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Finasteride increases anagen hair in men with androgenetic alopecia

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Summary

Background The growth of scalp hair is a cyclical process of successive phases of growth (anagen) and rest (telogen). In previous clinical trials in men with androgenetic alopecia, treatment with finasteride increased scalp hair counts in a defined area (i.e. increased hair density).

Objectives The current study used a phototrichogram methodology to assess the effect of finasteride on the phases of the hair growth cycle.

Patients/Methods Two hundred and twelve men, age 18–40 years, with androgenetic alopecia were randomized to receive finasteride 1 mg daily or placebo for 48 weeks. At baseline and at 24 and 48 weeks, macrophotographs were taken to measure total and anagen hair count in a 1-cm^2 target area of the scalp.

Results At baseline, mean total and anagen hair counts in the finasteride group were 200 and 124 hairs, respectively (% anagen = 62%) and the anagen to telogen ratio was 1·74 (geometric mean). In the placebo group, the respective values were 196 and 119 hairs (% anagen = 60%) and 1·57. At week 48, the finasteride group had a net improvement (mean ± SE) compared with placebo in total and anagen hair counts of 17·3 ± 2·5 hairs (8·3% ± 1·4%) and 27·0 ± 2·9 hairs (26% ± 3·1%), respectively ($P < 0·001$). Furthermore, treatment with finasteride resulted in a net improvement in the anagen to telogen ratio of 47% ($P < 0·001$). In this study, treatment with finasteride 1 mg day^{-1} for 48 weeks increased both total and anagen hair counts, and improved the anagen to telogen ratio.

Conclusions These data provide direct evidence that finasteride 1 mg daily promotes the conversion of hairs into the anagen phase. These data support that finasteride treatment results in favourable effects on hair quality that contribute to the visible improvements in hair growth observed in treated patients.

Key words: androgenetic alopecia, finasteride, increased hair growth, phototrichogram, randomized double-blind placebo-controlled clinical trial, scalp hair counts

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The growth of scalp hair is a cyclical process, made up of successive phases of growth (anagen) and rest (telogen).[1] In non-balding scalp, more than 90% of scalp hair is in anagen.[2,3] However, with androgenetic alopecia in men (male pattern hair loss) the progressive shortening of the anagen phase, as well as the increase in the duration of the lag phase (the interval between the shedding of a telogen hair and the emergence of a replacement anagen hair) with successive hair cycles, cause a progressive decrease in the percentage of hair follicles in anagen.[3] In men with male pattern hair loss, only 60–80% of total hair is in anagen.[2,3] This shortening of the anagen phase leads to progressive miniaturization of hairs, which contributes to a decrease of visible hair over affected areas of the scalp.[4–6]

Dihydrotestosterone (DHT), the 5α-reduced metabolite of testosterone, is a key factor in the pathogenesis of male pattern hair loss in men.[7,8] Finasteride, a specific inhibitor of the type 2 5α-reductase enzyme, decreases serum and scalp DHT levels.[9,10] In clinical studies, finasteride 1 mg day^{-1} was shown to slow the progression of hair loss and increase hair growth in men with male pattern hair loss.[11] Furthermore, with continued treatment over 2 years, progressive clinical improvement was observed in patients while hair density remained stable.[11] These data suggest that finasteride continued to improve the quality (thickness, length, growth rate, growth duration and/or pigmentation) of hair, perhaps by increasing the number and duration of hairs in anagen.

The hair count methodology used in previous studies with finasteride measured the effect of the drug on total (anagen plus telogen) hair count in a defined area of the scalp.[11,12] This methodology provided a static measure of an otherwise dynamic process of hair growth, stasis and loss, and did not differentiate hairs that were actively growing (anagen hairs) from those which were resting and non-growing (telogen hairs).

