Review Article

Drug Therapy

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TREATMENT OF HAIR LOSS

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HAIR loss is a common and distressing symptom. With the approval of two drugs that promote hair growth — finasteride and minoxidil — we can now treat patients with some types of hair loss. Both drugs influence the hair-growth cycle and increase the length and diameter of existing hair, although their mechanisms of action differ. In this article, I will focus on the treatment of two common problems, androgenetic alopecia and alopecia areata, both of which involve a reversible alteration of the hair-growth cycle.

THE HAIR-GROWTH CYCLE

Hair growth is cyclic, with phases of growth (anagen), involution (catagen), and rest (telogen) (Fig. 1).[1-3] The cycles of active growth and rest are regulated by complex messages between the epithelium and the dermis that are not yet well understood. In a normal scalp, most follicles are growing (90 to 95 percent), a few are undergoing involution (less than 1 percent), and the remainder are resting (5 to 10 percent).[4-6] At the end of telogen, hair is released and shed and the next cycle is initiated. Each day, up to 100 hairs in telogen are shed from the head and about the same number of follicles enter anagen. The duration of anagen determines the length of hair, and the volume of the hair bulb determines the diameter.

We are born with all our terminal hair follicles — approximately 100,000 on the scalp — that are predetermined to grow long, thick hair. Other follicles are predetermined to grow vellus hair, which is short, fine, and relatively nonpigmented and covers much of the body. Follicles can become larger or smaller under systemic and local influences that alter the duration of anagen and the volume of the hair matrix. Androgens are important in regulating hair growth. At puberty, androgens increase the size of follicles in the beard, chest, and limbs and decrease the size of follicles in the bitemporal region, which reshapes the hairline in men and many women.

ANDROGENETIC ALOPECIA

Androgenetic alopecia is hereditary thinning of the hair induced by androgens in genetically susceptible men and women.[7,8] This condition is also known as male-pattern hair loss or common baldness in men and as female-pattern hair loss in women. Thinning of the hair usually begins between the ages of 12 and 40 years in both sexes, and approximately half the population expresses this trait to some degree before the age of 50.[9,10] The pattern of inheritance is polygenic.[11,12]

Pathophysiology

In susceptible hair follicles of the scalp, dihydrotestosterone binds to the androgen receptor, and the hormone-receptor complex then activates the genes responsible for the gradual transformation of large, terminal follicles to miniaturized follicles.[13-16] With successive hair cycles, the duration of anagen shortens and the follicles become smaller, producing shorter, finer hairs that cover the scalp poorly. These miniaturized hairs of various lengths and diameters are the hallmark of androgenetic alopecia.[8,10,17] At the same time, the number of follicles per unit of area remains the same.

Dihydrotestosterone is formed by the peripheral conversion of testosterone by 5α-reductase. There are two isoforms of 5α-reductase — type 1 and type 2 — which, together with other enzymes, regulate specific steroid transformations in the skin. Young men and young women with androgenetic alopecia have higher levels of 5α-reductase, more androgen receptors, and lower levels of cytochrome P-450 aromatase, which converts testosterone to estradiol, in hair follicles in the frontal region of the scalp than in the occipital region.[18] The various clinical patterns of androgenetic alopecia in men and women may reflect quantitative differences in the levels of 5α-reductase, the number of androgen receptors, and the levels of aromatase in specific regions of the scalp at various ages.

Treatment in Men

In men, androgenetic alopecia ranges from the bitemporal recession of hair, to thinning of the frontal and vertex regions of the scalp, to complete baldness and loss of all hair except the occipital and temporal fringes. In some cases, men have diffuse thinning

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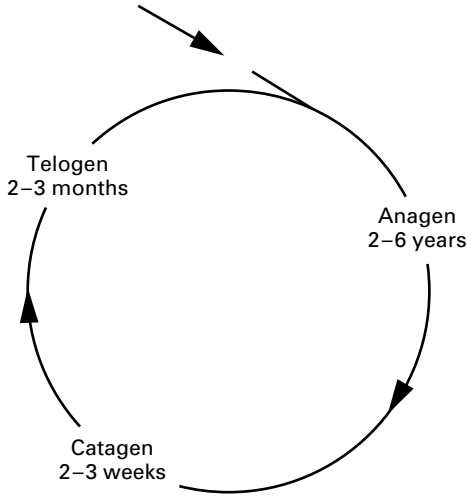

Figure 1. Cycle of Scalp-Hair Growth.

Every scalp hair has a phase of growth (anagen), which lasts two to six years; a phase of involution (catagen), which lasts two to three weeks; and a resting phase (telogen), which lasts two to three months and is followed by shedding of the hair. The cycle is then repeated. All hair loss affects or disrupts one of these phases.

