International Journal of Dermatology

Report

Effect of dutasteride 0.5 mg/d in men with androgenetic alopecia recalcitrant to finasteride

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Funding sources: None
Conflicts of interest: The authors state no conflict of interest.

Abstract

Background Finasteride at a dose of 1 mg/d has been reported to show no significant improvement in 30–50% of patients with androgenetic alopecia (AGA). Dutasteride, a dual inhibitor of both type I and type II 5 alpha-reductase, inhibits the conversion of testosterone to dihydrotestosterone, which is the key contributor of AGA.

Materials and methods Our aim is to evaluate clinical efficacy and tolerability of dutasteride in men with AGA who do not show clinical improvement to the conventional finasteride treatment. A total of 35 Korean men with AGA who had not shown significant clinical improvement when treated with finasteride 1 mg/d for at least six months received dutasteride at a dose of 0.5 mg/d for six months. Efficacy was evaluated by global photograph assessment and phototrichogram. Safety assessment was performed through physical examination and adverse event report.

Results Of the 31 patients who completed the treatment, 24 patients (77.4%) were improved by the global photography (17 were slightly, six moderately, and one markedly improved) compared with the post-finasteride treatment. There was no significant change in seven patients (22.6%), and aggravation was not reported. Hair density and thickness significantly increased by 10.3% (87 ± 12–96 ± 12/cm^2) and 18.9% (0.053 ± 0.012–0.063 ± 0.011 mm), respectively, in phototrichogram assessment. Side effects included transient sexual dysfunction in six patients (17.1%).

Conclusions Dutasteride is suggestive to be an alternative treatment option to patients with AGA who do not clinically respond to finasteride in six months.

Introduction

Androgenetic alopecia (AGA) is an androgen-mediated condition that is characterized by a progressive decline in visible scalp hair density. Genetically predisposed hair follicles are the target of dihydrotestosterone (DHT), which leads to the progressive miniaturization of hair follicles and hair thinning.[1] Due to the increasing incidence of AGA and high concerns about cosmetic appearance in modern society, treatment for this condition is in strong demand.[2,3]

Finasteride is a type II 5 alpha-reductase inhibitor that suppresses the conversion of testosterone to DHT, the androgen responsible for AGA in genetically predisposed men. The finasteride regimen, which has been used for AGA treatment worldwide, has been proved to stimulate new hair growth and produce significant improvement of scalp hair in affected people.[4–12] However, 30–50% of patients with AGA treated with finasteride have been reported to show clinically no improvement.[4,9] Though no more hair loss is also the therapeutic effect of finasteride, the fact that the patient's expectation from the treatment is not the maintenance of their alopecic appearance but rather the improvement in their hair count and density requires an alternative treatment for them.

Dutasteride, the inhibitor of both type I and type II 5 alpha-reductase, is approved for the treatment of symptomatic benign prostatic hyperplasia (BPH) at the daily dose of 0.5 mg. It is approximately three times more potent than finasteride in inhibiting type II 5 alpha-reductase, and 100 times in inhibiting type I 5 alpha-reductase.[13] As a result, dutasteride at a dose of 0.5 mg/d was proved to reduce serum DHT levels by more than 90%, while finasteride at a dose of 5 mg/d decreases serum DHT by 70%.[13,14] Though dutasteride has been approved for the treatment of symptomatic BPH, it has also been tried in the treatment of AGA. In studies where dutasteride was used as the primary drug

for the AGA treatment, dutasteride is proved to increase hair count, reduce further hair loss, improve scalp coverage, and fulfill patient satisfaction significantly.[15,16]

The aim of this study is to evaluate clinical efficacy and tolerability of dutasteride in men with AGA who showed clinically no improvement to the conventional finasteride treatment.