The quantification of hair growth by a phototrichogram technique is a non-invasive method to provide reproducible serial measures of the number of hair follicles in the anagen phase relative to the total hair count, providing dynamic measurements of the hair growth cycle.[2,3,13] Common to all phototrichogram methodologies is the use of two macrophotographs of a defined region of scalp hair taken a few days apart. Using this technique, hairs in anagen, which lengthen by about 0·35 mm day^{-1}, can be differentiated from resting, non-growing telogen hairs. This study is the first using a phototrichogram methodology to assess the effect of finasteride on the hair growth cycle in treated subjects.

Methods

Study population

Two hundred and twelve men, 18–40 years of age, in good physical and mental health, with mild to moderate vertex balding (IIv, IIIv, IV and V according to a modified Norwood–Hamilton classification scale) were randomized to treatment groups.[14,15] One hundred and seventy-seven patients completed the 48-week study. Exclusion criteria included significant abnormalities on screening physical examination or laboratory evaluation, prior surgical correction of scalp hair loss, use of topical minoxidil within 1 year, use of drugs with androgenic or antiandrogenic properties, use of finasteride or other 5α-reductase inhibitors, or alopecia due to causes other than androgenetic alopecia. Alterations in hair style or dyeing of the hair were not allowed during the study.

Study design

This was a randomized, multicentre, double-blind, placebo-controlled study conducted at 10 investigational sites in Europe and two in the United States. Institutional review board approval and informed consent were obtained before patients entered the study.

After a screening procedure, which included measurement of total hair count,[12] patients completed a 2-week, single blind, placebo run-in period. At the beginning of the placebo run-in period, total and anagen hair counts were measured 3 days apart. Anagen hair count was repeated at the end of the placebo run-in period in order to obtain a mean value for baseline anagen hair count for each patient that was the average of two pretreatment measurements. (Because telogen hairs are non-growing, total hair count measurements, unlike anagen hair count measurements, could not be repeated within the same hair growth cycle once the hair had been clipped to the surface of the scalp.) At the end of the placebo run-in, patients were randomized to receive finasteride 1 mg or matching placebo (1 : 1) daily for 48 weeks.

After randomization, patients reported to the clinic every 12 weeks. Macrophotographs measuring total and anagen hair counts were taken at baseline and

every 24 weeks. Reports of adverse events were collected throughout the study.

Evaluation procedures

Hair counts. Total and anagen hair counts were determined from colour macrophotographs of clipped hair in a 1-cm^2 circular target area at the anterior leading edge of the vertex balding scalp, centred by a dot tattoo.[11,12] Hair in the target area was first clipped to approximately 1 mm length for determination of the total hair count (Fig. 1a) and then further clipped to the surface of the scalp in order later to differentiate growing anagen hairs that lengthen about 0·35 mm day^{-1} from resting telogen hairs, in the target area (Fig. 1b). Three days later, a macrophotograph of the target area was taken for the determination of anagen hair count, based on the number of hairs that had lengthened over the intervening time period (Fig. 1c).

Macrophotographs (Kodak KR-64 35-mm slide film) were taken using Nikon N-6006 cameras at fixed focus, distance (primary magnification 1 : 1·4) and exposure with the use of a Nikon 60 mm f2·8 lens and Canfield Scientific Inc. (CSI, Fairfield, NJ, U.S.A.) twinflash mounted on a scalp template. All film was processed at Qualex Laboratories, Fairlawn, NJ, U.S.A. CSI served as the central photography centre for quality assurance and hair counting. At the end of the study, macrophotographs were enlarged into 8 × 10 inch (20·3 × 25·4 cm) colour transparencies (final magnification, 5·7 : 1)[12] and were converted into dot maps of each visible hair by trained technicians who were blinded to patient, treatment and time. Dot maps were converted into hair counts by means of computer-based scanners and imaging software.[12]

Safety measurements. Safety measurements included clinical and laboratory evaluations, and adverse event reports.

