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GUIDELINES

Androgenetic alopecia in women and men: Italian guidelines adapted from European Dermatology Forum/European Academy of Dermatology and Venereology guidelines

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ABSTRACT

Androgenetic alopecia (AGA) is the most common form of alopecia, affecting up to 80% of men and 50% of women in the course of their life. AGA is caused by a progressive reduction in the diameter, length and pigmentation of the hair, resulting from the effects of the testosterone metabolite dihydrotestosterone (DHT) on androgen-sensitive hair follicles. Clinical presentation is different in men and women. Trichoscopy is used routinely in patients with androgenetic alopecia, for diagnosis and differential diagnosis with other diseases, allowing staging of severity and monitoring the progress of the disease and the response to treatment. Medical treatment of AGA includes topical minoxidil, antiandrogen agents, 5-alpha reductase inhibitors and many other options. This guideline for the treatment of androgenetic alopecia has been developed by an Italian group of experts taking into account the Italian pharmacological governance. The article is adapted from the original of the European Dermatology Forum (EDF) in collaboration with the European Academy of Dermatology and Venereology (EADV). It summarizes evidence-based and expert-based recommendations (S3 level).

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KEY WORDS: Alopecia; Therapy; Guidelines.

Androgenetic alopecia (AGA) is the most common cause of non-scarring alopecia, affecting respectively up to 50% of women and 80% of men in the course of their life,[1] with a frequency that increases with age after puberty.

Androgenetic alopecia is characterized by a progressive miniaturization of hair follicles usually occurring in a pattern distribution. The term AGA was introduced to define a form of alopecia developing under the influence of androgens against a background of genetically determined susceptibility of the hair follicle. Hair loss represent a problem for the patient for cosmetic and psychological reasons because hair symbolizes an important mirror of our image and a physical attractiveness to self-perception of beauty. The primary objective of this Italian guideline is to describe complete information about the disease and prescribing treatment for androgenetic alopecia. These guidelines are adapted from the original article under the guidance of the European Dermatology Forum (EDF) in collaboration with the European Academy of Dermatology and Venereology (EADV). This article summarizes evidence-based treatment for androgenetic alopecia according to Italian legislation (S3 level),[2] associated also with expert-based recommendations and most frequently prescribed options (Table I).

TABLE I.—*Summary of the most common treatment options for androgenetic alopecia with level of evidence, efficacy and safety.*

Therapy	Level of evidence	Efficacy	Safety
Male AGA			
Finasteride 1 mg QD	1	+++	+++
Dutasteride 0.5 mg QD	1	+++	++
Minoxidil 5% solution/foam	1	+++	++++
Transplantation	2	-	++
LLLT	2	+/-	++
PRP	3	+/-	+
PG analogs	/	+/-	+++
Female AGA			
Minoxidil 2% solution BID	1	+++	++++
Minoxidil 5% solution QD	3	+++	++++
Hormones	3	+	+
Transplantation	4	-	++
LLLT	2	+/-	++
PRP	3	+/-	+
PG analogs	/	+/-	+++

1. General evaluation

Androgenetic alopecia is a progressive non-scarring miniaturization of hair follicles located in characteristic areas of the scalp, in genetically predisposed people.

The clinical presentation of androgenetic alopecia can be different in men and women, sharing the same pathogenesis. A correct diagnosis is the first step to choose an efficacious therapy.

1.1 Objectives

- Confirm the diagnosis of AGA;
- differential diagnosis from other causes of hair loss (telogen effluvium);
- specify the severity of the disease on the scalp;
- evaluate other associated conditions (hirsutism, acne, hormonal imbalances);
- consider therapeutic options and prognosis.

1.2 Pathogenesis

Hair thinning results from the effects of the testosterone metabolite dihydrotestosterone (DHT) on androgen-sensitive hair follicles, which are mainly present in the frontal and temporal regions and at the vertex. Androgen sensitivity is genetically determined and depends on androgen reception sensitivity and on the extent of DHT production through 5-alpha reductase enzymes. The sensibility of the hair follicle to androgens is determined by specific polymorphisms of the receptor gene. Among these, the Stu1 polymorphism has the most significant association.[3] Moreover, the role of prostaglandins in modulating the hair follicle cycle is emerging. Clinical studies have shown that PGD2 inhibits hair growth while PGE2/F2a promotes growth and the former has been shown to be elevated in male balding scalp while PGE2 has been shown to be reduced.