Materials and methods

Patient population

Men with mild to moderate AGA who did not show significant improvement when treated with finasteride at a dose of 1 mg/d for at least six months were enrolled. The response to the finasteride treatment was evaluated by two dermatologists using clinical photographs (a vertex view and frontal view). The history of finasteride treatment including patients' compliance, any adverse event, and concurrent topical minoxidil use before the enrollment was screened via electric medical record (EMR). Patients with low compliance to the finasteride who skip the medication for at least one week were excluded. The patients were required to have no history of systemic illness, no history of any systemic drugs other than finasteride within the past six months, and no significant abnormality in a physical and laboratory evaluation including complete blood count, liver function, and renal function test at the screening. All patients were instructed not to use topical minoxidil or any androgenic or antiandrogenic treatment during the course of the study. The study was approved by the Institutional Review Board in our hospital, and informed consents were obtained from all of the patients before initiating dutasteride treatment.

Study design

After the initial screening visit, patients eligible to enter the study were treated with dutasteride at a dose of 0.5 mg daily for 24 weeks. Follow-up visits were scheduled every four weeks. At each visit, a medical examination was done, and adverse effects were recorded. High-resolution digital photographs and phototrichograms were taken at every visit. Compliance to the treatment was screened by bringing residual drugs to the clinic at each follow-up visit. Patients who skipped the medication for more than one week at each visit were withdrawn.

Efficacy assessments

Global photographic assessments

Clinical assessments were performed by two blinded dermatologists using clinical photographs with a standardized vertex and frontal view. They independently reviewed the paired slides of scalp at the baseline, post-finasteride treatment and post-dutasteride treatment, using a seven-point scale as follows: greatly improved (score of +3); moderately improved (+2); slightly improved (+1); unchanged (0); slightly aggravated (−1); moderately aggravated (−2); and greatly aggravated (−3). This technique has been demonstrated to have excellent test–retest reproducibility.[4]

Phototrichogram assessments

To determine the hair density and thickness in the target area, the hair in a 70-mm^2 circle at the leading edge of the vertex bald spot was clipped to a length of about 1 mm. A central tattoo was placed to enhance the reproducibility of the assessment.[17] Using a semi-automatic hand-held phototrichogram, Follicoscope® (Lead M cooperation, Seoul, Korea), the number and the mean thicknesses of the hairs in the circle were measured automatically. Figure 1 shows how this measurement is performed using Follicoscope®. Because we use phototrichogram assessment for patients with AGA using Follicoscope® in a daily clinical setting, hair density and thickness at the baseline were also obtained by EMR.

Statistical analysis

Statistical analysis was performed using SPSS version 18. The significance of changes in the global photographic assessments and hair density and thickness was determined using the Mann–Whitney *U*-test. Differences among the results obtained from the baseline, post-finasteride treatment, and post-dutasteride treatment were analyzed using the Wilcoxon signed rank test. Statistical significance was accepted for *P*-values of less than 0.05.

Safety assessments

Safety assessment was performed through physical examination, laboratory evaluations, and reports of sexual function and adverse events every four weeks. Sexual function was evaluated by asking subjects the occurrence of decreased libido, erectile dysfunction, and ejaculation disorder.

Results

A total of 35 Korean men with mild to moderate AGA were enrolled in the study. Baseline characteristics of enrolled patients are summarized in Table 1. The patient age ranged from 20 to 60 years (mean ± SD, 33.7 ± 7.9 years). Duration of finasteride treatment ranged from 185 to 1036 days (mean ± SD, 402.4 ± 235.9 d). Twenty-four patients had a history of concurrent use of topical minoxidil with finasteride. Of the 35 patients, 31 patients completed the treatment, three patients were lost to follow-up, and one patient was dropped out due to the side effect of dutasteride–sexual dysfunction.