Statistical analysis

The baseline anagen hair count was defined as the mean of the two anagen hair counts obtained at the beginning and end of the placebo run-in period. Baseline total hair count was defined as the total hair count obtained at the beginning of the placebo run-in; if this value was not available, then the total hair count obtained just after the screening visit was used. Telogen hair count was defined as the difference between total and anagen hair counts. The changes in anagen and total hair counts were assessed by the differences between the counts at week 48 and baseline, and the mean values for each treatment group were determined using the SAS™ (SAS Institute Inc., Cary, NC, U.S.A.) Least Squares Mean program. The percentage of hairs in anagen (percentage anagen) at week 48 was compared with the percentage of hairs in anagen at baseline. The ratio of anagen to telogen hair count (anagen to telogen ratio), which was first calculated as the ratio for each patient and then summarized over the entire patient sample, was compared at week 48 with the ratio at baseline.

Hypothesis testing for anagen and total hair counts, percentage anagen and anagen to telogen ratio was performed using analysis of variance (ANOVA). The treatment effect for each measure was assessed based

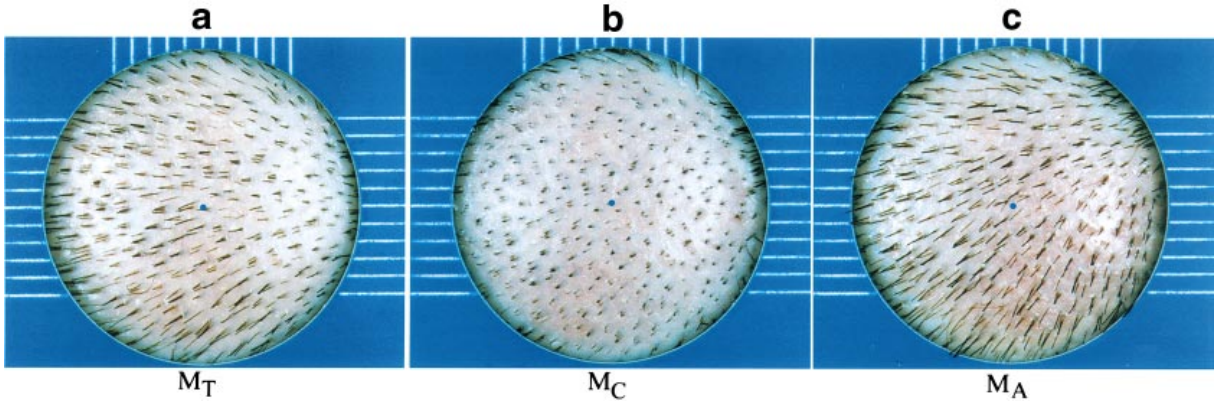

Figure 1. Phototrichogram methodology. Macrophotographs of a 1-cm^2 representative area of the balding scalp, centred by a dot tattoo. (a) Macrophotograph of target area for total hair count. (b) Macrophotograph of target area after hairs were further clipped to the surface of the scalp. (c) Three days later, macrophotograph of the target area for anagen hair count.

on the intention-to-treat principle, i.e. analysis included all men who had both baseline and at least one on-treatment measurement. Missing data were imputed by carrying forward the last on-treatment observation from the previous time point.

All efficacy analyses were corroborated with a non-parametric Cochran–Mantel–Haenszel (CMH) test. For all the efficacy analyses except for the anagen to telogen ratio, the CMH test yielded similar results to ANOVA. For the anagen to telogen ratio, the ratio in log scales satisfied the assumptions of homogeneity of variance and normality of distribution. Therefore, analysis of variance was performed on the log of the on-treatment to baseline anagen to telogen ratio (or change from baseline in log scale), and the geometric mean ratios are presented.

The focus of the safety analyses was on the biochemical measures, using ANOVA, and on adverse event reports. The between-group comparison of the proportion of patients with an adverse event was done using Fisher's exact test.