1.3 Patient's history

- The physician should ask for familiar history of AGA or hair loss;
- the physician should search for personal history of the patient, including drug intake and general condition;
- the physician should obtain a detailed medical history specifying the date of onset and evolution of signs and symptoms;
- the physician should understand about the history of hair loss: is it hair shedding or hair thinning? Increased hair shedding may not be associated with hair thinning as well as hair thinning may not be associated with increased loss of hair;
- it is also important to ask about the modality of onset of the disease and the course over time, that can be episodic or continuous; if past treatments have been prescribed and the response to these therapies.

2. Clinical examination

2.1 Male

In male androgenetic alopecia (MAGA) the physician can observe:

- classical pattern: fronto-temporal recession, hair thinning at the top of the head, thinning at the vertex, complete alopecia at the top of the head, maintenance of the hair in the parietal and occipital areas;
- non-classical/female pattern: the frontotemporal attachment is maintained, and the thinning affects the top of the head.

2.2 Female

In female androgenetic alopecia (FAGA) the physician can observe:

- classical pattern: enlargement of the central parting, enlargement of the central parting which becomes wider and accentuated in the frontal region (Christmas tree pattern), diffuse thinning without fronto-temporal recession;
- non-classical/male pattern: hair thinning associated with fronto-temporal recession or vertex hair thinning.

2.3 Scale of severity

The severity of the male AGA is commonly evaluated using the Hamilton-Norwood Scale that distinguishes 12 de-

grees of baldness based on the location and extent of the disease.

The severity of female AGA can be assessed using the Ludwig Scale, which distinguishes 3 stages, or the Sinclair (5 stages) or Savin scales (6 stages). Androgenetic alopecia is very common; therefore – not surprisingly – it may accompany other forms of hair loss. Cases of telogen effluvium often occur in patients with underlying androgenetic alopecia. Therefore, a search for treatable causes of telogen effluvium (*e.g.* anemia, hypothyroidism), especially in patients with an abrupt onset or a rapid progression of their disease, is indicated.[4]

3. Laboratory/instrumental investigations

• In male AGA laboratory exams are not required, except in case of personal history of specific deficiency or other condition that can induce blood abnormalities: in these cases, a complete blood tests series can be prescribed. In female, the disease can be associated with menstrual irregularities or amenorrhea, or other skin manifestations of hyperandrogenism such as acne or hirsutism: in this case the physician should evaluate the presence of ovarian or adrenal hyperandrogenism, prescribing the luteal phase the dosage of total testosterone, SHBG, DHEAS, androstenedione, progesterone, estradiol, 17-hydroxy-progesterone, prolactin and cortisol. The results may reveal that blockade of androgen action can restore the sensitivity of the GnRH pulse generator to estradiol and progesterone. They also suggest that reduction of excess androgen secretion or blockade of androgen action may be an important element in restoring normal ovarian regulation of GnRH secretion in polycystic ovarian syndrome and may have a place in therapeutic regimens aimed at establishing cyclic ovulation in women with PCOS;[5]

• the diagnosis of polycystic ovarian syndrome has to be excluded in case of moderate or severe alopecia, even in the absence of acne or hirsutism: the physician should confirm this association by an ovarian ultrasound;

• a collaboration with the gynecologist or endocrinologist in these cases is very important, even for the therapeutic management;

• in women, it is always important to exclude factors that may aggravate AGA, such as iron deficiency (recommended ferritin values >30 mcg/L), vitamin D deficiency[6] – although there is still no clinical evidence of therapeutic results – a thyroid dysfunction[7] and hypocaloric and/or unbalanced diets.[8]

3.1 Pull test

The pull test allows evaluating the phase in which the hair is located at the time of loss. It is important to quantify the number of hairs that have fallen out and it is simple to perform it: using the thumb and index exert a pull slight but steady of a tuft of 60 hair at 2 cm from the scalp. The hairs are obtained with a gentle traction. The test is usually performed in 4-6 different areas of the head: frontal, parietal and occipital part of the scalp. A positive pull test is indicated in the case of extraction of more than 6 hair but it is considerably influenced by the day of the last shampoo, daily cosmetic procedures, the traction force of the operator.