Global photographic assessment

Compared with the baseline, two of the 35 patients (5.7%) were slightly improved after finasteride medication in

Figure 1 Using Follicoscope® (Lead M cooperation, Seoul, Korea), the number (a) and the mean thicknesses (b) of the hairs in the circle were measured automatically

clinical photographic assessment (Fig. 2). The other 30 patients (85.7%) showed no change, and three patients (8.6%) reported even more hair loss despite the finasteride administration. Of the 31 patients who completed the six months of dutasteride treatment, 24 patients (77.4%) were improved (17 were slightly, six moderately, and one markedly improved). There was no significant change in seven patients (22.6%). No aggravation was reported. The mean global photographic assessment score for the post-finasteride treatment (mean ± SD, 0.10 ± 0.30) was not statistically significant compared with the baseline. Meanwhile, the score for the post-dutaseride treatment (mean ± SD, 1.06 ± 0.77) showed a significant increase compared with the post-finasteride treatment. Figure 3 presents clinical photographs that illustrate typical improvements of hair loss.

Table 1 Demographic characteristics

Characteristics	Dutasteride (n = 35)
Age (years), mean ± SD	33.7 ± 7.9
Finasteride treatment duration (days), mean ± SD	402.4 ± 235.9
Hamilton-Norwood type	
II	3
II vertex	5
III	10
III vertex	7
IV	10

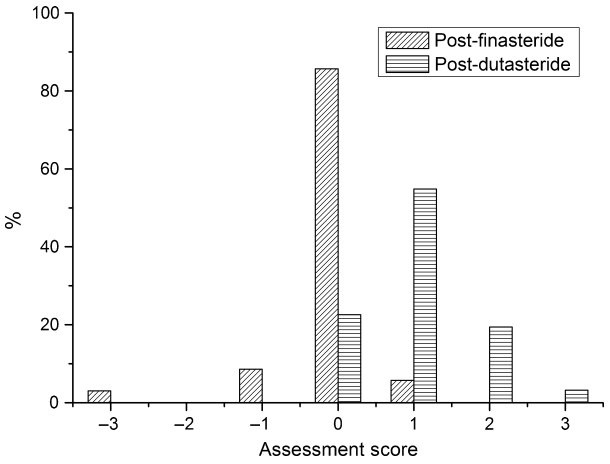

Figure 2 Global photographic assessment of patients with AGA after finasteride (post-finasteride) and dutasteride (post-dutasteride) compared with the baseline. Twenty-four out of 31 patients (77%) who showed little improvement after finasteride treatment were improved (17 were slightly, six moderately and one markedly improved) after dutasteride treatment

Phototrichogram assessment

Post finasteride, hair density was significantly increased while hair thickness was not significantly different. Six months after switching to dutasteride, there was significant improvement in both hair density and thickness (Fig. 4; Table 2).

Safety assessments

Two patients (5.7%) complained of transient decreased libido while taking finasteride. The sexual dysfunction disappeared in one of the patients and was relieved in the other after alternating medication to dutas-teride. Transient decreased libido was also reported in six patients (17.1%) receiving dutasteride. This includes the one patient who showed sexual dysfunction to a high degree while taking finasteride. One of the six patients discontinued the treatment because of that reason. Other adverse effects, such as impotence, ejaculation disorder, or gynecomastia, were not reported. No serious adverse effects were reported.

Discussion

Androgenetic alopecia is an androgen-mediated condition characterized by a progressive decline in visible scalp hair density. Genetically predisposed hair follicles are the target of DHT, which leads to the progressive miniaturization of hair follicles and hair thinning.[1] Finasteride is a type II 5 alpha-reductase inhibitor that suppresses the conversion of testosterone to DHT, the androgen responsible for AGA in genetically predisposed men.

The regimen of finasteride at an oral dose of 1 mg/d has been proved to stimulate new hair growth and produce significant improvement of scalp hair in patients with AGA.[4–12] When patients with AGA were treated with finasteride at a dose of 1 mg/d, vertex hair presented improvement in 48% of the patients after 12 months and 66% after 24 months.[4] No further vertex hair loss was reported in 83% of patients receiving finasteride for 24 months. In a 2-year trial of finasteride with the same dose, 39% of the patients showed significant hair growth in the vertex compared with the control group from six months after initiating the treatment to the end of the study.[9] No further vertex hair loss was reported in 55% of the patients, while 6% of the patients showed slight decrease in their vertex hair in 24 months.