TABLE 1. SELECTIVE ACTIONS OF TESTOSTERONE AND DIHYDROTESTOSTERONE.

Testosterone
Spermatogenesis
Increase in bone and muscle mass
Growth of phallus and scrotum
Deepening of voice
Sex drive
Growth of axillary and lower pubic hair
Dihydrotestosterone
Growth of prostate
Growth of terminal hair (beard, limbs, trunk, external ears, nostrils)
Bitemporal reshaping of hairline
Androgenetic alopecia
Acne

all over the scalp. The pattern of hair loss, combined with onset at an early age and the presence of miniaturized hairs, supports the diagnosis.

The goal of therapy is to increase coverage of the scalp and to retard further hair thinning. In the United States, oral finasteride, at a dose of 1 mg per day, and topical solutions of 5 percent and 2 percent minoxidil are currently the only drugs approved for promoting hair growth in men with androgenetic alopecia. Both drugs can increase coverage of the scalp by enlarging existing hairs, and both retard further thinning, in both the vertex and the frontal regions. However, neither drug restores all the hair, and the response differs among men. A good candidate for treatment has definite thinning and many miniaturized hairs. If thinning is minimal, the main perceived response may be retardation of further thinning. Neither drug benefits men who are completely bald or those with bitemporal recession without visible hair. In general, treatment for 6 to 12 months is needed to improve scalp coverage. Continued treatment is needed to maintain benefit; if treatment is stopped, the benefits will be lost within 6 to 12 months and hair density will be the same as it would have been without treatment.

Finasteride

Finasteride is a competitive inhibitor of type 2 5α-reductase and inhibits the conversion of testosterone to dihydrotestosterone.[19-22] The rationale for the use of finasteride to treat male-pattern hair loss is based on the absence of androgenetic alopecia in men with congenital deficiency of type 2 5α-reductase[19,23-26] and the presence of increased 5α-reductase activity and dihydrotestosterone levels in hair follicles of men with balding scalps.[16,18,27,28] Finasteride rapidly lowers serum and scalp dihydrotestosterone levels by more than 60 percent. It has no affinity for the androgen receptor and therefore does not interfere with the actions of testosterone (Table 1), and it has no androgenic, estrogenic, progestational, or other steroidal effects.[16,19]

In three randomized, double-blind, placebo-controlled studies, a total of 1879 men who were 18 to 41 years old with mild to moderately severe thinning of the hair but not complete baldness received oral finasteride at a dose of 1 mg per day or placebo for one year.[29-31] Two of these studies enrolled a total of 1553 men with loss of hair predominantly at the vertex, and the third enrolled 326 men with predominantly frontal hair loss. As compared with placebo, finasteride significantly increased hair counts and improved scalp coverage, as was evident in photographs of both vertex and frontal regions.[29-31]

In the men with hair loss at the vertex, the initial treatment was continued for a second year, but some men who received placebo for the first year were given finasteride and some who initially received finasteride were given placebo in the second year (Fig. 2). In the second year, hair counts remained stable at the increased level in the men who continued to receive finasteride. Hair counts decreased in the men who were switched from finasteride to placebo after one year, whereas the counts increased in those switched from placebo to finasteride. There was a progressive increase in scalp coverage, as determined by global photographs of the scalp, in 66 percent of the finasteride group, as compared with 7 percent of the placebo group, after two years.[29] These results indicate that the number of responding hairs is established after about one year and that continued

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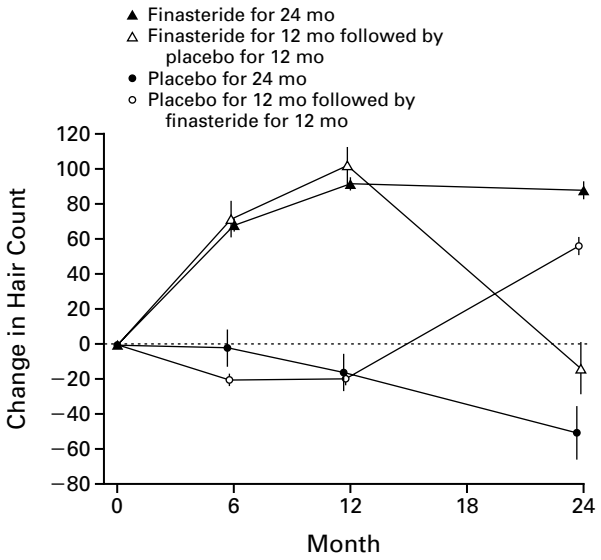

Figure 2. Change in the Mean (±SE) Hair Count from Base Line (Month 0) at the Anterior Leading Edge of the Vertex Thinning Area in Men Given 1 mg of Finasteride or Placebo Daily for 24 Months.