In androgenetic alopecia, the pull test typically shows telogen roots. A positive pull test at the level of the androgen dependent areas indicates the synchronization of the characteristic cycle of the disease. A positive pull test at the level of the entire scalp indicates an associated telogen effluvium.

3.2 Trichogram and phototrichogram

A clinical hair-pull test is supplemented by a trichogram, in which 20-50 hairs are epilated with a rubber-shod artery clamp and then analyzed under a microscope. The differently formed roots in each of the growth phases can then be counted. A percentage of hairs in the telogen phase that exceeds 20% indicates increased hair shedding. A non-invasive phototrichogram can also yield an estimate of the anagen-to-telogen ratio but cannot reveal root anomalies such as dystrophic hair.[9]

3.3 Trichoscopy

Scalp dermoscopy or trichoscopy represents a non- invasive technique for the evaluation of patients with hair loss that allows magnified visualization of the hair and scalp skin.[1, 10]

Trichoscopy reflects the pathophysiology of androgenetic alopecia because it shows the follicular miniaturization where the hair became shorter, thinner and paler, the diameter variability and a shorter anagen phase and it explains the empty follicle phenomenon due to the prolongation of kerogen phase.

Today, trichoscopy is the most important tool for diagnosing androgenetic alopecia and it completely substituted the scalp biopsy.

Trichoscopic signs of androgenetic alopecia are:[11]

• reduced hair thickness with the presence of:
  • increased number of hair with a diameter less than

0.03 mm due to hair miniaturization, especially evident in the frontal area. The presence of more than 10× of thin hair, below than 0.03 mm, in the frontal area is considered a major diagnostic criterion of androgenetic alopecia;

• anysotrichosis: as hair miniaturization does not equally affect all the hair follicles of the same area, the result is the simultaneous presence of terminal (>0.05 mm), intermediate (0.03-0.05 mm), and miniaturized hairs (<0.03 mm in diameter). In androgenetic alopecia a variation of the diameter that affects more than 20% of the hair of the androgen-dependent regions is considered a major diagnostic criterion of androgenetic alopecia. This sign, which is more easily evaluated at a magnification of 40-50×, is very useful for diagnosing initial AGA.

• Reduced number of hair:

• in severe AGA, the presence of yellow dots in androgen-dependent areas is characteristic: they correspond to empty follicles or they contain completely miniaturized hairs. The presence of empty follicles is due to a not accompanied telogen phase, a coincident new early anagen, but it ends with teloptosis leaving the follicle empty. In AGA, the number of follicles in kenogen phase increases in parallel with miniaturized hair.[12] If the scalp is exposed to the sun, these follicles appear as pinpoint white dots. These yellow-pink empty follicular openings are due to sebaceous hypertrophy and for this reason they have a sebaceous appearance. Males are more affected than females, especially on the frontal area, better seen with high magnification (40-50×).[13] In the frontal area, the presence of more than four yellow dots in four images at 70-times magnification is a major diagnostic criterion of AGA;

• reduced number of hair per pilosebaceous unit. Normally 1-3 hairs of the same follicular unit emerges from the same ostium,[11, 14] in AGA an increased percentage of single-hair per pilosebaceous units emerge in the ostium especially in the frontal area, always comparing with the occiput;

• trichoscopy can also show peripilar depressions, which appear as brown, slightly depressed halos, which extend for about 1 mm in diameter around the emergence of the hair shaft.[15] They are found more often in patients with initial forms, in the frontal area and high hair density. They are probably a sign of inflammation of the superficial perifollicular dermis in histological specimens, where it is related to mast cell activation with PGD5 secretion.[16]

