American Journal of Clinical Dermatology
https://doi.org/10.1007/s40257-022-00730-y

LEADING ARTICLE

What's New in Therapy for Male Androgenetic Alopecia?

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Accepted: 6 September 2022

Abstract

Male androgenetic alopecia is a common condition and represents a major concern for patients who experience this condition. While there are different treatments to stop hair loss and improve hair density, the 5-alpha reductase inhibitors have demonstrated to be effective in improving androgenetic alopecia in men and can maintain a positive response for many years. Oral finasteride 1 mg is a US FDA-approved option, but dutasteride 0.5 mg has been proven to induce better responses, especially in the frontal area. Both have been shown to be safe in clinical trials but there is widespread concern about sexual adverse effects among patients. The use of topical finasteride has increased during the last few years as a useful option to avoid systemic therapy. The efficacy of topical finasteride 0.25% daily has been demonstrated in clinical trials, with a less marked decrease in serum dihydrotestosterone levels than with oral intake. Mesotherapy with dutasteride has also become more widespread recently, although evidence of its effectiveness is limited to retrospective studies in real clinical practice. The use of oral minoxidil in androgenetic alopecia has not been approved by the FDA, however several clinical studies have shown that it is an effective treatment option. The initial dose recommended to treat male hair loss is 2.5 mg daily, although the dose is frequently increased to 5 mg daily. The main adverse effect of oral minoxidil is hypertrichosis, followed by dizziness or lower limb edema, which are much less common. Platelet-rich plasma is a non-pharmacological option to treat male androgenetic alopecia, with some clinical trials demonstrating an improvement in hair count after several months. Among the published studies, the main limitation to compare its efficacy is the heterogeneity of the procedure. The most frequent regimens propose treatment every 4 weeks for 3 months initially to assess the individual response. Another treatment alternative is the use of light devices with wavelengths of between 630 and 660 nm, known as low-level laser therapy. These devices can be used at home every day for 15–30 min. Their efficacy has been shown in a limited number of clinical trials; however, there is a lack of evidence about the efficacy of these devices compared with other medical options or as a complementary therapy in hair loss. The pipeline of potential new treatments for male androgenetic alopecia is strong. Pyrilutamide and GT20029 are being studied as topical antagonists of the androgen receptor, while cetirizine is another topical option with some initial promising results. Furthermore, according to isolated studies with heterogeneous treatment schemes, the use of botulinum toxin in the scalp might improve androgenetic alopecia, and lastly, scalp threading might increase the total hair count as growth factors are released during implantation.

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Published online: 28 September 2022

Key Points

The management of androgenetic alopecia in men is based on oral finasteride and topical minoxidil, both of which are US FDA-approved treatment options; however, several off-label treatments for this condition are available.

The efficacy of oral 5-alpha reductase inhibitors, such as finasteride and dutasteride, has been proven. The use of oral minoxidil is increasing, with promising clinical results.

Topical finasteride has proven its efficacy in a recent clinical trial. Other treatments such as platelet-rich plasma and low-level laser therapy may be useful as complementary treatments.

1 Introduction

Androgenetic alopecia (AGA) is the most frequent cause of hair loss in men and women. According to epidemiological studies, 80% of Caucasian men and 40–50% of women will develop AGA over the course of their lifetime [1]. AGA is characterized by a decrease in hair density in androgenetic areas of the scalp due to a progressive miniaturization of the hair follicle. The etiopathogenesis is multifactorial and complex [2].

The objective of this review was not to make a systematic review of the published evidence in male AGA but to compile the most interesting, updated options for this condition.

2 Oral 5-Alpha Reductase Inhibitors

Androgens play an important role in androgenetic hair loss. The influence of testosterone is especially relevant in men and is still controversial in women [3, 4]. Activity of the 5-alpha-reductase (5-AR) enzyme converts free testosterone into 5-alpha-dihydrotestosterone. Later, it binds to the androgen receptor in the dermal papilla of the hair follicle and activates the genes responsible for gradual hair loss; this occurs in genetically susceptible people. After several hair cycles, duration of the anagen phase shortens and the matrix size decreases, resulting in clinically evident miniaturized hairs [4].

