
31. Kanti V, Messenger A, Dobos G, Reygagne P, Finner A, Blumeyer A, et al. Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men – short version. J Eur Acad Dermatol Venereol. 2018;32:11–22.

Source of Support: This article has no funding source.

Conflict of Interest: The authors have no conflict of interest to declare.