Results

Baseline characteristics

Two hundred and twelve men with active mild to moderate hair loss in the vertex area enrolled in the study. The two treatment groups were generally similar in terms of baseline characteristics (Table 1), although slightly more patients were classified as II vertex or IV hair loss pattern in the finasteride group, while slightly more patients were classified as III vertex or V in the placebo group. Ninety (85%) finasteride-treated subjects and 87 (82%) placebo-treated subjects completed the 48-week study.

Hair count

Total hair count. Mean total hair counts at baseline and week 48 are listed in Table 2. At week 48, patients on finasteride had a mean increase of 7·2 hairs (95% CI: 3·7–10·7) in the 1 cm^2 circular target area, while patients on placebo had a mean decrease of −10·1 hairs (95% CI: −13·6 to −6·7). Thus, treatment with finasteride for 48 weeks led to a net improvement (mean ± SE) in total hair count of 17·3 ± 2·5 hairs (8·3% ± 1·4%) in the target area compared with placebo ($P < 0·001$, Fig. 2a).

Anagen hair count. Mean anagen hair counts at baseline and week 48 are listed in Table 2. Finasteride treatment led to a progressive increase in mean anagen hair count over 48 weeks ($P < 0·001$, Fig. 2b), while treatment with placebo led to a decrease in mean anagen hair count ($P < 0·001$, Fig. 2b). At week 48, patients on finasteride had a mean increase of 18·0 anagen hairs (95% CI: 13·9–22·0), while patients on placebo had a mean decrease of −9·0 anagen hairs (95% CI: −13·1 to −4·9). Thus, treatment with finasteride for 48 weeks led to a net improvement in anagen hair count of 27 ± 2·9 hairs (26% ± 3·1%) in the target area compared with placebo ($P < 0·001$). Furthermore, the difference between the treatment groups increased between week 24 and week 48 ($P = 0·02$). The percentage of hairs in anagen (i.e. percentage anagen) increased from 62% at baseline to 68% at week 48 in the finasteride group, while it decreased from 60% at baseline to 58% at week 48 in the placebo group, resulting in a net improvement of 8% in percentage anagen hair with finasteride compared with placebo ($P < 0·001$).

Table 1. Baseline characteristics of men randomized

	Finasteride 1 mg ($n = 106$)	Placebo ($n = 106$)
Age (mean ± SE)	30·2 ± 0·6	29·3 ± 0·6
Age at which hair loss began (mean ± SE)	23·7 ± 0·5	22·6 ± 0·5
Number (%) of patients with family history[a]	74 (70)	71 (67)
Baseline hair count (mean ± SE)[b]		
Total	198 ± 5	197 ± 5
Anagen	124 ± 5	119 ± 5
% Anagen	62 ± 2	60 ± 2
Anagen/telogen ratio	1·74 ± 0·15	1·57 ± 0·13
Number (%) of patients with hair loss pattern[c]		
Grade II vertex	40 (38)	35 (33)
Grade III vertex	25 (24)	35 (33)
Grade IV	29 (27)	18 (17)
Grade V	12 (11)	18 (17)

[a] Family history = Parents or siblings with male pattern hair loss. [b] Measured in a 1-^{cm2} circle. [c] According to a modified Norwood–Hamilton Scale.

Table 2. Hair count data (mean ± SE)

	Finasteride 1 mg ($n = 93$)		Placebo ($n = 91$)	
	Baseline	Week 48	Baseline	Week 48
Total hair count	200·0 ± 5·2	207·4 ± 5·4	195·8 ± 5·4	186·2 ± 5·0
Anagen hair count	124·4 ± 4·9	142·5 ± 5·4	119·0 ± 4·6	110·2 ± 4·7
Telogen hair count[a]	75·1 ± 4·0	64·2 ± 3·3	76·8 ± 3·5	76·0 ± 3·5
Anagen/telogen ratio[b]	1·74 ± 0·15	2·33 ± 0·20	1·57 ± 0·13	1·43 ± 0·13

[a] Telogen hair count = (Total hair count) − (Anagen hair count). [b] Anagen/telogen ratio = Geometric mean (anagen hair count/telogen hair count).