Peripheral antiandrogens, such as 5-AR inhibitors, have been proven to be effective in stopping this mechanism and also in reversing hair thinning. Oral finasteride, which inhibits the type II enzyme, is a US FDA-approved drug to treat AGA, while oral dutasteride inhibits both type I and II enzymes and has already been approved for the treatment of AGA in Japan and South Korea.

Several randomized clinical trials have demonstrated that oral dutasteride is better than placebo in improving hair density in male patients with AGA, and positive results have been seen by clinicians and patients after 6 months of daily intake of oral dutasteride (Fig. 1) [5, 6]. A randomized, double-blind clinical trial demonstrated statistically significant improvement in mean change from baseline in hair count, hair width, and panel global photographic assessment at month 6 favoring the use of oral dutasteride 0.5 mg/

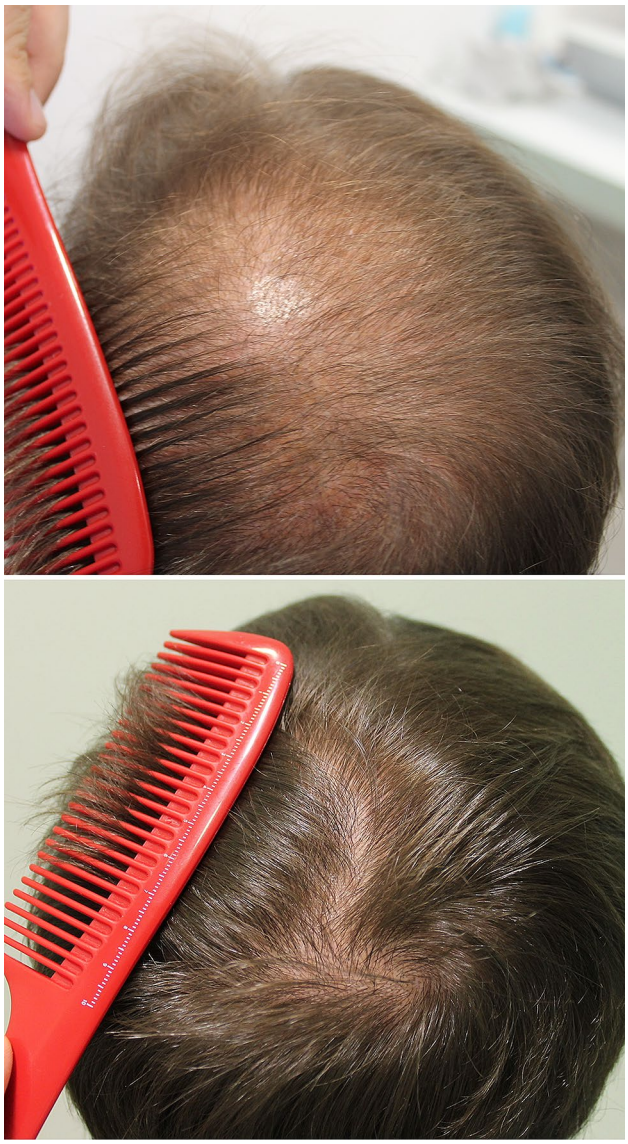

Fig. 1 A 34-year-old male patient with androgenetic alopecia. Quick response after 6 months under treatment with oral dutasteride 0.5 mg daily and mesotherapy with dutasteride 0.1%.

day compared with lower doses of oral dutasteride (0.02 and 0.1 mg/day), finasteride (1 mg/day), and placebo. The superior effectiveness of oral dutasteride when compared with finasteride 1 mg/day was especially significant in the frontal and superior area of the scalp [6]. A randomized, placebo-controlled, double-blind study demonstrated that serum dihydrotestosterone (DHT) concentrations are suppressed significantly when taking oral dutasteride or oral finasteride compared with placebo after the same period of time. Furthermore, scalp DHT concentrations were significantly reduced in all treatment modalities compared with placebo, with the 2.5 and 0.5 mg/day oral dutasteride treatment regimens obtaining a higher DHT reduction in the scalp (79% and 51% reduction from baseline, respectively). Doses of oral dutasteride 0.1 mg/day and oral finasteride 1 mg/day achieved similar reductions in scalp DHT levels (32% and 41%, respectively). When analyzing the data obtained, investigators discovered a statistically significant inverse correlation between hair count change from baseline and the mean scalp DHT percentage change from baseline (the lower the DHT levels after suppression, the higher the hair count) [7]. Another double-blind, placebo-controlled, randomized, two-center pilot study aimed to evaluate the effects of oral finasteride 5 mg/day on scalp DHT levels. After 1 month of treatment, DHT levels on bald scalp were reduced to the same levels as those of hair-bearing scalp [8].