3.4 Biopsy

In doubtful cases, a scalp biopsy (5 mm punch) can be performed. The detection of the miniaturized follicles is diagnostic. Important findings are a decrease of terminal hairs, anagen hairs and an increase of vellus like hairs, telogen hairs and fibrous streamers. A mild to moderately dense perifollicular lymphohistiocytic inflammatory infiltrate may be seen around the infundibulum. Biopsy of female AGA has similar features as male AGA.[1]

4. Therapeutic management

4.1 Objectives

• Arrest the progression of the disease;
• induction of hair regrowth;
• treat associated diseases, such as seborrheic dermatitis;
• treat associated conditions such as hirsutism, acne, hormonal imbalances, in synergy with the gynecologist or endocrinologist;
• choose the specific treatment based mainly on age and severity of the disease;
• limit the side-effects related to the therapy and evaluate the safety aspects of it;
• evaluate the efficacy, safety and tolerance of the treatment;
• improve the quality of life of patients: considering that the patient has to bear the full costs of the treatment, consideration of patient preference also regarding the costs is important to evaluate;
• the patient and the dermatologist should choose together the best option of treatment, considering evidence, expected results, compliance and costs.

4.2. Topical treatment

4.2.1 Minoxidil

Minoxidil still represent a milestone in the treatment of androgenetic alopecia: it has been known for over 30 years as "hair growth stimulator" even if the precise mechanism of its action is not completely understood.[17] The drug cannot be prescribed on the Italian National Health Service. We suggest prescribing the original formulation rather than the generic one, whose bioavailability is not always known and standardized, moreover its preparation can be also operator dependent.

• In males, the majority of studies assessing the efficacy of minoxidil in male AGA obtained grade A2 and B evidence (A2=22, B=18, C=8) resulting in evidence level 1.[2] Minoxidil 5% solution applied twice daily on androgen – dependent scalp areas are more effective than the 2% solution (level of evidence 2) in male AGA: in details, the 2% solution twice daily has a level of evidence

1. The dosage is 1 mL twice daily. Treatment should be continuous and should not be suspended to maintain efficacy;

• many studies investigate the efficacy of topical minoxidil in female patients with AGA. Seven studies obtained grade A2 evidence, nine studies grade B evidence, three studies grade C evidence resulting in an evidence level 1.[2] Minoxidil 2% solution twice daily was effective in preventing progression and improve AGA in female patients (evidence level 1). The dosage is 1 ml twice daily. The efficacy of minoxidil 5% solution applied once daily was comparable to minoxidil 2% solution applied twice daily (level of evidence 2). This option can be chosen on the basis of the preference of the patient considering life and work habits.

As in male AGA, treatment should be continuous and should not be suspended to maintain efficacy.

Some studies, starting with those of Bazzano in the 80s, suggest a role in topical all-trans-retinoic acid (tretinoin) alone and in combination with 0.5% minoxidil for the promotion of hair growth in subjects with androgenetic alopecia. After 1 year, the combination of topical tretinoin with 0.5% minoxidil resulted in terminal hair regrowth in 66% of the subjects studied. Tretinoin was shown to stimulate some hair regrowth in approximately 58% of the subjects studied. Tretinoin has been shown to promote and regulate cell proliferation and differentiation in the epithelium and may promote vascular proliferation.[18]

However, in other studies minoxidil would not be effective at low concentration[19] while the 5% minoxidil results suggest the introduction of retinoic acid in the treatment protocol, with optimal results both *in vitro* and *in vivo*. In this last case it is noted for the possibility of applying the solution once a day.[20, 21]

4.2.1.1 Response to treatment

It should be assessed at 3-6 months and then every year. This guidelines are based on pertinent articles retrieved by a selective search in PubMed, on the current German and European guidelines, and on the authors' clinical and scientific experience. At least presenting seasonal recurrences, go to: can be performed to assess the course of the disease and the response to the therapy monitoring with an objective method[22] (Figure 1).

4.2.1.2 Useful instructions for the patient

• A transitory increased telogen effluvium during the first month of the treatment can occurs;

• interruption of topical minoxidil is followed by increased hair loss, that starts 3-4 months after discontinuation of the drug.