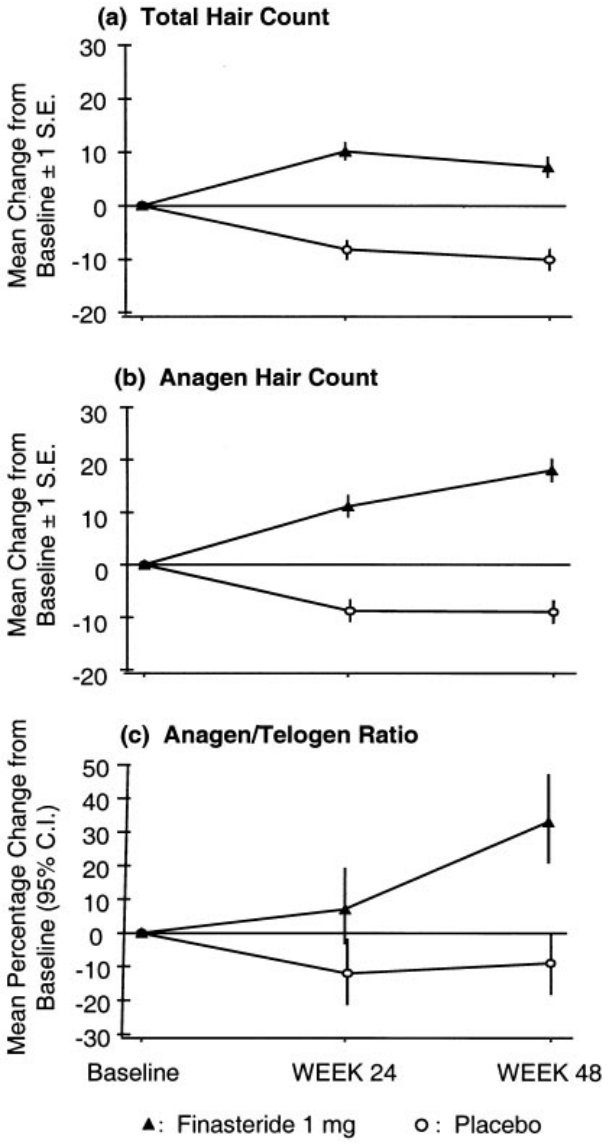

Figure 2. Hair count. Mean change (± SE) from baseline in (a) total hair count and (b) anagen hair count; (c) mean percentage change (± 95% confidence interval) from baseline in the anagen to telogen ratio.

Anagen to telogen ratio. Anagen to telogen ratios at baseline and week 48 are listed in Table 2. For the finasteride group, there was improvement in the anagen to telogen ratio ($P < 0·001$ at week 48), whereas treatment with placebo resulted in a decrease in the ratio that approached statistical significance ($P = 0·06$ at week 48) (Fig. 2c). At week 48, patients on finasteride had an increase in the anagen to telogen ratio of 33% (geometric mean; 95% CI: 21–47%), compared with patients on placebo who had a mean decrease of −9% (95% CI: −18% to 0%). This resulted in a net improvement in the anagen to telogen ratio of 47% for finasteride at 48 weeks compared with placebo (95% CI: 27–68%; $P < 0·001$). Furthermore, the difference between the treatment groups increased between week 24 and week 48 ($P = 0·023$).

Adverse events

Treatment with finasteride was generally well-tolerated. The incidence of drug-related adverse events was similar in the finasteride and placebo groups, and no patients discontinued the study due to an adverse event related to treatment with finasteride. In previous large clinical trials with finasteride 1 mg,[11] a few patients experienced reversible impairment of sexual function; no other adverse effects of finasteride were observed. In this study, drug-related sexual adverse events occurred in two patients (1·9%) in the finasteride group and in one patient (0·9%) in the placebo group. Of the two finasteride patients, one reported resolution of the adverse event while on therapy, whereas the other reported resolution of the adverse event 2 weeks after completion of therapy.