However, 30–50% of patients with AGA treated with finasteride have been reported to present no improvement in their hair count and density.[4,9] The fact that patients' expectations from the treatment is improvement in their hair count and density rather than alopecic appearance, an alternative treatment is necessary.

Dutasteride, an inhibiting agent of both type I and type II 5 alpha-reductase, is originally approved for the treatment of symptomatic BPH at a dose of 0.5 mg/d. It is approximately three times more potent than finasteride in inhibiting type II 5 alpha-reductase.[13] In addition, dutasteride also inhibits type I 5 alpha-reductase 100 times more effectively compared with finasteride. As a result, dutasteride at a dose of 0.5 mg/d was proved to reduce serum DHT levels by more than 90%, while finasteride at a dose of 5 mg/d decreases serum DHT by 70% in four weeks and 24 weeks.[13]

Recently, several studies have reported the efficacy of dutasteride in patients with AGA. When one of the 17 pairs of identical twins with AGA received dutasteride 0.5 mg/d for 12 months while the other received placebo, dutasteride significantly accelerated hair growth in investigator assessment and patient self-assessment ques-

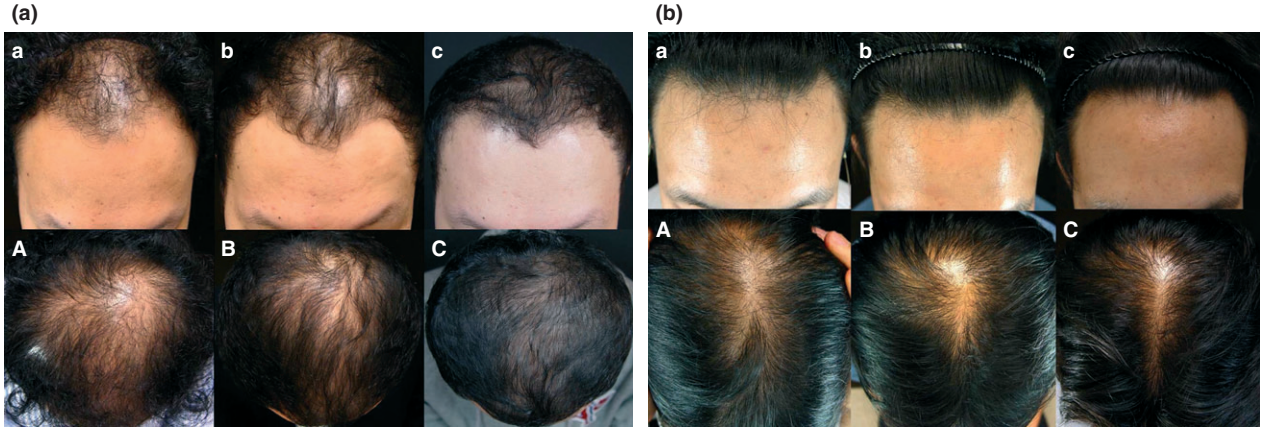

Figure 3 (a) Patient with AGA. At baseline (A), post-finasteride treatment (B) and post-dutasteride treatment (C). Clinical improvements were observed after dutasteride treatment. (b) Patient with AGA. At baseline (A), post-finasteride treatment (B) and post-dutasteride treatment (C). Clinical improvements were observed after dutasteride treatment in non-responsive to finasteride 1mg

