Male androgenetic alopecia (Part II)

Rodney D. Sinclair

Abstract

Androgenetic alopecia only becomes a medical problem when the hair loss is excessive, premature and distressing to the patient. A number of medical treatments aimed at arresting the progression of the hair loss have become available in recent years, and surgical treatments are constantly being refined. The three distinct aims of therapy for male androgenetic alopecia are: to arrest further progression, to stimulate regrowth and to conceal the hair loss. Topical minoxidil stimulates regrowth but may or may not arrest further progression. Oral 5 alpha reductase inhibitors arrest further progression but may or may not stimulate regrowth. Hair transplantation, coloured hair sprays, wigs and toupees conceal the hair loss but do not stimulate regrowth or arrest further hair loss. Hair transplantation redistributes hair more evenly over the scalp. Substantial efforts have been undertaken to refine the methods used to evaluate therapeutic response and define acceptable primary and secondary endpoints for clinical trials. Currently the US Federal Drug Association (FDA) accepts numerical hair count data and patient subjective response as primary endpoints and standardized scalp photography as a secondary endpoint. This difficulty in evaluation of outcome is magnified in clinical practice where hair counts are not feasible and the clinician relies overly on patient subjective assessment. Serial scalp photography is especially valuable in this setting. © 2005 WPMH GmbH. Published by Elsevier Ireland Ltd.

Introduction

Patterned hair loss involves androgen-mediated miniaturization of genetically susceptible terminal hairs into vellus hairs on affected regions of the scalp. The key androgen is believed to be an active metabolite of testosterone called dihydrotestosterone, rather than testosterone itself. The type 2 isoenzyme of 5 α reductase is the principle catalyst for conversion of testosterone and the main target for therapeutic interventions aimed at arresting the hair loss process.

Susceptibility to androgenetic alopecia is inherited as a complex polygenic trait. Only one gene has been implicated to date, the androgen receptor gene on the x chromosome. Twin studies suggest that the age of onset, rate of hair loss and pattern of hair loss are all primarily genetic [1]. The role of diet, stress, climate, hair grooming practices and other putative environmental factors in the development of androgenetic alopecia appear to be minimal. Ipsofacto this article contains no recommendations on these matters.

There is regional specificity in hair follicle response to androgens. Some follicles enlarge (e.g. beard, axilla and pubic), some miniturize (vertex and frontal scalp), while some are unaffected (eyebrow and eyelash). The hair loss pattern seen in androgenetic alopecia reflects this. Regional specificity is explained in part by in vitro experiments where androgen stimulation of scalp dermal papilla cells induces TGF-β production and androgen stimulation of beard dermal papilla cells induces IGF-1 as a second messenger. The donor dominance seen in hair transplantation experiments prove that this regional response is innate. Donor dominance is shown when hairs moved from one anatomical site to another respond to androgens as though they were still in the original site.

Keywords
Finasteride
Minoxidil
Propecia
Androgenetic
Bald
Management

A number of options are available to balding men. Firstly, as the condition is not life-threatening and the morbidity is variable, a reasonable option is to have no treatment and allow the balding to progress naturally. In fact, this is what most men elect to do. Regardless of whether or not patients pursue treatment, an adequate explanation of the pathogenesis of the disease, how common it is in the community and the various treatment options available form an important part of the support and counselling of each patient.

Medical management

Topical minoxidil and oral finasteride are the only treatments approved by the Food and Drug Administration (USA) for the treatment androgenetic alopecia.

Minoxidil

Minoxidil is an antihypertensive that was found to cause hypertrichosis [2]. A topical preparation was formulated for the treatment of androgenetic alopecia. Hairs are recruited into a prolonged anagen, accompanied by enlargement of miniaturized hair follicles [3,4]. Minoxidil and other potassium channel agonists (diazoxide and pinacidil) have long been recognized to stimulate hair growth in vivo, but the specific mechanism of action is unknown. Minoxidil sulfate, the active metabolite is postulated to open the adenosine triphosphate (ATP) sensitive potassium channel (KATP channel) which renders the intracellular potential more negative. This negative gradient would promote depletion of intracellular calcium. In the presence of calcium, epidermal growth factor has been shown to inhibit hair follicular growth in vitro. The conversion of minoxidil to minoxidil sulphate is higher in hair follicles than in the surrounding skin and may suppress epidermal growth factor-induced inhibition of growth, prolonging the anagen growth phase of hair follicles [5].