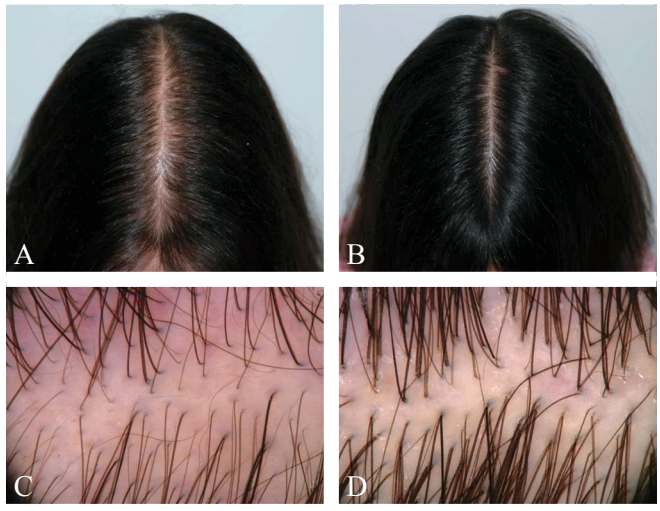

Figure 1.—Female patient affected by AGA treated with minoxidil 2% lotion, twice a day: A) clinical picture at the first visit; B) clinical picture after six months of therapy; C) trichoscopic picture at the first visit; D) trichoscopic picture after 6 months of therapy.

4.2.1.3 Side effects of minoxidil

• Hypertrichosis: it can be due to local spreading that induce contamination of adjacent skin or to individual sensitivity;

• contact dermatitis: an irritant dermatitis is often cause by the 5% minoxidil solution that contain high content of propylene glycol, while the allergic form can be due to the glycol or the minoxidil itself (patch testing is required to confirm the diagnosis);

• minoxidil vehicle in foam is a good alternative option for patients with contact allergy to propylene glycol but is not available in Italy. It can be ordered on-line or bought in USA or in galenic form.

4.2.1.4 Pregnancy and lactation

The discontinuation of topical minoxidil is recommended, because until up today few studies have defined the safety profile of minoxidil when taken during pregnancy. The drug is capable of crossing the biologic barriers, accumulating into the lipids, so that brain and fetal concentrations may be higher than those found in serum.

4.2.2 Prostaglandin analogs

The prostaglandin analogs (PGAs), such as Latanoprost®, and Bimatoprost® are used topically in the treatment of

glaucoma and ocular hypertension but used topically they cause eyelash growth and pigmentation. Bimatoprost® is the only FDA-approved topical drug for hypotrichosis of the eyelashes, because it increases the anagen phase in telogen hair follicles through targeting the dermal papilla. The use of these drugs in androgenetic alopecia is suggested by the literature but not yet supported by trials and is off-label in Italy, and they cannot be prescribed on the Italian National Health Service. The prescription requires a patient informed consent form.

Only one study, a randomized comparison study, evaluates the use of topical latanoprost 0.1% *versus* placebo in 16 men with mild (Hamilton II-III) patterned alopecia. In 50% of cases a "good clinical response" was evident.[23]

4.2.2.1 Response to treatment

• Clinical and trichoscopical examination should be performed every 3-6 months;

• the treatment should be continued at least for 2-3 years if efficacy is evident.

4.2.2.2 Side effects

• Folliculitis, erythema, and sensation of burning.

4.3 Systemic treatment

4.3.1 Alpha-reductase inhibitors

4.3.1.1 Finasteride in male

In males, the intake of finasteride 1 mg daily led to a significant increase in total hair counts compared to placebo (evidence level 1).[2] It can be prescribed only if the beard is completely formed. The efficacy of finasteride is related to administration and for the maintenance of results the treatment should be protracted over time.

Finasteride 1 mg and 5% topical minoxidil is the best combination therapy in male AGA and led to considerable improvement better than monotherapy.