In the second year, some men who received placebo during the first 12 months were given finasteride and some who initially received finasteride were given placebo. The dotted line indicates no change. Adapted from Kaufman et al.[29] with the permission of the publisher.

treatment increases the length, diameter, and pigmentation of these hairs so that coverage of the scalp increases.

After two years of treatment with finasteride, about two thirds of men have improved scalp coverage, about one third have the same amount of hair as they did at the outset, and about 1 percent lose hair. Since the miniaturization of follicles occurs over the course of many years, reversal of this process also takes many years. With treatment for more than two years, the clinical impression is that scalp coverage continues to increase; five-year controlled studies are in progress to verify this impression. It is not known to what extent follicles will enlarge, and there is no way to identify the men who will have the best response.

In December 1997, 1-mg tablets of finasteride were approved by the Food and Drug Administration (FDA) for the treatment of androgenetic alopecia in men. It is to be given once daily, with or without food. No dosage adjustments are needed on the basis of age or renal function. It is metabolized in the liver and should be used with caution in men with abnormal liver function. In men who are 60 years of age or older, finasteride may not be an effective treatment for male-pattern hair loss, because type 2 5α-reductase activity in the scalp may not be as high as in younger men. This decreased activity may partly explain why there have been few reports of reversal of male-pattern hair loss in men who were predominantly in their 60s and 70s and who were treated with 5 mg of finasteride daily for benign prostatic hyperplasia.

Finasteride at a dose of 1 mg daily is safe and well tolerated. The only adverse effects in the clinical trials, which included 1879 men, were reversible and were reported by slightly more men in the finasteride than in the placebo group; these effects included decreased libido in 1.8 percent of the men in the finasteride group, as compared with 1.3 percent in the placebo group; erectile dysfunction in 1.3 percent and 0.7 percent, respectively; and ejaculatory dysfunction in 1.2 percent and 0.7 percent.[31] These sexual adverse effects gradually disappeared during prolonged treatment and disappeared in days or weeks after treatment was discontinued.

In men 18 to 41 years old who were taking 1 mg of finasteride daily, serum prostate-specific antigen levels decreased by 0.2 ng per milliliter,[31] which was not a clinically important reduction. However, in older men with benign prostatic hyperplasia, finasteride at doses of 1 mg or 5 mg daily decreases serum prostate-specific antigen levels by about 50 percent. In older men who are taking finasteride, the results of a prostate-specific antigen test should be doubled to compensate for the effect of the drug.[32-34]

Minoxidil

Minoxidil promotes hair growth when it has been affected by various conditions, including androgenetic alopecia. It increases the duration of anagen and enlarges miniaturized and suboptimal follicles, irrespective of the underlying cause. For example, in addition to its effectiveness in patients with androgenetic alopecia, minoxidil promotes hair growth in patients with alopecia areata, congenital hypotrichosis, and loose anagen syndrome. Minoxidil was developed to treat hypertension, and this aspect of the drug's action is the one that is best understood. It is a potassium-channel opener and vasodilator. Its mechanism of action with respect to the stimulation of hair growth is not known, but it appears to be independent of vasodilatation.[35-38] The addition of minoxidil to cultures of hair follicles increases survival.[35]

A 2 percent solution of topical minoxidil was approved by the FDA in 1988 for promoting hair growth in men with androgenetic alopecia. Its efficacy was established in a 12-month placebo-controlled study of 2294 men who were 18 to 50 years old and had mild-to-moderate thinning of the hair at the vertex. Treatment with minoxidil significantly increased hair counts.[10,39-41] Histologic studies confirmed that minoxidil increases the diameter of the hair shaft.[42]

In 1997, a 5 percent solution of topical minoxidil was approved by the FDA as an over-the-counter treatment for promoting hair growth. In a 48-week study

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of twice-daily treatment with the 5 percent solution, the 2 percent solution, or placebo in 393 men who were 18 to 49 years old and had mild-to-moderate thinning at the vertex, hair counts were 45 percent higher among the 157 men in the group receiving 5 percent minoxidil than among the 158 men in the group receiving 2 percent minoxidil and almost five times as high as those among the 78 men in the placebo group.[43]