There are two topical preparations of minoxidil available: 2% and 5% solutions. Both are available over-the-counter in most countries for promoting hair growth and have been shown to be effective in increasing hair counts [6–9].

On commencing treatment, minoxidil may cause a surge in the growth of miniaturised hairs and induction of anagen from resting hair follicles. This may produce an early onset telogen effluvium that lasts 4–6 weeks. This temporary shedding may be interpreted as a clinical indication that the minoxidil is having a beneficial effect. The effect of minoxidil only lasts as long as the patient continues to use the preparation. Once the treatment is stopped all minoxidil, dependent hairs will be shed and the overall density will return to a point determined by the natural history [9].

Because minoxidil works as a non-specific promoter of hair growth, the slow miniaturisation of hair follicles induced by androgens continues in spite of treatment. Evidence for this is seen in a 120-week double-blind study, comparing the clipped hair weight of men treated with 5% minoxidil, 2% minoxidil and placebo and a group with no treatment [9]. As expected, the minoxidil groups experienced a surge in hair weights at the induction of therapy. The 5% group had a higher initial peak in hair weights than the 2% group. Both were superior to placebo and no treatment groups. However, after the initial surge, all groups (minoxidil, placebo and no treatment) showed a similar progressive 6% per annum decrease in hair weights during the treatment period. This would mean that patients using minoxidil as mono-therapy for androgenetic alopecia continue to bald in spite of treatment.

Minoxidil should be used twice daily, with 1 millilitre spread evenly into the entire scalp. Side effects are uncommon, with skin irritation [10,11] being the most frequently reported event. Dizziness and tachycardia [10], and contact allergic dermatitis have also been reported.

Finasteride

Finasteride is a synthetic azo-steroid that is a potent and highly selective antagonist of 5α-reductase type 2. Being a non-competitive antagonist, it binds irreversibly to the enzyme and inhibits the conversion of testosterone to dihydrotestosterone (DHT). Thus, while the pharmacokinetic half-life is about 8 hours, the biological effect persists for much longer. The underlying principle for its use is the reduction of DHT production thus limiting its action on scalp hair follicles.

Various studies [12–20] have shown the beneficial effects of finasteride on reversing the
pathogenesis of androgenetic alopecia. A study measuring hair counts using macrophotographs [12] found that both total and anagen hair counts increase with treatment of finasteride. An increase in the anagen to telogen ratio was also achieved. This shows the ability of finasteride to stimulate conversion of hair follicles into the anagen phase, possibly through reversion of the decrease in anagen phase and the increase in lag phase. A study looking at scalp biopsies [13] found that finasteride stimulates an increase in terminal hair counts and a decrease in vellus hair counts. Another study using hair count and hair weight as an objective measure of outcome [14] demonstrates that both hair count and hair weight increases, with a larger extent of increase achieved in hair weight. Factors that affect hair weight include the number of hairs, hair growth rate and hair thickness. These findings show the ability of finasteride to reverse the miniaturisation process, producing hair of greater length and thickness, and possibly with a greater growth rate.

A daily oral dose of 1 milligram reduces scalp DHT by 64% and serum DHT by 68% [15]. Finasteride is also approved for the treatment of benign prostatic hypertrophy at a dose of 5 milligrams daily. Dose-ranging studies have found no statistically significant difference in clinical benefit between 5 and 1 milligram daily regimens [16], nor is there any meaningful further reduction of scalp or serum DHT levels. Finasteride has a long biological half life and patients can still get a biological effect when taken weekly, however the magnitude of that effect has not been prospectively investigated [21]. A 5-year multinational study looking at the effect of finasteride on treatment of androgenetic alopecia found finasteride to be superior to placebo [19]. The placebo group suffered a progressive decline in hair count, losing about 26% of terminal hairs compared with baseline counts at the end of the 5-year study. In contrast, patients taking finasteride have a 10% increase in hair count at the end of the first year. Hair count declined thereafter but remained above baseline throughout, remaining at 5% above the baseline hair count after 5 years of treatment. This decline rate of hair count in the finasteride group is statistically significantly less than that of the placebo group. Taken together, there is a progressive increase in the difference between treatment and placebo group over time. This shows the effects of finasteride in stimulating a substantial amount of hair regrowth, reaching its peak efficacy after 1 year of treatment, and slowing the progression of hair loss thereafter.