Two different meta-analyses have demonstrated that oral dutasteride is more effective than oral finasteride for the treatment of male AGA. The network meta-analysis performed by Gupta et al. [9] showed that oral dutasteride 0.5 mg/day achieved a larger increase in total hair count at 24 weeks (first end point), and when compared with finasteride 1 mg/day, a mean difference of 7.1 hairs/cm^2 was obtained, favoring the use of oral dutasteride, although the quality of evidence for this comparison was considered to be low.

The meta-analysis performed by Zhou et al. also found statistically significant data to conclude that oral dutasteride is more effective than oral finasteride [10]. The mean change in total hair count was higher in the dutasteride group than in the finasteride group, and this difference was present in the vertex and the frontal area.

In a milligrams-to-milligrams comparison, dutasteride was demonstrated to be three times more potent than finasteride in inhibiting 5-AR type II, and 100 times more potent in inhibiting 5-AR type I in a double-blind, placebo-controlled, parallel group evaluation of five dosing regimens of dutasteride and finasteride [11]; however, this may be partly addressed by the different dosing schedules used in clinical practice.

Interestingly, lower doses of dutasteride have been demonstrated to be superior to placebo. Oral dutasteride 0.1 mg/day induced a mean change in hair count from baseline that was similar to oral finasteride 1 mg/day [6]. This opens the possibility of using lower doses of oral dutasteride to improve hair density (Fig. 2). An observational, retrospective study included 12 patients with an oral dutasteride 0.5 mg dose of three or fewer times per week. In this small cohort, 33% of patients remained stable and 66% of patients had mild clinical improvement. None of these patients presented adverse events [10].

