An open, randomized, comparative study of oral finasteride and 5% topical minoxidil in male androgenetic alopecia.

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**BACKGROUND AND AIM:** Androgenetic alopecia (AGA) is undoubtedly the most common form of hair loss in males. It is a condition which may cause cosmetic and psychosocial problems in androgen-dependent cases. In this open, randomized and comparative study we evaluated the efficacy of oral finasteride and 5% topical minoxidil treatment for 12 months in 65 male patients with mild to severe AGA.

**METHODS:** We randomly assigned 40 (61.53%) patients to receive 1 mg/day oral finasteride for 12 months, and 25 (38.47%) patients applied 5% topical minoxidil solution twice daily for 12 months.

**RESULTS:** There were no significant differences between the 2 groups considering age, age of onset of hair loss, family history and type of hair loss (p > 0.05). In the clinical evaluation at the endpoint of treatment, the clinical cure rates (i.e. increased intensity of hair) were 80% (32/40) for the oral finasteride group and 52% (13/25) for the 5% topical minoxidil group. Encountered side effects were all mild, and there was no need to stop the treatment. In the group given oral finasteride, side effects were noted in 7 patients: 6 patients suffered from loss of libido, and 1 patient had an increase in other body hairs; irritation of the scalp was seen in 1 patient in the group administered 5% minoxidil. These adverse events disappeared as soon as the treatment was stopped. The laboratory data on both drug groups did not show any statistically or clinically significant intragroup changes from baseline values to the endpoint (p > 0.05), except the level of serum total testosterone which was increased, and free testosterone and serum prostate-specific antigen in the finasteride group which were statistically decreased from baseline values to the endpoint (p < 0.05).

**CONCLUSION:** In this comparative study of systemic finasteride and topical minoxidil, it was concluded that both drugs were
effective and safe in the treatment of mild to severe AGA, although oral finasteride treatment was more effective \( (p < 0.05) \). Adverse events were not considered important either, and these side effects disappeared as soon as the treatment was stopped.

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Using contrast-enhanced phototrichogram (CE-PTG) at monthly intervals during 48 months, we measured the duration of the hair cycle, i.e. anagen, catagen and telogen at the exclusion of exogen. Exogen, a recently identified phase of the hair cycle, is characterized by weakening of anchorage of the club hair to the surrounding epithelium. The processing of the club hair terminates at the time of exogen hair release, i.e. hair shedding. We combined a noninvasive exogen sampling before each CE-PTG so that the area contained only anagen, catagen and telogen hair or empty follicular openings. During the first 24 months of this study, natural regression of hair cycling in early i.e. preclinical stages of androgenetic alopecia (AGA) in androgen sensitive areas was documented. Shortening of the hair cycle of thicker hair characterized progression of AGA. During the next 24 months, finasteride (1 mg/day) was introduced into the system. Shortening of the hair cycle was reversed by finasteride in androgen sensitive sites as long as the affected follicle was able to produce a thick hair fiber at the time of treatment initiation. Compared to the baseline period, responding follicles did not produce thicker hair. On average, they initiated active growth more rapidly by reducing the duration of the lag phase by 40%. The duration of the anagen phase of thick hair showed an average 23% increase. In this particular experiment, the already miniaturized follicles producing thinner hair (<40 microm thickness) at the time of finasteride introduction regressed further on treatment. Our results seem to indicate that reversal of 'hair loss' by finasteride probably means that the terminal type follicles that are functionally deficient—a stage of reversible hypotrophy—will be reactivated by two non-mutually exclusive mechanisms: faster regrowth followed by extension of the duration of anagen. In our study, there was no clear evidence in favour of reversal of miniaturized hair into terminal hair. This new interpretation indicates that miniaturized hair follicles may be
an important diagnostic marker of AGA in males but also that it might be less contributive to the therapeutic response to finasteride. Our results highlight that precise measurement of terminal type hair follicle functionalities opens up avenues for the selection of ‘drug-responsive organs’ in the human scalp in vivo and these may possibly serve to predict ‘quality of response to treatment’. 2006 S. Karger AG, Basel

Finasteride in the treatment of Taiwanese men with androgenetic alopecia: a 12-month open-label study.