The response to treatment is the following:

• it is evident after 6-8 months, and it is higher at the vertex than in other affected areas;

• it should be assessed at 6 months and then every year, and the treatment should not be stopped to maintain efficacy (Figure 2);

• clinical results in patient of more than 40 years old are lower than in younger patients.[24]

The side effects are the following:

• sexual sphere: loss of libido, erectile dysfunction, and problems with ejaculation;[25, 26]

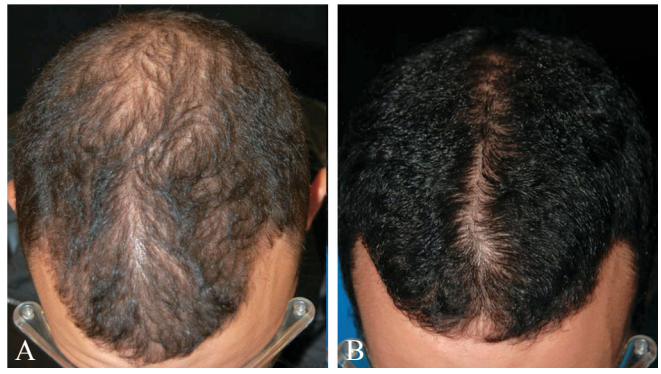

Figure 2.—Important improvement of a male patient affected by AGA treated with Finasteride 1mg/day: A) clinical picture at the first visit; and B) after 1 year of therapy.

• these effects occur usually at the first administration and they disappear with the withdrawal of the drug;

• other reported side-effects of finasteride are gynecomastia, testicular pain, hypersensitivity reactions;

• a possible depressive alteration of mood after finasteride use has been reported in patients with a predisposition to psychological disorders;[27, 28]

• post-finasteride syndrome (PFS): symptom persist for months or years after drug discontinuation,[29] including sexual dysfunction, depression, suicidal ideation, impaired cognition, probably occurring in men with history of sexual deficit or psychological or psychiatric illness. The existence and entity of this condition is currently a subject of debate among the experts;

• in patients with active depression or current sexual dysfunction finasteride is therefore contraindicated;

• reduction of prostate specific antigen: it is important in the screening procedure for prostate cancer in men.

4.3.1.2 Finasteride in female

Finasteride is not licensed for women, and the prescription is in off-label regimen: for this reason it can't be prescribed on the Italian National Health Service and a patient informed consent form is required.

In females, oral finasteride should only be prescribed in post-menopausal women or in women willing to use oral contraceptives. From a review of the literature, the estimated effective dosage is 5 mg in female normo-androgenetic pre- and post-menopausal patients, but there are not placebo-controlled clinical trials in this population and additional research is required, including younger female patients and patient with hyperandrogenism. finasteride could also be used for topical use, as shown in several studies[30-34] and it represents a very interesting field in hair

research but there are not yet standardized usage protocols, therefore its use remains off label.

In females, as for male patients, the response to treatment is evident in clinical and trichoscopical examination after 6-8 months and it should be assessed every 1 year, and the treatment should not be stopped to maintain efficacy.

In pregnancy and lactation the drug is contraindicated in women that may become pregnant (or already pregnant), since it can cause feminization of a male fetus. Moreover, if taken by women of childbearing age, the use of a safe contraceptive method is indispensable.

4.3.1.3 Dutasteride (Avodart®)

Dutasteride is a more potent reductase inhibitor than finasteride, as it inhibits both types I and II 5 -reductase. It is currently FDA approved for the treatment of symptomatic benign prostatic hypertrophy (BPH), but not for the treatment of patterned alopecia.[35] The drug cannot be prescribed on the Italian National Health Service and its prescription requires a patient informed consent form.

• In males, dutasteride, a synthetic 4-azasteroid, is a selective and competitive inhibitor of both type-1 and type-2 isoenzymes of 5-α-reductase. In men, five studies (4/5 placebo-controlled) investigating dutasteride in AGA were included in the evidence-based evaluation, resulting in a level of evidence 1.[2] In all studies, significant mean increases from baseline hair count were reported for dutasteride 0.5 mg daily. This daily dosage results more rapid and potent at type II inhibition, producing a greater reduction in serum DHT (90%) as compared to finasteride at 1 mg daily (70%). In the treatment of male AGA there is clear evidence of its validity.[36] Hair improvement is also evident with different dosages and *versus* finasteride.[37] It can be an alternative in patients non-responsive to a 1- year therapy with finasteride. The response to treatment shows an evident improvement in clinical and trichoscopical examination after 6-8 months. Monitoring should be assessed every 1 year, and the treatment should not be stopped to maintain efficacy. As finasteride, the side effects are the same reported after the use of dutasteride.