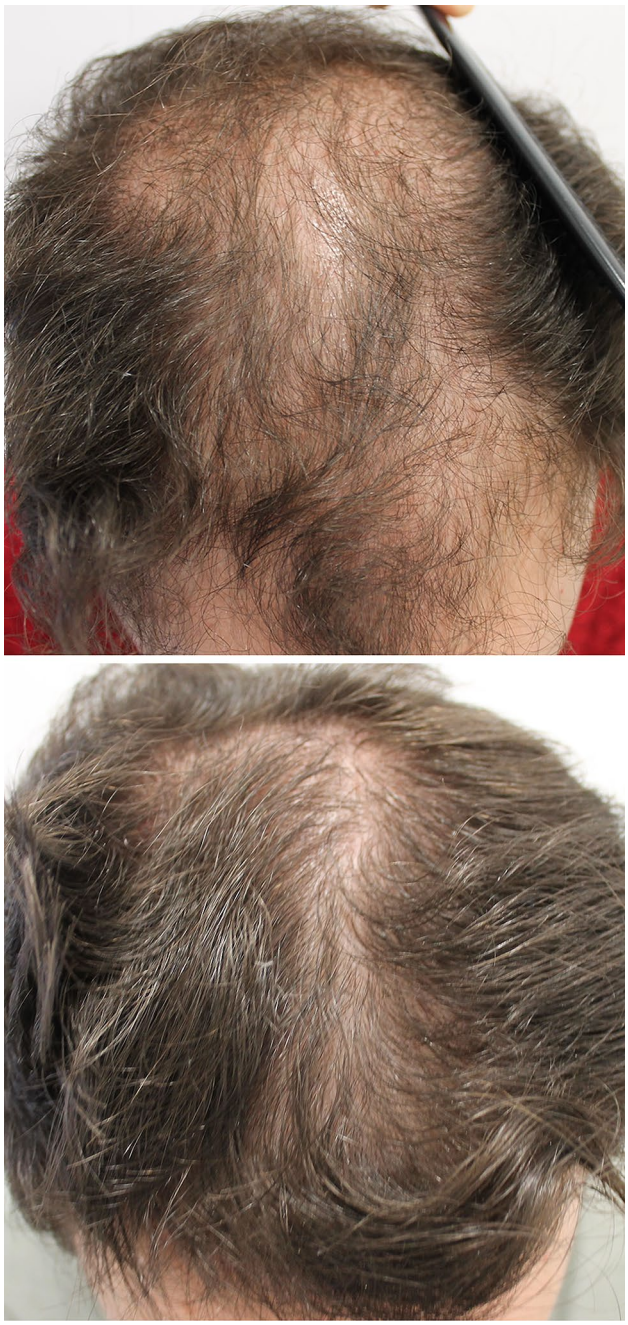

Fig. 2 A 24-year-old male patient with androgenetic alopecia. Clinical improvement after 1 year with oral dutasteride 0.5 mg three times weekly and mesotherapy with dutasteride 0.025%.

The systemic use of 5-AR inhibitors has been related to sexual adverse effects (AE), including sexual impotence, ejaculation disorders, and decreased libido. For this reason, the clinical trials of oral dutasteride have examined in great detail these AEs. A randomized, double-blind clinical trial showed that the incidence of AEs (mainly altered libido) was similar in the active treatment groups and lower with placebo (with no evidence of a dose-dependent increase in incidence in the dutasteride group) and without statistically significant differences between active treatment groups and placebo [6].

Other studies have failed to demonstrate that the use of these drugs results in a statistically significant increase in sexual AEs [5, 7]. A pharmacovigilance analysis demonstrated that the signal of sexual AEs associated with finasteride after 2012 was more than three times greater than the signal for reports before 2012, suggesting a confounding bias due to stimulated reporting [13]. However, the controversy continues as the large difference in signal size between finasteride and minoxidil makes it unlikely that only confounding factors are responsible for the signal observed.

Despite the evidence-based data, these AEs represent a primary concern for patients considering treatment, and the possibility of sexual AEs due to a nocebo effect must be considered. Most of these patients have resolution of sexual AEs after discontinuation of 5-AR inhibitors, although some studies describe a group of patients with persistent sexual dysfunction after stopping treatment [14]. This condition, termed post-finasteride syndrome, is still a controversial issue in the medical community.

According to the data published, the number of drug-related adverse events recorded in clinical trials is very low and there are no statistically significant differences between oral dutasteride and placebo. Patients with AEs had no relevant alterations on laboratory evaluations and physical examinations [5].

The rate of AEs in real clinical practice is low. A retrospective study with 307 patients observed dutasteride-related AEs in 20 patients (6.5%), with decreased libido, erectile dysfunction, and mood disorders being the most frequent [12]. All AEs resolved after discontinuation of dutasteride. Interestingly, no AEs were detected in patients taking 0.5 mg three or fewer times per week, with or without other concomitant medication. It is unclear if the absence of AEs was because of the lower doses of the drug or due to the lower risk of the nocebo effect, as patients were taking less capsules.

To reduce the potential AEs of oral dutasteride, mesotherapy use has become more widespread in recent years. Mesotherapy is performed using the nappage technique: intradermal injections of 0.05 mL solution at a 1 cm interval at an angle of 60°. The total volume injected each session ranges from 1.5 to 3 mL. A randomized, placebo-controlled trial with monthly dutasteride microinjections in male patients with AGA (microinjections were performed on a weekly basis during the first month) was performed. The dutasteride group had an increased mean hair shaft diameter and an 80% improvement in independent observer assessment (IOA) [15]. The efficacy of this treatment has been compared with placebo in two more studies (one of them being non-randomized) [16, 17], providing a significant improvement in most cases. Patient perception of the effectiveness of this mesotherapy is also positive [18]. The treatment regimen is not standardized. Some authors defend a monthly treatment, although it has been suggested that treatment every 3 months is also effective [19]. A retrospective study of 86 patients treated by mesotherapy with dutasteride as monotherapy showed a marked clinical improvement in 38.4% of patients [20]. All patients received microinjections every 3, 4, or 6 months during the first year. In our experience, performing mesotherapy every 3 months is sufficient to obtain a significant clinical improvement.

The main AE of this technique is mild to moderate pain during the procedure. Local anesthetic blockade before the microinjections is highly recommended. Edema on the forehead is possible the day after the procedure, but is usually mild, not painful, and will disappear without treatment [21]. Other uncommon AEs are facial edema, local hematoma, and transient folliculitis [20].