The efficacy of drugs that stimulate hair growth can also be assessed by clipping and weighing hair grown in a small, marked area on the scalp.[44,45] This method was used in a 96-week double-blind study of four groups of nine men with androgenetic alopecia.[45] Three groups received one of the following: 5 percent topical minoxidil, 2 percent topical minoxidil, or placebo; the fourth group received no treatment. Hair samples were taken from the frontal area of the scalp. After 96 weeks, treatment was stopped and the men were followed for 24 more weeks. Both solutions of minoxidil were significantly superior ($P< 0.05$) to placebo or no treatment in promoting hair growth and slowing hair loss, with the 5 percent solution having the greater efficacy (Fig. 3); the placebo and untreated groups had a steady decrease in hair weight of about 6 percent per year. In the groups receiving minoxidil, the peak hair weight was followed by a similar small decline during this period. Nevertheless, the hair weight in the minoxidil groups was about 30 percent greater than that in the placebo and untreated groups. The rapid loss of hair weight after treatment with minoxidil was stopped (Fig. 3) confirms its substantial growth-promoting effect.

Minoxidil initially causes a surge of growth in miniaturized hairs (Fig. 3). These hairs continue to have a shortened growth cycle and fall out quickly, which explains the temporary increase in shedding that patients may notice after 10 to 12 weeks of therapy.

One milliliter of minoxidil solution must be applied twice daily to achieve and then maintain efficacy.[46] The solution is applied to the scalp and spread lightly with a finger; massage is not needed. Spray applicators are not recommended, because most of the solution reaches the hair rather than the scalp. Men using minoxidil who wish to take finasteride should continue to apply minoxidil for at least four months after starting finasteride to prevent the loss of hair that occurs after the cessation of minoxidil treatment (Fig. 3).[45] The combined use of minoxidil and finasteride has not been studied in humans, but in a study in stumptail macaques the effect of minoxidil and finasteride combined was greater than the effect of either drug alone.[47]

The adverse effects of topical minoxidil are mainly dermatologic. Irritation of the scalp, including dryness, scaling, itching, and redness, occurs in approximately 7 percent of patients who use the 2 percent solution and in more of those who use the 5 percent solution because of its higher content of propylene glycol. Minoxidil or the formulated solution may also cause allergic contact dermatitis or photoallergic contact dermatitis.[48-50] Hypertrichosis is another dermatologic adverse effect, which occurs in women but is rare in men.

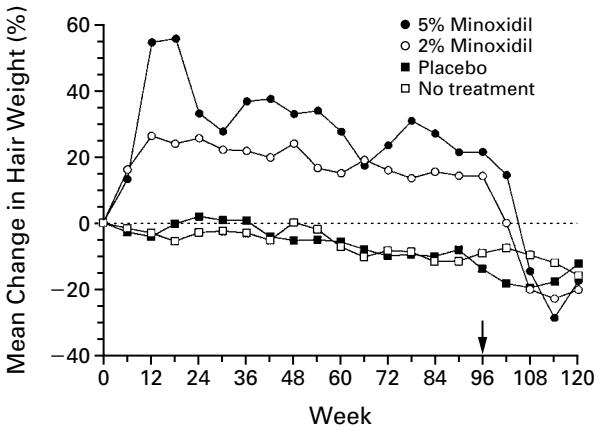

Figure 3. Mean Percent Change in Hair Weight per Square Centimeter of Scalp from Base Line (Week 0) among Men with Androgenetic Alopecia Who Received 5 Percent Minoxidil, 2 Percent Minoxidil, Placebo, or No Treatment for 96 Weeks.

The dotted line indicates no change, and the vertical arrow at 96 weeks marks the cessation of treatment. Adapted from Price et al.[45] with the permission of the publisher.

Neither the 5 percent nor the 2 percent solution of minoxidil alters systolic or diastolic blood pressure, pulse rate, or body weight when applied twice daily.[43,51] With the 5 percent solution, the mean serum level of minoxidil is 1.2 ng per milliliter, well below the level of 20.0 ng per milliliter at which minimal hemodynamic changes in pulse rate and blood pressure occur.[51]

Treatment in Women

Androgenetic alopecia occurs as often in women as in men but is camouflaged by hair styling (Table 2). In women, the thinning of hair is diffuse but is most marked on the frontal or parietal areas of the scalp. The process is milder in women than in men because of differences in the level of 5α-reductase and cytochrome P-450 aromatase and in the number of androgen receptors in the hair follicles of the scalp.[18] Women typically retain a rim of hair along the frontal hairline, even when the scalp is visible.[8,10,52] Increased spacing between hairs makes the "central part" look wider over the frontal region of the scalp than over the occipital region. The patient may note that her "ponytail" is much thinner. The diagnosis of androgenetic alopecia is supported by these clinical features, the presence of miniaturized hairs with large variation in diameter and length, and onset at an

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Table 2. Misconceptions and Facts about Androgenetic Alopecia in Women.