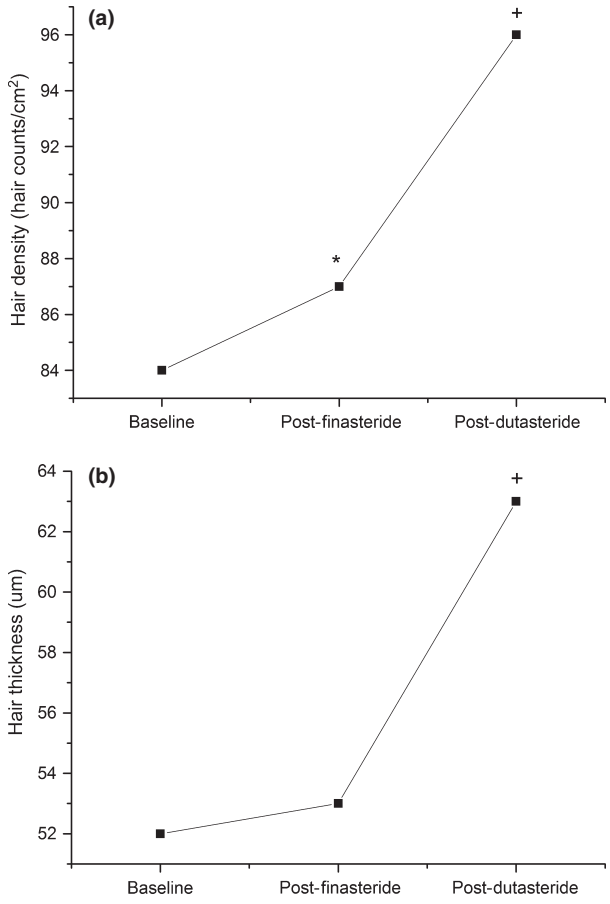

Figure 4 Change in hair density (a) and hair thickness (b) after finasteride and dutasteride treatment, respectively. *$P < 0.05$, compared with the baseline. †$P < 0.05$, compared with post-finasteride

Table 2 Hair density and hair thickness (mean ± SD) assessed at the baseline, after finasteride treatment and after dutasteride treatment

	Baseline	Post-finasteride	Post-dutasteride
Hair density (hair counts/cm^2)	84 ± 13	87 ± 12*	96 ± 12†
Hair thickness (μm)	52 ± 12	53 ± 12	63 ± 11†

*$P < 0.05$, compared with the baseline. †$P < 0.05$, compared with post-finasteride.

tionnaires.[18] Also, dutasteride increased hair growth significantly in patients with AGA in a dose-dependent manner in a phase II, double-blinded, placebo-controlled, 24-week study.[15] This study proved that dutasteride at a dose of 0.5 mg/d increased hair growth significantly after 12 and 24 weeks compared with the control. This result was at least comparable with finasteride at a dose of 5 mg/d. In addition, treatment with dutasteride at a dose of 2.5 mg/d was superior to that of finasteride in increasing hair growth in 12 and 24 weeks. However, dutasteride-related sexual dysfunction including decreased libido (13%) also increased compared with dutasteride at a dose of 0.5 mg/d (1%) and with finasteride at a dose of 5 mg/d (4%).

A randomized, double-blinded, placebo-controlled phase III study compared the efficacy, safety, and tolerability of a daily dose of 0.5 mg of dutasteride for six months vs. placebo in patients with AGA.[16] Dutasteride was found to be significantly more effective than placebo in the aspects of hair count, self-assessment, and

global photographic assessment. Dutasteride-related sexual dysfunction occurred in only 4.1% of the dutasteride group, which was similar to the frequency with finasteride previously reported.[4]

Our study showed that the treatment with dutasteride at a dose of 0.5 mg/d was effective in improving the appearance of scalp hair by increasing hair density and thickness in Korean men who had previously shown clinically no improvement in hair growth to the conventional finasteride treatment. After six months of dutasteride treatment, 77.4% of the patients showed significant improvement in global photographic assessment. Compared with the post-finasteride treatment, hair density and thickness significantly increased by 10.3% and 18.9%, respectively, in phototrichogram assessment.