3 Oral Minoxidil

Topical minoxidil is an FDA-approved treatment for AGA in men. Applied on the scalp, minoxidil molecule is converted into minoxidil sulfate by sulfotransferase enzymes located in the outer root sheath of the hair follicle.

Oral minoxidil is approved as an antihypertensive, with doses ranging between 10 and 40 mg daily [22]. The most frequent AEs are hypertrichosis, tachycardia, and lower-limb edema. Recently, multiple studies have shown the efficacy and safety of low-dose oral minoxidil (<5 mg daily) for treating hair loss. All clinical studies found oral minoxidil to be effective in male AGA. In a retrospective study of 41 men with AGA receiving oral minoxidil 2.5–5 mg daily, 37 patients showed moderate or marked improvement (the latter defined as an improvement of one grade or more on the Norwood–Hamilton scale) [23]. Current data suggest that the use of a 2.5–5 mg daily dose of oral minoxidil is more effective than lower doses in male patients (Fig. 3) [24]. These doses have been demonstrated to improve hair density in both the frontal area and vertex, with a significant clinical improvement [23, 25]. Lueangarun et al. communicated their experience of treating men with oral minoxidil 5 mg daily and found a significant improvement in the vertex area [25]. Unfortunately, none of the previously mentioned

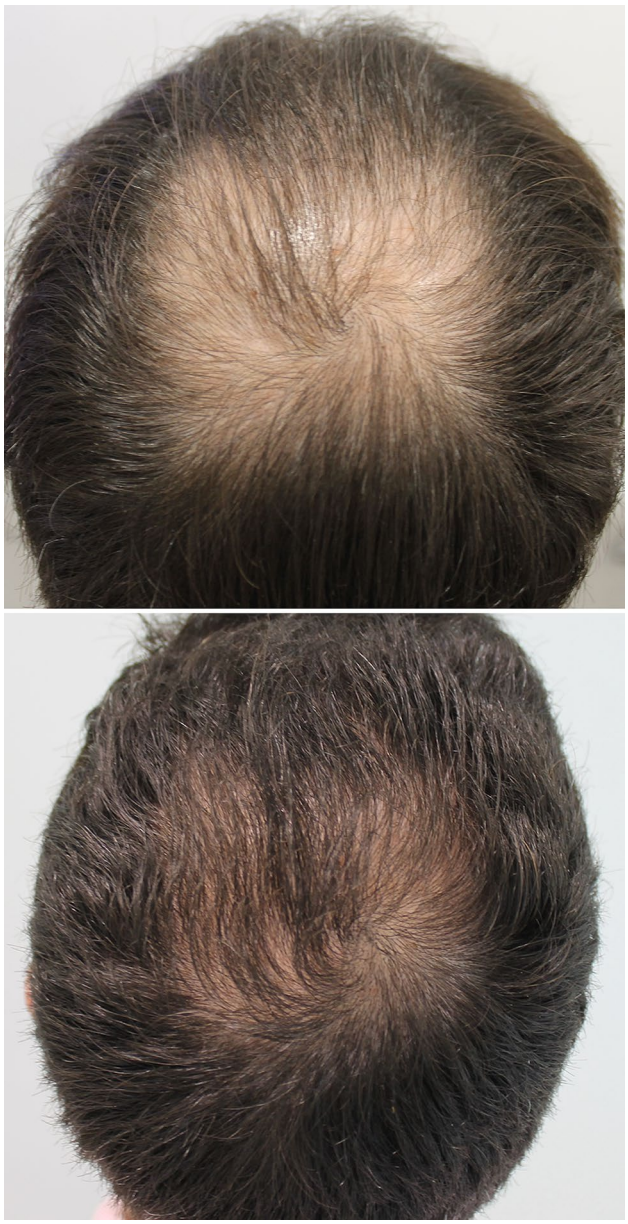

Fig. 3 A 44-year-old male with androgenetic alopecia on the vertex. Clinical response after 6 months with oral minoxidil 5 mg, oral dutasteride 0.5 mg, and mesotherapy with dutasteride 0.025%.

studies included an objective method of assessment, apart from an independent assessment of clinical images.

