Androgenetic alopecia: therapeutic options

J. Jimenez-Cauhe, D. Saceda-Corralo, A. Hermosa-Gelbard, M. Dominguez-Santas, D. Buendia-Castaño, S. Vaño-Galvan

Androgenetic alopecia is the most frequent type of alopecia and a very common condition in dermatology daily practice. However, a limited number of therapies are approved for this indication, which make the use of off-label treatments a necessary practice for dermatologists. In this article, we review the main treatments for androgenetic alopecia and propose an algorithm for its management.

Androgenetic alopecia (AGA) if the most frequent type of alopecia, affecting 80% of men and 40% of women at some point of their life. AGA in men is also termed 'male pattern hair loss' (MPHL) and it usually starts between 16 and 30 years of age. Female pattern hair loss (FPHL) has two peaks of incidence at 20-30 (premenopausal FPHL) and 50-55 years of age (postmenopausal FPHL). Genetics and hormones are the main etiopathogenic factors of AGA. Androgens (testosterone transformed by the enzyme 5-α-reductase into dihydrotestosterone) exert a miniaturizing effect on hair follicles in genetically predisposed men. In addition to the hormonal mechanism, recent studies highlight other possible factors, such as microinflammation, and alteration of the prostaglandin or Wnt/β-catenin pathways. [1]

Management of AGA should include continuous medical treatment, complemented with a hair transplant in selected cases. Currently, the only approved treatments in most countries are topical minoxidil (for both FPHL and MPHL) and oral finasteride 1 mg (for MPHL). Other antiandrogens have been recently approved for MPHL in some countries, such as topical finasteride (Portugal, Spain) and oral dutasteride (Japan, South Korea). Given this paucity of treatments, the use of off-label therapies is a common practice among dermatologists (Table 1). In this article we will review the therapeutic options for AGA.

Table 1. Currently approved and off-label therapies for treatment of androgenetic alopecia.

Approved therapies	Off-label therapies
Topical minoxidil 2 – 5%	Oral minoxidil 0.5 – 5mg
Oral finasteride 1mg (MPHL)	Oral finasteride 5mg (FPHL)
Topical finasteride 0.22% *(approved for MPHL in Spain, Portugal and Italy)*	Oral spironolactone 100mg *(approved for hyperandrogenism, not alopecia)*
Oral dutasteride 0.5mg *(approved for MPHL in Japan and South Korea)*	Oral contraceptives *(approved for hyperandrogenism, not alopecia)*
	Oral bicalutamide 10 – 50mg
	Mesotherapy with PRP or dutasteride

Minoxidil

Minoxidil is an arteriolar vasodilator approved by FDA in 1979 as an antihypertensive drug. It mainly acts by opening potassium channels in vascular smooth muscle, although other mechanisms have been proposed, such as anti-inflammatory properties, stimulation of Wnt/β-catenin pathway, and even anti-androgen effect. Through these still unknown mechanisms of action, minoxidil promotes hair regrowth by increasing hair diameter and prolonging the anagen phase. [2]

Topical minoxidil is approved for both male and female AGA, and can be used in foam or solution, at 2% or 5%. Although it is an effective option for AGA, it has a poor compliance due to the low tolerability and cosmetic properties.

Since first reports in 2015, low-dose oral minoxidil (LDOM) has been increasingly used for AGA. This off-label treatment is now one of the most important therapies for hair loss, with numerous studies supporting its effectiveness and favorable safety profile.[3] It is especially useful in women (for FPHL and telogen effluvium), with doses ranging from 0.25 – 2.5mg (0.5mg and 1mg are the most common ones). In MPHL it improves hair density but does not stop androgen miniaturization, so it needs to be combined with anti-androgens. Doses range from 2.5 – 5 mg. [2,3]

Hypertrichosis is the most frequent adverse effect (AE) and the main limiting factor for increasing the dose of LDOM. It usually appears in the first 3 months of treatment, more frequently on the temples, sideburns, upper lip and arms. [4] In men it is usually not relevant; in women it can be managed by different hair removal methods before treatment adjustment. In cases of significant hypertrichosis it is necessary to reduce