• Studies with this drug in women are lacking. The prescription is off label in Italy for female androgenetic alopecia. As for the other mentioned treatment, it cannot be prescribed on the Italian National Health Service and a patient informed consent form is needed. One report of successful treatment with the use of dutasteride for female pattern hair loss (FPHL) has been published, with no observed side effects in a 46-year-old patient who had failed both minoxidil and finasteride treatment.[38]

With regard to the response to treatment, as for male AGA, it is recommended to monitor the patient after 6 months from starting therapy and then every 1 year if efficacy is present.

In pregnancy and lactation the drug is contraindicated in women that may become pregnant (or already pregnant), since it can cause feminization of a male fetus; if taken by women of childbearing age, the use of a safe contraceptive method is indispensable.

4.3.2 Hormones

In males, there is no evidence to support the use of oral estrogens or anti-androgens in male patients (evidence level 4).

In females, four studies met the inclusion criteria, of which only one was placebo-controlled, resulting in level of evidence 3.[2] There is limited data that oral cyproterone acetate (CPA) may be helpful in women with AGA and hyperandrogenism.[39]

4.3.2.1 Cyproterone acetate (Androcur®)

It acts by interfering with the binding of 5-alpha DHT to the androgen receptor and by inhibiting the secretion of FSH and LH, as the result of its progestinic action. Contemporary administration of estrogen (ethynyl estradiol or oral contraceptives) is mandatory, to enhance the antiandrogen activity.

Side effects include mood changes, fatigue, mastodynia, hypertension, and weight gain. an increased risk of venous thromboembolism in patients taking estrogen-containing oral contraceptives is reported, which may be greater in those taking cyproterone acetate (CPA) than other oral contraceptives. moreover, it is contraindicated in patients with liver disease due to potential liver toxicity.

4.3.2.2 Spironolactone (Aldactone®)

Spironolactone arrests hair loss progression with a favorable long-term safety profile.

It was prescribed for the treatment of polycystic ovary syndrome and associated hypertension, with the noted benefit of improved hirsutism. Since then it has been used off-label as medical treatment for hirsutism, thanks to the reduction of adrenal androgen production and the competitive blockade on androgen receptors in target tissues.

It is FDA approved for primary hyperaldosteronism;

edematous conditions secondary to liver failure, heart failure, or nephrotic syndrome; and hypertension. It has been accepted but not approved as a treatment for acne, hirsutism, and FPHL due to the antiandrogen properties.

The drug cannot be prescribed on the Italian National Health Service and its prescription requires a patient informed consent form.

The standard dosage for FPHL is 100-200 mg daily. There have been no randomized controlled trials evaluating the efficacy of spironolactone on FPHL, but some case series support its benefit. In a case study of four patients, spironolactone at the dose of 200 mg daily reduced hair loss by 50-62.9%, increasing the total number of anagen hairs.[40-42] Higher doses are likely to be more effective.[43-46]

Side effects of spironolactone are dose dependent, and include hypotension, hyperkalemia, fatigue, headache, weight loss, increased urinary frequency, and dry skin. Among the side effects menstrual irregularities, gynecomastia, and breast tenderness can appear due to the antiandrogenic effect were also observed.

spironolactone is pregnancy category D (considered teratogenic) and has been shown to be tumorigenic in chronic toxicity studies in rats[47] and should only be used in pregnancy or lactation when maternal benefit outweighs fetal risk. Co-administration with an oral contraceptive is recommended. Moreover, blood pressure should be monitored and the dose should be reduced if there are reported symptoms of hypotension.