Very low doses of oral minoxidil may induce mild improvement of hair density and stabilize the progression of hair loss. The study performed by Pirmez and Salas-Callo showed improvement or stabilization of hair density after 24 weeks in 25 male patients taking 0.25 mg daily. They observed an increase in total hair density in all parameters analyzed by trichoscopy, in the frontal scalp and vertex [26].

In clinical practice, the effectiveness of oral minoxidil may be proportional to the dose taken by the patient. Clinical improvement can be observed after 12 weeks of treatment, but longer duration of treatment gives better results [27]. This makes oral minoxidil one of the most rapidly acting agents for the treatment of AGA. For treating male AGA, it has been proposed to start with a dose of 2.5 mg daily, increasing to 1.25 mg every 3 months until a dose of 5 mg daily or clinical improvement is observed. This approach is also recommended to test the tolerability of the treatment [28]. There are no studies evaluating whether oral minoxidil maintains a sustained long-term response.

Oral minoxidil is generally well tolerated and only minor AEs have been described. A multicenter study that analyzed 1404 patients detected a rate of discontinuation of only 1.2% [29]. The most common AE is hypertrichosis, which is not considered by most male patients to be a concerning issue; they usually notice it on the beard and eyebrows [25, 26]. Hypertrichosis is clearly dose-related, being more frequent with doses of 5 mg daily [23, 29, 32], and also seems to be more common in younger patients [30].

Cardiovascular AEs are less frequent (5.5%), with dizziness, lower limb edema, and tachycardia being the most common AEs [29, 33]. Lightheadedness is more probable in patients with a history of syncope and in those who take calcium channel blockers for hypertension. Lower limb edema is related to water and sodium retention, and may also appear as periorbital fluid retention. Tachycardia is the result of reflex sympathetic activation, as the vasodilatory effect of oral minoxidil increases the cardiac output. In most cases, reflex tachycardia is transient. Other uncommon AEs detected were insomnia or intense hair shedding. All the described AEs are dose-related and improve with dose tapering or the discontinuation of treatment. Interestingly, the systemic AEs tend to appear in specific periods of time. The described electrocardiogram (ECG) alterations related to oral minoxidil are mild and are not relevant for clinical management, therefore baseline ECG is unnecessary [33].

Sublingual minoxidil has been proposed as an alternative route of administration to obtain the same improvement in hair density with lower doses. Moreover, a sublingual dose would avoid hepatic first-pass metabolism and may reduce the AEs. The results of the first phase 1B clinical trial have recently been published [34]. Patients receiving sublingual minoxidil 0.45 mg daily had a significant improvement in hair density after 6 months. Higher doses (1.35 and 4.05 mg) were also effective. None of the patients reported AEs and investigators did not find significant changes in blood pressure.

4 Topical Finasteride

Finasteride is an FDA-approved treatment for male AGA. Clinical studies of oral finasteride 1 mg daily demonstrated that treatment stopped hair loss and improved hair density,

compared with placebo. There is also sufficient data to confirm a sustained effect for 5–10 years after the start of treatment [35]. Finasteride is generally well tolerated but the use of 5-AR inhibitors is associated with sexual AEs. Oral finasteride has also been related to an increased risk of depression. A population-based, retrospective, matched cohort study was designed to evaluate whether 5-AR inhibitors were associated with an increased risk of depression or committing suicide. While the suicide risk did not vary, there was an increase in the incidence of depression in the 5-AR inhibitor cohort [36]. Topical use of finasteride may reduce or avoid these systemic AEs while maintaining clinical efficacy.

In the last few years, some clinical studies have demonstrated that topical finasteride can be effective in treating AGA in men and women. The first study was carried out by Mazzarella et al. [37] and included 28 male patients with AGA who obtained a hair loss reduction without any significant changes in hormone plasma levels (total testosterone, free testosterone, and DHT) compared with placebo [37]. Phase I–II clinical trials of finasteride 0.25% topical solution have also been conducted in male AGA patients, providing good efficacy results, reducing the scalp concentration of DHT, and with less effect on serum DHT levels than the oral counterpart [38, 39]

Recently, a phase III trial evaluated the efficacy and safety of topical finasteride 0.25% applied once daily, compared with placebo [40]. This trial included 458 patients (189 treated with topical finasteride, 184 treated with placebo, and 85 treated with oral finasteride). After 24 weeks of treatment, the mean change in hair growth was higher with topical finasteride than with placebo, and similar to oral finasteride. The AEs related to the use of topical finasteride were pruritus (2.2%), erythema (2.2%), and reduction in libido (0.6%); however, the detection of sexual dysfunction was not different between topical finasteride and placebo. The values in DHT serum analysis fell by an average of 34% compared with baseline (and compared with a 55% reduction in men taking oral finasteride).