Factor	Misconception	Fact
Decade of onset	50s, 60s, or 70s	Teens, 20s, 30s, or 40s
Incidence	15–20 percent	50 percent of women <50 yr of age*
Mode of transmission	Maternal	Polygenic
Menses and pregnancy	Abnormal	Normal
Androgen levels	High	Normal
Need for hormonal evaluation	Extensive evaluation indicated	None needed unless any of the following are present: irregular menses, infertility, hirsutism, severe cystic acne, virilization, or galactorrhea
Restrictions on hair care and grooming	Use of teasing, hair spray, hair color, or permanents or frequent washing forbidden	Use of hair styling, teasing, hair spray, hair color, or permanents encouraged; no restrictions on the frequency of washing

*The incidence is the same as that among men.

Table 3. Evaluation of Women with Androgenetic Alopecia.

Conditions to Be Ruled Out or Assessed	Means of Evaluation
Androgen excess*	Measurement of serum total or free testosterone, dehydroepiandrosterone sulfate, and prolactin
Hypothyroidism and hyperthyroidism	Measurement of serum thyrotropin
Chronic inadequate intake of dietary protein	History taking
Chronic blood loss	Measurement of serum iron, iron-binding capacity, ferritin, and hemoglobin
Severe acute or chronic illness	Tests as indicated

*Androgen excess should be considered if any of the following are present: irregular menses, infertility, hirsutism, severe cystic acne, virilization, or galactorrhea.

early age. Biopsy of the scalp is not routinely needed but is helpful when the diagnosis is uncertain.

Most women with androgenetic alopecia have normal menses, pregnancies, and endocrine function, including normal serum androgen levels. Extensive hormonal evaluation is not usually needed unless other symptoms and signs of androgen excess are present (Tables 2 and 3). Other causes of hair loss may need to be ruled out (Table 3).[53]

Women with androgenetic alopecia are often more devastated by their thinning hair than are men.[54,55] They need reassurance that they will not become bald and that they may safely use hair sprays, dyes, and permanents to make their hair appear fuller (Table 2).

Minoxidil

Topical minoxidil solution is the only drug available for promoting hair growth in women with androgenetic alopecia. The 2 percent solution of minoxidil was approved for this use by the FDA in 1991 after it was found to be effective in two double-blind, placebo-controlled, 32-week studies of 550 women who were 18 to 45 years old.[56,57] The minoxidil-treated women had significantly higher hair counts than the women who received placebo. In a third 32-week study (of eight women), in which hair weight was the primary end point, the average total hair weight increased by 42.5 percent in the minoxidil group as compared with 1.9 percent in the placebo group.[44]

The 5 percent solution of topical minoxidil was compared with the 2 percent solution in a total of 493 women with androgenetic alopecia in two placebo-controlled studies, one 32 weeks long and the other 48 weeks long. On the basis of hair-count data, the 5 percent solution was not significantly more effective than the 2 percent solution. An ongoing 52-week placebo-controlled study of more than 500 women is comparing the effectiveness of the two solutions.

Minoxidil solution must be applied twice daily, which is a large drawback for some women. If the hair has been washed, the scalp must be completely dry before minoxidil is applied. The solution must be applied directly to the scalp with a dropper or extended spray applicator.

The severity and type of adverse effects of minoxidil in women are the same as those in men, except that hypertrichosis is more common. The incidence of hypertrichosis is about 3 to 5 percent among women who use 2 percent minoxidil and is higher among those who use the 5 percent solution, although precise data are lacking. It occurs above the eyebrows, in the malar region, laterally on the cheeks, and occasionally above the upper lip and on the chin. Hypertrichosis diminishes or disappears after about one year, even with continued use of minoxidil, and it resolves within one to six months after the drug is stopped. Bleaching of the longer, darker hair usually suffices for cosmetic purposes; hair-removal procedures are seldom needed. The reason for this symmetric, dose-related hypertrichosis is not clear; local intravascular spread by the extensive blood supply of the scalp, inadvertent manual transfer of minoxidil to the face, and contact with a pillow onto which minoxidil has been transferred from the scalp have been suggested as possible explanations.[10]

Finasteride

Finasteride is contraindicated in women who are or may become pregnant, because 5α-reductase inhibitors may cause abnormalities of the external genitalia of male fetuses. This contraindication is based

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on findings in men with 5α-reductase deficiency.[19,23] In 136 postmenopausal women with androgenetic alopecia who were given 1 mg of finasteride or placebo daily for one year, both groups lost hair and there was no significant difference in hair loss between the finasteride and placebo groups.[58]