Discussion

Treatment with finasteride 1 mg day^{-1} has been demonstrated to improve scalp hair growth in men with male pattern hair loss,[11] confirming that DHT is a

key factor in the pathophysiology of androgenetic alopecia in men. The current study furthers our understanding of the pathophysiology of male pattern hair loss and the effect of DHT suppression with finasteride on the hair growth cycle in men with this condition.

In this study, finasteride treatment increased the amount and percentage of anagen hair and improved the anagen to telogen ratio in men with male pattern hair loss. Anagen hair count, first measured at 24 weeks, increased progressively over 48 weeks for finasteride-treated subjects. In contrast, placebo-treated subjects lost anagen hair during the study, consistent with the progressive shortening of the anagen phase duration that leads to the hallmark of androgenetic alopecia, follicular miniaturization. By 48 weeks, treatment with finasteride had resulted in a 26% net improvement in anagen hairs compared with placebo. This increase in anagen hair count, together with the increase in the anagen to telogen ratio, is direct evidence that treatment with finasteride promotes the conversion of hair follicles into the anagen phase.

While the duration of the anagen phase decreases between successive growth cycles in male pattern hair loss, the length of the lag phase also increases, contributing to the rate of apparent hair loss.[3] Thus, the increase in the anagen hair count observed with finasteride treatment could be due to the reversal of both of these processes. A more precise characterization of the effect of finasteride on the duration of the specific phases of the hair growth cycle would require that individual hair follicles be followed over successive cycles and the length of each phase measured.[3] Regardless, the results of this study confirm that finasteride treatment increases total hair count by increasing actively growing anagen hair.

The ratio of anagen to telogen hairs was also shown to increase progressively over 48 weeks of finasteride treatment. The increase in the anagen to telogen ratio with finasteride treatment at 24 weeks reflected primarily the changes in anagen hair count, as telogen hair count had not significantly changed from baseline. As the duration of the telogen phase is not altered in male pattern hair loss,[3] finasteride treatment is not likely to affect this phase directly. Rather, as anagen phase is prolonged, fewer hairs are in telogen. Thus, the telogen hair count would be expected eventually to decrease with finasteride, due to continued prolongation of the anagen phase. This is consistent with the observation that, in this study, the reduction in the telogen hair count, and its favourable effect on the anagen to telogen ratio, followed the increase in the anagen hair count with finasteride. These positive changes in the hair cycle, associated with the progressive improvement in scalp coverage observed in treated subjects, imply favourable consequences on clinically important aspects of hair quality (thickness, length, growth rate, growth duration and/or pigmentation) in men on treatment.

As in men, similar hair growth cycle abnormalities are observed in women with androgenetic alopecia.[16,17] However, results from a placebo-controlled study of postmenopausal women with androgenetic alopecia demonstrated no benefit of finasteride after 1 year.[18] This difference in treatment efficacy between men and women may be due to gender differences in the role of type 2 5α-reductase in the pathophysiology of androgenetic alopecia. Despite this, use of a type 2 5α-reductase inhibitor such as finasteride is contraindicated in women during pregnancy due to the potential risk of undervirilization of a male fetus.[19]

In conclusion, the results of this study confirm that in men with male pattern hair loss, treatment with finasteride 1 mg day^{-1} favourably affects the hair growth cycle by promoting hair follicles into the anagen phase. Anagen hair count and the anagen to telogen ratio increased progressively with continued treatment with finasteride over the duration of the 48-week study. In contrast, these parameters decreased with placebo treatment, consistent with the progressive follicular miniaturization that is the hallmark of male pattern hair loss. Finasteride 1 mg day^{-1} was generally well tolerated by men in this study and adverse events related to therapy with finasteride were minimal.

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