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Finasteride 1 mg/day is effective in the treatment of androgenetic alopecia (AGA). Our open-label study assessed the efficacy and safety of finasteride for the treatment of Taiwanese men with AGA. We enrolled 34 Taiwanese men (aged 18-40 yr) with AGA of modified Norwood/Hamilton scale (MNHS) grade II-V. In investigator assessments at 12 months, five of 21 subjects (23.8%) had two-grade improvement in MNHS grade and 12 of 21 subjects (57.1%) had one-grade improvement; the others remained at the same grade. In global photographic evaluation, five of 31 subjects (15.1%) had observable hair growth at 6 months and 11 of 21 subjects (52.4%) had observable hair growth at 12 months. Patient self-assessment of hair growth was favorable across all questions in the treatment course, more significantly at 12 months than at 6 months; nine of 21 subjects (42.9%) were satisfied with their overall appearance at 12 months. Serum prostate specific antigen levels had decreased by 23.4% at 12 months. Adverse effects, including abnormal liver function (5/34), were minimal, and the causal relationship with finasteride could not be established. Thus, in Taiwanese men with AGA, finasteride 1 mg/day for 1 year slowed the progression of hair loss and increased hair growth.
In men who are genetically predisposed to develop androgenetic alopecia (AGA; male pattern hair loss), endogenous androgens alter scalp hair follicles, resulting in production of vellus-like, miniaturised hair, rather than cosmetically significant terminal hair. This change leads to a progressive decline in visible scalp hair density, readily perceived by the patient as thinning and, eventually, baldness. Dihydrotestosterone (DHT), a metabolite of testosterone produced by the enzyme 5alpha-reductase, has been implicated as the specific androgen in the pathogenesis of AGA. Men genetically deficient in the Type 2 isoenzyme of 5alpha-reductase do not develop AGA. Moreover, Type 2 5alpha-reductase has been detected in scalp hair follicles, and balding scalps contain increased Type 2 5alpha-reductase activity and DHT levels. Taken together, these findings provide a rationale for the use of Type 2 5alpha-reductase inhibitors in the treatment of men with AGA. Finasteride, a specific and potent inhibitor of human Type 2 5alpha-reductase, decreases the formation of DHT from testosterone. Originally developed for the treatment of men with benign prostatic hyperplasia (BPH) as a 5 mg tablet, finasteride was subsequently evaluated as a treatment for AGA. Clinical studies in balding men demonstrated that finasteride reduced scalp DHT levels and improved hair growth, confirming the role of DHT in the pathophysiology of AGA. Dose-ranging studies established the optimal dose of 1 mg/day for the treatment of men with this disorder. Large, multicentre studies established the safety and efficacy of finasteride 1 mg, leading to marketing of Propecia (finasteride 1 mg) as a new treatment for men with AGA.

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BACKGROUND: 5% topical minoxidil solution has been widely used to stimulate new hair growth and help stop hair loss in men with androgenetic
alopecia (AGA). However, it is not convenient for patients to continue applying the solution twice daily on a regular basis. Tretinoin is known to increase the percutaneous absorption of minoxidil and, therefore, to enhance the response of AGA to minoxidil. For this reason, it was assumed that tretinoin would be helpful in alleviating the inconvenience associated with the recommended twice-daily application of minoxidil. OBJECTIVE: To compare the efficacy and safety of therapy using a combined solution of 5% minoxidil and 0.01% tretinoin once daily with those of the conventional 5% topical minoxidil therapy applied twice daily in the treatment of AGA. METHODS: A total of 31 male patients (aged 28-45 years, mean 39.7+/-.5) with AGA (Hamilton-Norwood classification type III-V) were randomly assigned into two groups, one in which 5% minoxidil was applied to the scalp twice daily and the other in which the combined agent was applied once daily at night together with a vehicle placebo in the morning. The efficacy parameters were: (i) changes in total hair count, non-vellus hair count, anagen hair ratio, linear hair growth rate, and mean hair diameter assessed by macrophotographic image analysis; and (ii) the patient's and investigator's subjective assessments. RESULTS: After therapy, increases in the macrophotographic variables of total hair count and non-vellus hair count were shown in both treatment groups. There were no statistically significant differences between the two treatment groups with respect to changes in macrophotographic variables or scores on subjective global assessments by patients and the investigator. The incidence of adverse effects such as pruritus or local irritation was similar in the 5% minoxidil group (4 of 14 subjects) and the combined agent group (5 of 15 subjects). CONCLUSION: The efficacy and safety of combined 5% minoxidil and 0.01% tretinoin once-daily therapy appear to be equivalent to those of conventional 5% minoxidil twice-daily therapy for the treatment of AGA.

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Results for one of the most promising new treatments for hair loss in the FDA approval pipeline were released last week at the American Academy of Dermatology (AAD) meeting in San Francisco.

Roger S. Rittmaster, MD, produced Phase II (small scale human studies) study results for the new Glaxo-Wellcome drug Dutasteride (GI198745), a dual 5-alpha reductase inhibitor. Hair loss is linked to the hormone Dihydrotestosterone (DHT), a male hormone created when the enzyme 5-alpha reductase converts Testosterone into DHT. Propecia (Finasteride), the latest approved medication for hair loss, inhibits one of the two types of this enzyme which turns Testosterone into DHT. Dutasteride, the medication discussed in this article, blocks both types of the enzyme and so it is believed it will be more effective at treating hair loss.