4.3.2.3 Flutamide (Drogenil®, Eulexin®, Flutamide®)

Flutamide is a nonsteroidal selective antiandrogen that inhibits the binding of androgens to their receptors. Flutamide may be a treatment option in patients with normal androgen levels, but a standardized dosage has not been established (250 mg/day, 125 mg/day, or 62.5 mg/day).[48]

An open-label study suggested that flutamide at a dose of 250 mg daily resulted in the most improvement in hair growth when compared to finasteride 5 mg daily and cyproterone acetate 50 mg daily.[49]

Side effects are hepatic dysfunction (dose dependent) and liver enzymes should be monitored periodically. Hepatic failure is rare.

Monitoring hormones treatment includes a performance of clinical and trichoscopical examination every 3-6 months. During hormones therapy, a collaboration with the gynecologist or endocrinologist is very important, in order to choose the most suitable drug and for the therapeutic management.

The treatment should not be stopped at least for 2-3 years if efficacy is evident.

5. Platelet-rich plasma

Two studies assess the efficacy of platelet-rich plasma (PRP) in male and female patients with AGA, resulting in level of evidence 3.[50, 51]

New clinical studies are needed to standardize the technique. Important questions remain open: additional components, minimum required frequency of treatments for effective results and optimal duration of the therapy to maintain the results. Moreover, there is no official protocol, so in the literature there are different data without standardization and there is no consensus if PRP has a proved efficacy except a placebo-controlled based on 2 studies where is evidence to support the use of PRP in men and women with AGA.[52, 53]

Side effects include pain, edema, tenderness: these signs can be observed after the procedure and are usually transient. There are also rare side effects as persistent trichodynia, telogen effluvium, scalp psoriasiform reaction and scarring.

6. Surgery

Severe AGA scarcely benefits from medical cure: whatever the improvement the patient achieves, the alopecia remains evident. Hair transplantation can be a possible solution in these cases.

In (male) AGA, there are few studies that compare hair surgery *vs*. no hair transplantation, and a level of evidence 2 has been attributed. In female AGA, there is lack of evidence concerning hair surgery. Hair transplant surgery creates consistently natural appearing hair. As with all techniques, there are controversies regarding the optimal method for performing the procedure. Some of the current controversies in hair transplant surgery include optimal donor harvesting techniques, elliptical donor harvesting *versus* follicular unit extraction. The final result can be assessed after 9-12 months. Combination with other therapies, such as minoxidil, can be prescribed to reduce postoperative progression of the disease.[54]

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Among contraindications surgery should does not be performed in patients with body dysmorphic disorder or unrealistic expectations.

7. Low-level laser (light) therapy (LLLT, laser hair comb)

Both in male and female AGA, these techniques reach a level of evidence 2, but further controlled randomized clinical studies are required to establish their efficacy and safety profile. The therapy is performed at home by the patient and is very easy to use.

Low-level light therapy (LLLT) utilizes devices with light-emitting diodes (650-900 nm) which alter cellular function, such as levels of prostaglandins, cytokines, and tumor necrosis factor: it has been hypothesized that light may activate hair follicles, increasing blood flow to the hair follicles, or stimulating hair into the anagen phase.

In 2007, the HairMax® laser comb (Lexington International LLC, Boca Raton, FL, USA) was approved by the FDA as the first and only medical laser device marketed for the treatment of male pattern hair loss, with subsequent approval for FPHL in 2011. Most recently, The Oaze® (Won Technology, Daejoen, Korea), a helmet-shaped LLLT device emitting wave lengths of 630 nm, 650 nm, and 660 nm, was evaluated in a randomized, double-blind, sham device-controlled trial including men and women with patterned hair loss. Investigator global assessments showed improvements in the treatment group, but patient perception was not positive. Lasers are a valid option for patient with adverse effects to other treatments, or as adjuvant to other medical therapies.[55] Reported adverse events include scalp irritation or erythema.

Conclusions

Androgenetic alopecia is a progressive disease that, if left untreated, tends to worsen with time. Progression of the disease can be slow or very fast, especially in patients with a strong family history or with hormonal disturbances. Regular clinical, trichoscopical and (photo)trichogram follow-ups are very important to monitor the disease activity and treatment tolerance. If used correctly, in most of cases available medical treatments for AGA arrest the progression of the disease and reverse miniaturization. In some advanced cases hair replacement surgery is the only option.

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