There are few studies that compare the effectiveness of topical finasteride with other options for the treatment of hair loss. A randomized, double-blind, comparative study assessed the efficacy of topical minoxidil 3% versus a topical combination of finasteride 0.1% with the same concentration of topical minoxidil, in 40 men with AGA [41]. After 24 weeks, both groups had a significant increase in hair density and the combined topical solution was superior compared with minoxidil by global photographic assessment. According to another study, topical finasteride might be used as a substitute following oral administration [42]. The investigators assessed the response to a combination topical treatment of minoxidil 5% and finasteride 0.1% in five male patients who stopped oral finasteride 1 mg after 2 years of treatment. Four of these patients maintained a good hair density despite the discontinuation of oral treatment. Further studies will be needed to analyze the effectiveness and safety of topical finasteride in clinical practice. Current evidence suggests that topical finasteride is a good choice for patients who need 5-AR inhibitory treatment and prefer not to take oral medication.

5 Platelet-Rich Plasma

Platelet-rich plasma (PRP) has been accepted as a potential therapy for hair loss, and consists of autologous blood-derived plasma with increased platelet concentrations. The patient's own blood is centrifuged to obtain this product. The platelets contain multiple growth factors and once activated, they are released into the scalp after local injection. Some of these growth factors are the vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-β, epithelial growth factor (EGF), and insulin-like growth factor (IGF) [43].

There are several factors in the preparation of PRP that may change the final composition of the product and change the efficacy of the treatment and the final outcomes (such as the speed of centrifugation or use of additional agents and activation with calcium). There are no standardized protocols for PRP preparation; however, there are several commercialized PRP preparation systems for obtaining centrifuged PRP in the same way between procedures (number of times, speed, and time of centrifugation). We encourage use of any of these systems to perform a standardized protocol in clinical practice and gain clinical experience over time.

Activation of PRP before injection is a controversial issue. One study suggests that the use of non-activated PRP can be more effective than calcium-activated PRP. The study contains some limitations but it highlights how routine practices can be questioned.It is likely the platelets can be activated in vivo after injection as thromboxane A_2 is produced [44].

The injection of PRP is similar to other treatments based on scalp mesotherapy: multiple subcutaneous injections done in a nappage technique at 0.5–1 cm intervals with a 27- or 30-gauge needle. The total volume injected each session ranges from 1.5–4 mL. The treatment schedule is not standardized either. The most common regimen is performing PRP injections every 4–6 weeks for 3 or 6 months, after which a maintenance regimen can be followed, with PRP injections administered every 3 or 6 months. A significant increase in the mean anagen hairs, hair density, and terminal hairs can be observed after the first 3 months of treatment [45–47]. In a randomized, placebo-controlled study, Alves and Grimalt observed a mean increase of 14.86 hairs/cm^2 compared with baseline after 3 months of treatment

[46]. This improvement was maintained after 6 months, with a mean increase of 12.86 hairs/cm^2. The control areas showed a decrease of hair density, and the difference between the areas treated and the control areas was statistically significant.

The main AE during PRP injections is pain during the procedure, which can be reduced with local anesthesia. Topical lidocaine has been demonstrated to be effective if it is applied 30–60 min before the procedure. Another medical option is to use intralesional anesthesia administered in a ring-block distribution. Considering the pain associated with injections is generally well tolerated, the use of ice packs or vibrating tools might be enough to minimize pain.

6 Low-Level Laser Therapy

Low-level laser therapy (LLLT) is a non-invasive therapy for treating hair loss. It has been demonstrated that low fluences of light devices can induce hair thickening and longer anagen phases [48]. LLLT may have anti-inflammatory properties, as was observed in the treatment of other cicatricial alopecias [49]. The use of LLLT in clinical practice is not well standardized. The devices used vary from helmets or caps to combs [50, 52]. According to the evidence, it is recommended to use wavelengths of between 630 and 660 nm, for 15–30 min, and with a periodicity between daily or three times per week [53]. In fact, one of the limitations found in this meta-analysis was the high heterogeneity among clinical trials. Despite continuing controversy, LLLT is one of the male AGA treatments that has more available published evidence for its use [53].