Estrogen

The role of estrogen in hair growth in humans is not clear. Estrogen, both oral and topical, has been used in women with androgenetic alopecia, although no controlled studies have been done. Since topical minoxidil solution seems to be more effective than estrogen in terms of improving scalp coverage and slowing further hair loss, in my own practice, I no longer prescribe estrogen for women with androgenetic alopecia. Nevertheless, the activity of aromatase in hair follicles in the frontal and occipital regions of the scalp hair is significantly higher in women with androgenetic alopecia than in men with this condition. This higher activity may have a role in the milder expression of this trait in women.[18]

When an oral contraceptive or a combination of estrogen and progestin is prescribed for women with androgenetic alopecia, care should be taken to select a progestin with little or no androgenic activity, such as norgestimate or ethynodiol diacetate. Women with this condition should not take testosterone or androgen precursors, such as dehydroepiandrosterone (known as DHEA).

Spironolactone

Spironolactone is a weak competitive inhibitor of the binding of androgen to its receptor, and it decreases the synthesis of testosterone as well. It has some efficacy in the treatment of hirsutism.[59] It seems to have little efficacy in women with androgenetic alopecia, but no controlled studies have been done and there are no data on hair count or hair weight, nor are there any photographic data.

ALOPECIA AREATA

Alopecia areata is an autoimmune disease that affects almost 2 percent of the U.S. population.[60] It ranges in severity from small, round patches of hair loss that regrow spontaneously to persistent, extensive patchy involvement to the loss of all scalp hair (alopecia totalis) or all scalp and body hair (alopecia universalis). Alopecia areata affects both sexes equally and occurs at all ages, although children and young adults are affected most often. Spontaneous remission and recurrence are common. The patients are usually otherwise healthy, but atopy, thyroid disease, and vitiligo are more common among them than among the general population. Measurement of serum thyrotropin is recommended for children with alopecia areata, as well as those with a family history of thyroid disease.

The assumption that alopecia areata is an autoimmune disease is based on the presence of activated CD4 and CD8 lymphocytes around affected anagen hair bulbs[61,62] and on the ability to transfer alopecia areata by T lymphocytes from affected scalp to explants of human scalp on mice with severe combined immunodeficiency.[63] As is the case with many other autoimmune diseases, there is a strong association of alopecia areata with certain HLA class II alleles, especially DQB1*03 and DRB1*1104, which appear to be markers of general susceptibility to alopecia areata.[64-66] In addition, the frequency of two other alleles — DRB1*0401 and DQB1*0301 — is significantly increased among patients with alopecia totalis and those with alopecia universalis, the most extensive form of the condition.

Treatment

Patients with alopecia areata are treated with either immunomodulating therapies, such as glucocorticoids, topical immunotherapy, or anthralin, or biologic-response modifiers, such as minoxidil.[61,67,68] These treatments stimulate hair growth but do not prevent hair loss and probably do not influence the course of the disease. Treatment should be continued until remission occurs or until residual patches of alopecia are concealed by regrown hair, which may take months or years. The choice of therapy depends primarily on the patient's age and the extent of the hair loss (Table 4).[67,69] Treatment is most effective in milder cases; no treatment works well for patients with total (100 percent) loss of scalp hair. Hair follicles are not destroyed in patients with

TABLE 4. TREATMENT FOR PATIENTS WITH ALOPECIA AREATA, ACCORDING TO AGE AND SEVERITY OF CONDITION.*

Patients ≤10 years of age
5% Topical minoxidil solution, topical glucocorticoid, or both
Anthralin (short contact)†
Patients >10 years of age
<50% of scalp affected
Intralesional glucocorticoid, 5% topical minoxidil solution, or both, with or without topical glucocorticoid
Anthralin (short contact)†
≥50% of scalp affected
5% Topical minoxidil solution, with or without topical glucocorticoid
Topical immunotherapy
Anthralin (short contact)†
Oral glucocorticoid
Scalp prosthesis
Eyebrows and beard affected
Intralesional glucocorticoid, 5% topical minoxidil solution, or both

*The National Alopecia Areata Foundation, 710 C St., Ste. 11, San Rafael, CA 94901-3853 (telephone number, 415-456-4644; Web site, www.alopeciaareata.com), provides informational brochures, newsletters, research updates, sources of scalp prostheses, videotapes for schoolchildren, and locations of support groups and holds an annual conference to help patients cope with the condition.

†Anthralin is left on the scalp for 20 to 60 minutes.

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TABLE 5. SUGGESTED METHODS OF TREATMENT FOR ALOPECIA AREATA.