According to Rittmaster, men born with the type I 5-alpha reductase enzyme but without the type II 5-alpha reductase enzyme (the kind DHT blocks) experience hair loss when given Testosterone injections. He believes this shows that the type I enzyme does play a role in hair loss.

The early studies presented in San Francisco measure Dutasteride's ability to block DHT in comparison to Finasteride and a placebo. The Phase II studies involved 416 men aged 21-45 with Norwood patterns IIIv, IV, and V. The study lasted for 6 months and was randomized and double-blind (meaning the investigators did not know who was getting which medication). Placebo and Proscar were compared to 0.05, 0.1, 0.5, and 2.5mg of Dutasteride. Proscar (the 5mg form of Finasteride - Propecia is the 1mg form) was used because Propecia was not available at the time the studies started.

The first figures presented were the IC50 values for Propecia vs. Dutasteride. The IC50 value is the concentration of the drug needed to cause a 50% inhibition. The numbers below may not tell you much if you don't have a scientific background, but what it shows is that very little Dutasteride is required to inhibit type 1 5-alpha reductase but very large quantities of Propecia are required to do so. For type 2 5-alpha reductase (the type Propecia is intended to block), even less Dutasteride is required to block it than Propecia. So small doses of Dutasteride provide very good inhibition of both types of the 5-alpha reductase enzyme.

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<th>IC50 Values for Propecia vs. Dutasteride</th>
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<td>5-Alpha Reductase Enzyme Type</td>
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Both Serum (level circulating in the blood) Testosterone and Dihydrotestosterone were measured to evaluate Dutasteride's performance in comparison to Finasteride and placebo. The results showed that the placebo showed no inhibition, Finasteride was similar to the 0.1mg dose of Dutasteride for serum DHT inhibition (about 70%), and the higher doses of Dutasteride provided the greatest serum DHT inhibition (90% for 0.5mg and 96% for 2.5mg). Testosterone increased 4.4% for Finasteride, 6.4% for 0.05mg Dutasteride, 16% for 0.1mg Dutasteride, and 27% for 0.5mg and 2.5mg Dutasteride. Although the rise in Testosterone may seem high, the Testosterone levels were almost always within normal range according to Rittmaster.

Scalp DHT measurements were also assessed for both DHT and Testosterone. Scalp DHT was decreased 27% for 0.05mg Dutasteride, similarly for Finasteride (38%) and Dutasteride 0.1mg (37%), 54% for 0.5mg, and 82% for 2.5mg Dutasteride. Rittmaster concluded that these results show that most of the DHT in the scalp comes from type 1 5-alpha reductase.
Scalp Testosterone rose 24% for Finasteride, 46% for 0.05mg Dutasteride, 44% for 0.1mg Dutasteride, 104% for 0.5mg Dutasteride, and 154% for 2.5mg Dutasteride. Those results were the primary results detailed in this presentation. No results regarding efficacy or side effects were presented, other than a statement by Rittmaster that sexual side effects have occurred in the studies.

Dutasteride at this point remains on hold for Phase III studies. It is unknown why the company has not decided yet whether to proceed with Phase III trials. The two most likely reasons may be that either the company believes the drug will not make enough money if released (Propecia sales have been described as disappointing in several press articles evaluating sales) or that the company does not believe the treatment will be approved for the cosmetic purpose of hair loss due to side effects. Glaxo-Wellcome made a statement that a decision would be made in February regarding the trials, however to date no decision has been publicly announced.

The good news is that Phase III trials have already been completed for Benign Prostatic Hyperplasia (BPH, also known as enlarged prostates) and the drug is scheduled to be submitted to the FDA for approval sometime this year and approved and marketed sometime next year. Finasteride followed a similar course and was first approved for BPH and then later for hair loss. Readers of this site and other online sources will know when the drug is available for BPH and should be able to obtain it this way. The bad news is that the masses will most likely not know as only sources such as this web site provide this information. Regrowth.com has an official contact at Glaxo-Wellcome and has been keeping in touch with them regarding the status of Phase III trials for Dutasteride for hair loss. We will be contacting them this week to obtain an update.

**Ketocazole as an adjunct to finasteride in the treatment of androgenetic alopecia in men.**

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Dihydrotestosterone (DHT) binding to androgen receptors (AR) in hair follicles is commonly accepted as the first step leading to the miniaturizing of follicles associated with androgenetic alopecia (AGA). Testosterone is converted to DHT by the enzyme 5alpha-reductase. Finasteride a 5alpha-reductase inhibitor blocks the production of DHT and is currently used to treat AGA. The inhibition is not complete but a reduction of DHT systemically and in the scalp is accomplished. Ketoconazole has been clinically shown to be effective in the treatment of AGA. In this paper, evidence is presented to support the hypothesis that ketoconazole 2% shampoo has a local disruption of the DHT pathway. It is proposed that using ketoconazole 2%
shampoo as an adjunct to finasteride treatment could lead to a more complete inhibition of DHT and thus better treat AGA.