7 New Emerging Therapies

New investigational drugs are being developed for AGA. Although some preliminary results are promising, we advise caution and waiting for new data.

Topical antiandrogens can be useful in the management of AGA. Besides topical finasteride, antagonists of androgen receptors such as pyrilutamide have been developed. This drug has been evaluated in phase I clinical trials for AGA in men and the results are not available yet [54]. If it is shown to be safe and effective, its topical administration would open the doors to the use of direct androgen receptor antagonists in men. Further interesting research is focused in GT20029, a molecule that will be evaluated in phase I clinical trials [55]. It would be the first topical drug that uses the PROTAC (Proteolysis Targeting Chimera) technology for hair loss. It captures the androgen receptor and induces its degradation through ubiquitin-mediated proteolysis.

Another potentially effective topical option is cetirizine. A study in 85 male patients showed that topical cetirizine 1% might induce an improvement of total hair density compared with placebo after 6 months [56]. The possible explanation for these results is that cetirizine may reduce the levels of prostaglandin D2, which is supposed to stop hair loss in AGA. However, the study had significant limitations, as the control group was much smaller than the treatment group and it was clearly not randomized. In addition, the presentation of the results was confusing and there are no other studies supporting this therapy.

The pathway of prostaglandin synthesis has captured the interest of researchers in the last few years. A prostaglandin D2 inhibitor, setipiprant, was a very interesting option for the treatment of AGA. A phase III clinical trial comparing it with placebo and finasteride has recently finished [57]. Male patients with grade III or higher AGA took 1g of setipiprant every 12 hours for 24 weeks. The outcomes at week 24 and week 32 showed that setipiprant was not better than placebo in AGA.

Botulinum toxin (BT) is a well-known treatment in aesthetic dermatology. In the last few years it has been proposed as a treatment option in AGA. There are a couple of hypotheses of how it might work in hair loss. Firstly, the block of presynaptic release of acetylcholine may induce a relaxation of scalp muscles that promotes a local increase of blood flow with an increase of oxygen and a decrease of DHT. Secondly, BT has demonstrated to reduce the gene transcription of TGF-β that is induced after the activation of the androgen receptor by DHT [58]. TGF-β is a promoter of follicular fibrosis associated with miniaturization in AGA. Two studies propose injections in 30 different sites of 5 IU of BT (a total of 150 IU) with different treatment regimens. First, Freund et al. treated 40 subjects every 6 weeks, and observed an increase in total hair count of 18% after 1 year [59]. Second, Singh et al. performed the injections every 4 weeks for 6 months in 10 patients [60]. They observed a clinical improvement in 7 patients. Further research is needed to consider BT as a useful treatment in AGA.

Finally, an interesting non-medical treatment for AGA has arisen with scalp threading. Scalp microneedling releases growth factors, e.g. platelet-derived growth factor, and it is believed that the use of polydioxanone (PDO) threads can induce the same effect. A pilot study showed an increase in total hair counts at 12 weeks in 5 patients [61]. Further research will elucidate if it is an effective treatment for AGA.

8 Conclusions

The options for treatment in male AGA have multiplied in recent years. According to the published evidence, oral dutasteride and oral minoxidil are probably some of the most

effective medical treatments available. However, their use is limited as neither are FDA-approved options in hair loss. For patients concerned about AEs produced by oral medication, topical finasteride is very useful. Mesotherapy with dutasteride, PRP and LLLT remain as complementary options for patients who are receiving other concomitant treatment.

Declarations

Author contributions RG, SV-G, and DS-C designed the article and DS-C wrote the majority of the article. MD-S corrected and supervised the information and RG undertook the final corrections.

Funding No sources of funding were received to assist in the preparation of this article.

Conflicts of interest David Saceda-Corralo, Miguel Domínguez-Santas, Sergio Vañó-Galván, and Ramón Grimalt have no conflicts of interest in relation to the subject matter of this article.

Ethics approval This was a review and hence ethical approval was not required.

Consent to participate/publish Not applicable.

Availability of data and material Not applicable.

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