Dermatology Department, Hospital Universitario Ramón y Cajal, Departamento de Medicina, Facultad de Medicina, Universidad de Alcalá, IRYCIS; Trichology Unit, Grupo Pedro Jaen, Madrid, Spain.

the dose. Systemic AE occur in about 5% of patients and are usually mild. Most of them are resolved by adjusting LDOM dose, and <2% of patients require treatment discontinuation. These AE have been observed to occur at a specific chronological pattern: tachycardia and lightheadedness usually appear within the first week of treatment; headache is rare and may occur after 15-30 days; fluid retention (pedal edema, rarely periorbital edema) generally appears after 2 months. [2]
Severe cardiovascular AE were described with standard doses used for hypertension (20-80 mg), but they are extremely rare with low doses used for alopecia. In fact, most reports of serious AE with LDOM are usually linked to compounding errors (marketed oral minoxidil is not available in several countries). [5]
In addition, recent studies described the safety of LDOM in special situations, such as pediatric population and patients with hypertension or arrhythmia. [6,7]
This favorable profile in effectiveness, safety and compliance make LDOM a first-line treatment in both female and male AGA, ahead of topical minoxidil.

Oral anti-androgens in MPHL

5-α-reductase inhibitors (5-ARIs), are the most effective and important treatment for male AGA. 5-ARIs inhibit the enzyme 5-α-reductase, preventing the conversion of testosterone to DHT and halting the progression of AGA. Finasteride inhibits 5-α-reductase type 2 and has a plasmatic half-life of 5 hours. Dutasteride inhibits 5-α-reductase type 2 (much more potent than finasteride) and type 1, and has a half-life of 5 weeks. [1,8]
Several clinical trials and meta-analysis have demonstrated a better efficacy and similar safety profile of dutasteride 0.5mg daily, compared to finasteride 1mg daily. Regarding AE, a reduction of libido and ejaculation volume are relatively common, but their actual impact is controversial and they disappear after drug discontinuation. Gynecomastia and mood disorders are rare. [1,8]
A Spanish study described the usefulness of low-dose regimens of oral dutasteride (0.5mg, 1-3 capsules per week), which showed to be better tolerated (no reported AE) with a slightly lower effectiveness, compared to standard doses. [8]
In spite of being off-label, available data make oral dutasteride a first-line treatment for male AGA, ahead of finasteride. Given its longer half-life, low doses of dutasteride may be considered in these situations: 1) occurrence of AE with daily doses; 2) patients fearful of possible AE; 3) mild forms of MPHL; 4) as a maintenance therapy after maximal improvement of alopecia. [9]

Oral anti-androgens in FPHL

5-ARIs are also used (off-label) in female AGA, with similar management as in men. Finasteride is used at 2.5-5mg daily, and dutasteride at 0.5mg daily or low-doses (2-3 capsules per week). In post-menopausal women, dutasteride is usually a first-line treatment. However, in women of childbearing age, pregnancy should be avoided after 1 (finasteride) and 6 (dutasteride) months of discontinuation (both are included in FDA category X). For this reason, in premenopausal women other effective anti-androgens can be considered ahead of 5-ARIs. In women with personal history of breast cancer it is also recommended to avoid 5-ARIs or to consult with an oncologist, since there are controversial data of a theoretical increased risk of hormone-dependent cancer due to unopposed elevation of estradiol. [1,9]
Spironolactone is a diuretic drug with anti-androgenic activity. It acts by blocking the androgen receptor, and it is especially useful in premenopausal women with alopecia and other signs of hyperandrogenism (seborrhea, acne or hirsutism). [10] In addition, it is safe in patients with history of breast cancer, being the antiandrogen of choice in these cases. [11]
The optimal dose is 100 mg daily (doses lower than 100 mg appear to be ineffective in FPHL), but it is advisable to start at 50 mg (half tablet) the first weeks, and increase the dose if well tolerated. [10] Regarding AE, menstrual irregularities and headache are relatively common and usually self-limiting. Gynecomastia and hiperkalemia are rare (in patients >45 years of age it is recommended to monitor creatinine and potassium blood levels). Spironolactone should be stopped 1 month before pregnancy (FDA Category C).
Bicalutamide is another androgen receptor antagonist (approved for metastatic prostate cancer) that has shown to be effective in FPHL, especially when associated with hyperandrogenism or polycystic ovary syndrome (PCOS). Doses range between 10-50 mg daily (being 25-50 mg daily the most effective ones). The most common AE is elevation of transaminases, which is usually mild and transitory, and requires monitoring hepatic and lipid profile every 3-6 months. [12]
Pregnancy should be avoided during treatment and 2 months after discontinuation (FDA Category X)