Intralesional glucocorticoid

All sites
The preferred compound is triamcinolone acetonide (10 mg/ml),* administered with a 3-ml syringe with a 30-gauge, 1/2-in.-long needle. Inject 0.1 ml or less into the mid-dermis at multiple sites 1 cm apart; do not raise wheal or inject into subcutaneous tissue. Repeat every 4 to 6 weeks; if atrophy of the skin occurs, do not reinject affected site until atrophy resolves. Optional topical anesthesia may be used: apply a mixture of 2.5% lidocaine and 2.5% prilocaine (Emla cream) in a thick layer to intact skin and cover with occlusive dressing for one hour before injections are given; remove cream immediately before injections.

Scalp
The maximal dose is 20 mg per visit. When more than 50% of scalp is affected, inject only selected sites.

Eyebrows
The maximal dose is 1.25 mg per visit injected into the mid-dermis of each brow at 5 or 6 sites (for a total of 2.5 mg to both brows).

Beard
The maximal dose is 7.5 mg per visit.

5% Topical minoxidil solution

Scalp and beard
The maximal dose is 1 ml per application. Apply twice daily to affected sites. Spread solution with fingers. Wash hands afterward. This treatment is not effective for patients with total (100 percent) loss of scalp hair.

Eyebrows
Apply two applications to each eyebrow with a finger twice daily, using a mirror to ensure precise placement. Hold a cotton ball over the eye for protection. Wash hands afterward.

Anthralin (short contact)†

Apply 0.5 to 1% anthralin cream to affected scalp once daily; leave on 20 to 30 minutes daily for 2 wk, then 45 minutes daily for 2 wk, up to a maximum of 1 hour daily. Wash hands afterward and avoid getting anthralin in the eyes. Remove from scalp with mineral oil, then wash off with soap and water. Do not use on brows or beard. Some patients tolerate overnight application.

Topical glucocorticoid

Apply twice daily.

Topical immunotherapy

Use diphencyprone or squaric acid dibutyl ester to induce contact sensitization. For initial sensitization, apply 2% solution of selected contact allergen in acetone to a 4-cm^2 area on one side of the scalp. After initial sensitization, apply diluted solution of contact allergen weekly to same half of scalp in two coats. The patient washes off the allergen after 48 hr after both the sensitizing application and subsequent weekly applications. Adjust concentration of allergen according to the response to the previous week's treatment. Desired responses include mild itching, erythema, and scaling. Concentrations of allergen that elicit responses range from 0.0001%, 0.001%, 0.01%, 0.025%, 0.05%, 0.1%, 0.25%, 0.5%, and 1.0% to 2.0%. After hair growth is established on the treated side (in 3 to 12 months), then both sides of the scalp are treated. Apply contact sensitizer with wooden applicator tipped with generous amount of cotton (the physician or nurse applying weekly treatment must wear gloves). To minimize side effects, it is recommended that the allergen be applied in a physician's office and not given to the patient for use at home.

Oral glucocorticoids

Active, extensive, or rapidly spreading alopecia areata
For patients weighing ≥60 kg the recommended treatment is 40 mg of oral prednisone daily for 1 wk; then 35 mg daily for 1 wk; 30 mg daily for 1 wk; 25 mg daily for 1 wk; 20 mg daily for 3 days; 15 mg daily for 3 days; 10 mg daily for 3 days; and 5 mg daily for 3 days. Prednisone may be used with 5% topical minoxidil solution twice daily and intralesional triamcinolone acetonide injections given as above, every 4 to 6 weeks. Topical therapy should be continued twice daily, with or without intralesional injections every 4 to 6 weeks, after prednisone is tapered.

Active, less extensive alopecia areata
Twenty mg of oral prednisone should be given daily or every other day; dose should be tapered slowly by increments of 1 mg after the condition is stable.

*Concentrations of 2.5 to 8 mg per milliliter may also be used.

†Anthralin is left on the scalp for 20 to 60 minutes.

alopecia areata, and the potential for regrowth always remains. Alopecia areata can be psychologically devastating. The National Alopecia Areata Foundation is a useful resource for patients with this condition (Table 4).