Though finasteride at a dose of 1 mg/d was generally well-tolerated, finasteride-related sexual dysfunction, including decreased libido, ejaculation disorder, and erectile dysfunctions, has been reported in 1–4% of the patients.[4,5,11,19] Though dutasteride was also well tolerated in many studies, dutasteride-related sexual dysfunctions have been reported as well.[20–22] Three percent of the patients receiving dutasteride at a dose of 0.5 mg/d for 24 weeks complained of decreased libido and ejaculation disorder.[15] When the daily dose of dutasteride was 2.5 mg, the incidence of decreased libido also increased, reported in 12.7% of the patients. In the study by Eun *et al.*, sexual dysfunction occurred in 4.1% at the same dose of dutasteride for 24 weeks.[16]

However, sexual adverse events were reported in 17.1% (6/35) of the patients in our study, which was quite higher than the previous two studies. One explanation is the possibility of placebo effect. While dutasteride-related sexual dysfunctions have been reported in 3–4.1% of the patients in the studies by Olsen and Eun, the same adverse events were also observed in 7.8% and 5.3% of the patients in the placebo group, respectively.[15,16] Sexual disorders, including decreased libido, ejaculation disorder, and impotence, have psychological factors in their pathophysiology. Therefore, the obsessive idea that they are taking the drug that could possibly influence their sexual dysfunction could increase the incidence of sexual dysfunction. It could happen in the dutasteride-treated group as well as the control group, resulting in the high incidence of sexual dysfunction.

The other explanation is that dutasteride-related sexual dysfunction occurs most frequently early in therapy. Roehrborn *et al.* reported the incidence of dutasteride-related sexual dysfunction, including impotence, decreased libido, and ejaculation disorder, decreased consequently at 11.7, 2.1, 2.4, and 0.5% after 1, 2, 3, and 4 years, respectively.[20] Especially, the incidence of decreased libido, which was observed as 17.1% in our 24-week study, was observed in a decreasing manner as 3.6, 0.5, 0.5, and finally 0% after four years. Similarly, Debruyne *et al.* also reported dutasteride-related sexual dysfunction in 11.5, 2.8, 2.1, and 0.6% of the patients receiving dutasteride at a dose of 0.5 mg/d after 1, 2, 3, and 4 years.[21] In our study, the study period, 24 weeks, might be too short to observe the decrease of dutasteride-related sexual dysfunction.

Those patients with AGA who did not respond to finasteride after six months were selected by clinical assessment. Several studies have reported that finasteride at a dose of 1 mg/d improved scalp hair in patients with AGA within three months.[4] However, because the response to finasteride is not linear, continued treatment with finasteride may lead to improved hair growth beyond the initial six months or even 24 months of treatment period. One explanation for this delayed response to finasteride is that the patient's hair count significantly increases during the initial treatment period, but an improvement in global photographic score may not be apparent until six months. Though patients who do not show improvement clinically with the use of finasteride for six months were enrolled in our study, phototrichogram revealed significantly increased hair density compared with that before the initiation of finasteride. Therefore, the term "slow-responders" to finasteride is more appropriate rather than non-responders.

This study attempted to address the hypothesis that switching slow-responders to finasteride who have not demonstrated increased hair growth on finasteride to dutasteride provides incremental improvement in hair growth. There is still the possibility of an increase in hair growth if finasteride is continued. However, due to the absence of a parallel control group of patients who continued on finasteride, our study has limitations to clearly prove the hypothesis. Nevertheless, clinicians usually confront the situation where patients with AGA do not show clinical improvement in hair growth despite the long-term use of finasteride. This study could provide the therapeutic basis for dutasteride as an alternative treatment option for patients with AGA recalcitrant to finasteride over six months. Further research is required to decide how long finasteride should be maintained and when to switch to dutasteride if there was no clinical improvement.

In conclusion, dutasteride at a dose of 0.5 mg/d is suggested to be an alternative therapeutic option for patients with AGA if there is no clinically significant improvement in hair growth with the treatment of finasteride for six months. However, the incidence of dutasteride-related sexual dysfunction is reported to be higher than with finasteride; thus, it is premature to insist that dutasteride at a dose of 0.5 mg/d be the primary treatment for AGA. Further research is required to identify the incidence of

dutasteride-related sexual dysfunction and the timing to switch to dutasteride if there was no clinical improvement.

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