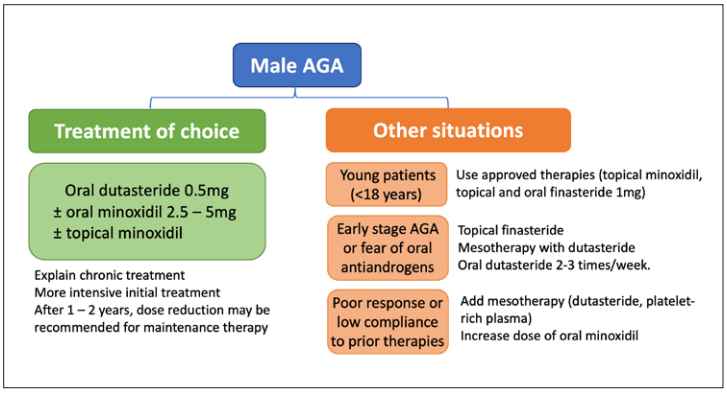

Figure 1. Proposed treatment algorithm for MPHL

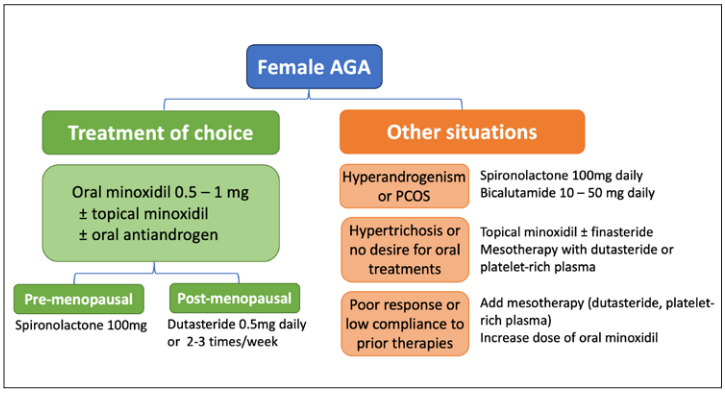

Figure 2. Proposed treatment algorithm for FPHL

Oral contraceptives may be indicated in premenopausal women, either to improve AGA and hyperandrogenism, or to prevent pregnancy in women treated with other Category X drugs. When choosing an oral contraceptive, those containing an anti-androgenic action progestogen (drospirenone, dienogest, chlormadinone or nomegestrol) should be prioritized. [9] Cyproterone acetate is now rarely used after a health warning of increased risk of meningioma. [9]

Infiltrated therapies

Scalp microinjections of different products (mesotherapy) is a safe procedure that has shown to be effective in both male and female AGA. Of course, it is less effective than oral therapies, but it is useful in 1) patients with fear or occurrence of AE with oral treatments; 2) patients with mild or initial forms of alopecia; 3) as a complement to oral drugs in patients with severe forms of alopecia. **Mesotherapy with dutasteride** is effective in AGA, even in monotherapy. Several protocols exist, with different concentration and frequency of sessions.[13] From our experience, we use dutasteride 0,1% in sterile vials, 1 session every 3 months. **Mesotherapy with platelet rich plasma** has been evaluated in numerous studies and meta-analysis, supporting its effectiveness in AGA. [14] However, protocols are widely variable among centers and several issues remain to be elucidated, such as the optimal frequency of sessions, or the need for plasma activation.

Conclusion

AGA is an extremely common condition and the majority of therapies are used off-label. For this reason, dermatologists should be updated in Its management, which is in continuous evolution. In this review we provide a summary of current therapies for hair loss and propose a treatment algorithm based on both scientific evidence and clinical experience (Figure 1 and 2).