At the end of the first year, some in the placebo group were swapped onto receiving finasteride for the remaining 4 years. These patients had a decrease in hair count during the first year with placebo, followed by an improvement in the subsequent 4 years with finasteride. The improvement was similar to that of the group who received finasteride for 5 years throughout the study. However, mean hair count level was less than that of the patients who had taken finasteride ‘a year earlier’ at comparable times, with the difference being similar to the amount of hair loss sustained during the year of placebo treatment. This shows the relative benefits of early commencement of treatment with finasteride. Some of the finasteride patients were also crossed over to receive placebo after a year of finasteride treatment. A decrease in hair count was observed 12 months later, indicating the reversal of the beneficial effects of treatment obtained during the first year.

Further evidence of the efficacy of finasteride in the treatment of androgenetic alopecia was seen in a randomized, double-blind, placebo-controlled twin study [20]. At month 12, all subjects in the finasteride group had an increase in hair count, and a decrease was found in 44% of the placebo group. Serum DHT levels were significantly decreased in the finasteride group, with no significant change observed in the placebo group. Global photography assessment shows significant improvement on hair growth in vertex and superior-frontal scalp in the finasteride group, with no significant differences between treatment groups observed in the temporal or anterior hairline views. This finding shows the relative effectiveness of finasteride on protecting hair loss over the vertex and superior-frontal regions of the scalp, compared with the minimal response over the temporal and the anterior hairline regions.

Few adverse side effects were reported in the 5-year data. In the finasteride group loss of libido was reported in 1.9% and erectile dysfunction in 1.4% in the first year. The placebo groups reported these same events with fre-
quencies of 1.3% and 0.6% respectively. These events appeared to resolve on cessation of the treatment and, in some cases, during continued treatment. It has been suggested that even these figures overstate the true incidence of sexual dysfunction [22]. Of note, older men who received finasteride experienced a 50% reduction in serum prostate specific antigen (PSA) levels, which could result in an underestimation of prostatic cancer risk. Urology literature shows that PSA levels remain valid while patients are taking finasteride, but a calculation should be made by the laboratory to correct for the finasteride effect [23–25]. Men between 18 and 41 years old have a negligible decrease in measured PSA [26].

Topical finasteride has been investigated as a potential variation in drug delivery. Although 0.05% of finasteride solution applied to the scalp was well absorbed and produced a 40% reduction in serum DHT, it had no effect on hair regrowth. One explanation for this is that inhibition of prostatic DHT production is an important factor in preventing hair loss with finasteride, i.e. a reduction in circulating DHT is required in addition to the local blockade of 5α-reductase at the hair follicle [27].

Medical treatment should be continued indefinitely because the benefit will not be maintained after ceasing therapy. Up to one year of treatment may be required before any clinical response is noticeable. The monitoring of this response can be problematic. Patients inspect their hair on a daily basis and subtle changes over time may not be readily observable. Doctors are essentially reliant upon the patients’ subjective assessment of their hair density over time. Baseline photographs are helpful, but unlikely to detect changes of less than 20% in hair density. We use a camera mounted on a stereotactic device; a system that is identical to the set-up used in the phase III finasteride trials [27]. Photographs are taken of the vertex and frontal hairline at 6-monthly to yearly intervals; hair densities at these times can be readily compared. This set-up is proving to be useful in the long-term monitoring of treatment response (Figure 1). Patients are able to observe their regrowth during treatment; the photographs serve as a motivating factor, improving long-term patient compliance to medical treatment. Similar set-ups using Polaroid photographs also appear useful [28].