Glucocorticoids

Intralesional injection of a glucocorticoid is the most common treatment for alopecia areata in the United States for patients with limited scalp involvement; the brow and beard area may also be injected (Tables 4 and 5).[67,69] The preferred treatment is triamcinolone acetonide, 10 mg per milliliter. I inject it undiluted in all sites, although others use dilutions of 2.5 to 8 mg per milliliter. Very small volumes (0.1 ml or less) are injected into the mid-dermis in multiple sites 1 cm apart. New hair growth is usually visible in four weeks. The main side effect is local skin atrophy, which can be minimized by injecting small volumes only into the mid-dermis, taking care not to

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inject the solution into the epidermis or fat, and repeating the injections only every four to six weeks. Some patients with mild disease do not have a response, possibly because the glucocorticoid receptors in the scalp bind the injected glucocorticoid poorly.[70]

Topical glucocorticoid therapy is favored by some clinicians, especially for children,[71,72] although I have not found it very effective when used alone. However, topical glucocorticoids may be beneficial in combination with other therapies, such as 5 percent minoxidil, anthralin, or injected glucocorticoids.[67,69,71,72]

Oral glucocorticoids are effective but are seldom used in this chronic condition because of their many adverse effects. However, they may be indicated in patients with progressive alopecia areata, either to slow progression or to initiate growth (Table 5).[67,73]

Minoxidil

Several concentrations of topical minoxidil have been evaluated in adults and children with more than 25 percent hair loss due to alopecia areata. Among them, the 5 percent solution of minoxidil was the most effective.[72,74-77] It stimulates hair growth in patients with patchy and extensive alopecia areata but not in patients with total loss of scalp hair.[74,75] It can be used on the scalp and eyebrows in women and children and on these areas and the beard in men (Table 5). Minoxidil solution must be applied twice daily. Hair growth usually appears within 12 weeks, and the response is usually maximal by 1 year; continued application is needed until full remission occurs. In patients with 25 to 99 percent loss of scalp hair, treatment with 5 percent minoxidil resulted in the growth of cosmetically acceptable hair (sufficient growth to conceal areas of residual hair loss) in about 40 percent of the patients after one year.[74]

Anthralin

Anthralin has a nonspecific, immunomodulating, anti–Langerhans'-cell effect.[78] It is safe, and therefore it is frequently selected for use in children and adults with extensive alopecia areata, including those with total loss of scalp hair. Growth of new hair may be seen in two to three months after the start of treatment, and about 25 percent of patients may have cosmetically acceptable growth in about six months.[79]

Anthralin is potentially irritating and may cause redness, itching, and scaling. For this reason, anthralin cream is often applied and then removed 20 to 60 minutes later (short-contact therapy), although some patients tolerate overnight application (Table 5). Clinical irritation is not necessary for effectiveness, and skin irritants are not effective in the treatment of alopecia areata.[80,81]

Topical Immunotherapy

Topical immunotherapy (contact sensitization) is one of the more effective treatments for patients with chronic alopecia areata affecting more than 50 percent of the scalp.[67,69] Unfortunately, it is investigational and is offered at only a few centers in the United States. The patient is sensitized by application to the scalp of a potent contact allergen, and allergic contact dermatitis is subsequently elicited by weekly applications of the same agent. The allergens used include diphenylcyclopropenone or diphencyprone and squaric acid dibutyl ester.[67,82] Mild itching, erythema, and scaling are sufficient to induce hair growth[67,82-86] (Table 5). The efficacy of topical immunotherapy has been shown by studies in which half the scalp was treated and the other side served as a control.[82-86] Unilateral application of the allergen is the recommended method; after growth is established on one side (in 3 to 12 months), the other half of the scalp is treated as well.[67,82-86] The mechanism by which contact sensitization suppresses alopecia areata is uncertain but may involve the generation of nonspecific suppressor T cells or the inhibition of proinflammatory cytokines.

Among patients with loss of 50 to 99 percent of scalp hair, cosmetically acceptable hair growth occurs in 40 to 60 percent.[67,82,86] In those with total loss, only about 25 percent have cosmetically acceptable growth. Children as young as seven years have been treated with topical immunotherapy in Europe.[87-89]

The adverse effects of topical immunotherapy include itching and cervical lymphadenopathy, which are invariably present.[67,85,86] Severe blistering and disseminated eczema may occur. Less commonly, hyperpigmentation, hypopigmentation,[90] contact urticaria, and erythema multiforme–like reactions have been reported.[69,86] To minimize side effects, it is recommended that the allergen be applied in the physician's office.

CONCLUSIONS

The treatment of hair loss has been advanced by two drugs. Finasteride is a highly specific inhibitor of type 2 5α-reductase activity and is approved for the treatment of androgenetic alopecia in men. Minoxidil is a nonspecific drug that is useful in men, women, and children with various conditions including androgenetic alopecia and alopecia areata. Future success in treating these and other problems of hair loss will require continued research on the regulation of the hair-growth cycle and basic hair biology, the development of new therapeutic approaches, and the judicious use of existing drugs.

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