Keywords

Minoxidil - hair loss - androgenetic alopecia - side effect – hyperandrogenism – dutasteride

References

1. *Dominguez-Santas M, Diaz-Guimaraens B, Saceda-Corralo D, Hermosa-Gelbard A, Muñoz-Moreno Arrones O, Pindado-Ortega C, et al. The state-of-the-art in the management of androgenetic alopecia: A review of new therapies and treatment algorithms. JEADV Clinical Practice. 2022;1(3):176–85.*
2. *Vañó-Galván S, Pirmez R, Hermosa-Gelbard A, Moreno-Arrones ÓM, Saceda-Corralo D, Rodrigues-Barata R, et al. Safety of low-dose oral minoxidil for hair loss: A multicenter study of 1404 patients. J Am Acad Dermatol. 2021 Feb 24;*
3. *Jimenez-Cauhe J, Saceda-Corralo D, Rodrigues-Barata R, Moreno-Arrones OM, Ortega-Quijano D, Fernandez-Nieto D, 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 Nov;33(6):e14106.*
4. *Jimenez-Cauhe J, Saceda-Corralo D, Rodrigues-Barata R, Hermosa-Gelbard A, Moreno-Arrones OM, Gil-Redondo R, et al. Characterization and management of hypertrichosis induced by low-dose oral minoxidil in the treatment of hair loss. J Am Acad Dermatol. 2021 Jan;84(1):222–3.*
5. *Moreno-Arrones OM, Rodrigues-Barata R, Morales C, Imbernon-Moya A, Saceda-Corralo D, Matji A, et al. Serious adverse effects from compounding errors with low-dose oral minoxidil for alopecia treatment. Actas Dermosifiliogr. 2022 Aug;113(7):T725–7.*
6. *Jimenez-Cauhe J, Pirmez R, Müller-Ramos P, Melo DF, Ortega-Quijano D, Moreno-Arrones OM, et al. Safety of low-dose oral minoxidil in patients with hypertension and arrhythmia: A multicenter study of 264 patients. Actas Dermosifiliogr. 2023 Nov 3;S0001-7310(23)00867-0.*
7. *de Nicolas-Ruanes B, Moreno-Arrones OM, Saceda-Corralo D, Hermosa-Gelbard A, Rodrigues-Barata R, Gil-Redondo R, et al. Low-dose oral minoxidil for treatment of androgenetic alopecia and telogen effluvium in a pediatric population: A descriptive study. J Am Acad Dermatol. 2022 Apr 26;S0190-9622(22)00696-X.*
8. *Vañó-Galván S, Saceda-Corralo D, Moreno-Arrones OM, Rodrigues-Barata R, Morales C, Gil-Redondo R, et al. Effectiveness and safety of oral dutasteride for male androgenetic alopecia in real clinical practice: A descriptive monocentric study. Dermatol Ther. 2020; 33:e13182.*
9. *Vañó S, Jaén P. Manual Práctico de Tricología. #TricoHRC. 2° Edición. 2023.*
10. *James JF, Jamerson TA, Aguh C. Efficacy and safety profile of oral spironolactone use for androgenic alopecia: A systematic review. J Am Acad Dermatol. 2022 Feb;86(2):425–9.*
11. *Bommareddy K, Hamade H, Lopez-Olivo MA, Wehner M, Tosh T, Barbieri JS. Association of spironolactone use with risk of cancer: A systematic review and meta-analysis. JAMA Dermatol. 2022 Mar 1;158(3):275–82.*
12. *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 Nov;83(5):e355–6.*
13. *Saceda-Corralo D, Moustafa F, Moreno-Arrones Ó, Jaén-Olasolo P, Vañó-Galván S, Camacho F. Mesotherapy with dutasteride for androgenetic alopecia: A retrospective study in real clinical practice. J Drugs Dermatol. 2022 Jul 1;21(7):742–7.*
14. *Zhang X, Ji Y, Zhou M, Zhou X, Xie Y, Zeng X, et al. Platelet-rich plasma for androgenetic alopecia: A systematic review and meta-analysis of randomized controlled trials. J Cutan Med Surg. 2023;27(5):504–8.*

Corresponding author

Juan Jimenez-Cauhe

E-mail: jjimenezc92@gmail.com