Finasteride is a teratogen. Male rats exposed to finasteride in utero develop hypospadius with cleft prepuce, decreased anogenital distance, reduced prostate weight and altered nipple formation [26]. As the drug is secreted in the semen and can be absorbed through the vagina during intercourse, it was originally advocated that men taking finasteride should avoid unprotected intercourse with pregnant women. In practice, the concentration of finasteride in the semen is well below the minimum effect dosage, and no recommendation to use condoms is made in the production information leaflet. There are no reports of adverse pregnancy outcomes among women exposed to finasteride. Finasteride has no effect on spermatogenesis or semen production [26]. With regards long term safety, finasteride has now been in use for over 10 years. Many recipients are elderly men taking 5 mg per day. Very few side-effects have been observed. There is no effect of long-term use on bone mineral density [29,30]. Reversible painful gynaecomastia has been reported [31] and the incidence is thought to be around 0.001% [32]. Work is underway to determine whether finasteride 5 mg daily is protective against the future development of prostate cancer [33].

Future drug development: topical anti-androgens

Oral anti-androgens (e.g. spinorolactone, cyproterone acetate) have been widely used to treat women with androgenetic alopecia. However it has been contraindicated in treatment of androgenetic alopecia in men due to its systemic androgenic effects in the body, affecting libido, male sexual functions and secondary sexual characteristics development. A topical anti-androgen, fluridil has recently been rationally developed for use in male androgenetic alopecia. It is designed to be locally metabolized, not systemically resorbable, and degradable into inactive metabolites without antiandrogenic activity [34]. A double-blind, placebo-controlled study showed that patients using topical fluridil had an increase in the anagen to telogen ratio, and the maximum attainable effect is achieved within the first 90 days of daily use. No side effects on libido and sexual performances have been found. Nevertheless, a longer study is required to further investigate fluridil’s long-term
safety and effectiveness in male androgenetic alopecia.

Other 5α-reductase inhibitors are in development [35]. Dutasteride, a combined type 1 and type 25α-reductase inhibitor, has undergone phase 2 trials and appears to have greater efficacy in reducing circulating and tissue levels of DHT, and stimulating hair regrow, albeit sexual side effects are more prevalent [36].

Non-medical treatments

Patients who do not pursue medical treatments have various camouflage methods available to them. Spray-on scalp dye treatments disguises bald scalp and gives the impression of thicker hair for patients with mild androgenetic alopecia. For those with advanced disease good quality synthetic, acrylic or natural fibre wigs can be entirely imperceptible.

Scalp surgery can involve excision of bald scalp, scalp flaps as well as transplantation. There are various scalp autograft transplantation techniques in use typically involving the transplantation of occipital scalp hair follicles to the bald areas. A strip of full-thickness occipital scalp is harvested and with the aid of a dissecting microscope, cut down to small subunits. Minigrafts containing a cluster of hairs are transplanted into slits made with a small scalpel blade. A modified technique uses ‘follicular units’ containing one to four hair follicles, which are inserted into smaller needle holes. Both techniques can achieve good results, but follicular unit transplantations have the advantage of being able to achieve much greater hair densities. The disadvantages are increased time and labour requirements, which translate to greater cost for the patient. Good surgeons can transplant up to 3000 units per ‘megasession’, the number of sessions required depends on the area to be transplanted. Transplanted hairs seem to immediately go into a telogen resting phase after insertion. Thus surgical results can only be
adequately assessed at least 3 months after surgery. There is always a degree of graft failure. Various reasons account for dead grafts including the skill of the surgeon, the density of graft placement, careless handling and preparation of the graft units, and desiccation of the grafts while awaiting insertion. These techniques have been recently reviewed in detail [37].

Conclusion

Androgenetic alopecia is increasingly common among men as they age. Many men find it a distressing and unwelcome event and some seek treatment to prevent further hair loss and reverse the process. A number of therapeutic options are now available for these men. In addition, androgenetic alopecia may be a marker of increased risk for the development of prostate cancer, and prophylactic treatment with 5 α reductase inhibitors is currently under investigation. The hair follicle is a complex organ biologically. The changes in the hair follicles that lead to baldness have caught the interest of stem cell scientists, geneticists, developmental biologists and immunologists and hair biology has become an increasingly fruitful field of scientific endeavour.

References


