



ORIGINAL ARTICLE

Safety and Tolerability of the Dual 5-Alpha Reductase Inhibitor Dutasteride in the Treatment of Androgenetic Alopecia

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Background: After the approval of dutasteride for androgenic alopecia (AGA) in 2009, Korean authority required a post-marketing surveillance to obtain further data on its safety profile. **Objective:** The objective was to monitor adverse events (AEs) of dutasteride 0.5 mg in Korean AGA male patients in a clinical practice environment. **Methods:** Open label, multi-center, non-interventional observational study was done from July 2009 to July 2013. AGA subjects (18~41 years of age) with no experience of dutasteride were enrolled. Dosage regimen was recommended according to the prescribing information. The incidences of any AEs, serious adverse events (SAEs), and adverse drug reactions (ADRs) were evaluated. Multiple logistic regression method was used to identify risk factors related to ADRs. Effectiveness was generally evaluated by physicians. **Results:** During study period, 712 subjects were enrolled. The subjects of 29.3 ± 6.0 years old exposed to dutasteride for 204.7 ± 161.5 days. One hundred and ten (15.4%) of sub-

jects reported 138 AEs. Four subjects (0.6%) reported 5 SAEs (right radius fracture, 2 events of chronic follicular tonsillitis, influenza infection, and acute appendicitis). Sixty-six subjects (9.3%) reported 80 ADRs. Most frequent ADRs were libido decreased (9 subjects, 1.3%), dyspepsia (8 subjects, 1.1%), impotence (7 subjects, 1.0%), and fatigue (5 subjects, 0.7%). Other interested ADRs were sexual function abnormality (4 subjects, 0.6%), gynecomastia (2 subjects, 0.3%), and ejaculation disorder (1 subject, 0.1%). Most subjects (78.6%) showed overall improvement after treatment of dutasteride in the effectiveness. **Conclusion:** Dutasteride 0.5 mg is to be well-tolerated in 18 to 41 years old AGA patients in a clinical practice environment. (*Ann Dermatol* 28(4) 444~450, 2016)

-Keywords-

Alopecia, Drug-related side effects and adverse reactions, Dutasteride, Product surveillance, postmarketing, Safety, Treatment outcome

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Conflict of interest: Yil-Seob Lee and Joon Hyung Kim are employees of GlaxoSmithKline and have stock/stock options in the company. Any other potential conflict of interest relevant to this article was not reported.

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INTRODUCTION

Androgenetic alopecia (AGA) is an androgen-induced, progressive disorder, which is the most common type of alopecia after puberty. In AGA patients, hairs in affected area get thinner and shorter. A hairline recedes at the temples and the vertex gets bald.

AGA is often perceived as normal aging process, but many patients are suffering from AGA. DeMuro-Mercon et al.¹ revealed that 90% of Norwegian men aged 26~50 years self-reported having at least some hair loss. In this study, men who perceive themselves as having greater

hair loss are more suffered from their hair loss. The prevalence of AGA in North East Asian (Japanese, Taiwanese, Chinese, and Korean) is lower than in Caucasians²⁻⁵. Patients visiting clinics are getting younger⁶, and hair loss can significantly cause psychosocial manifestations, leading to economic on household health expenditure particularly in young patients⁷.

Given the high prevalence, the treatment option for AGA is relatively limited though minoxidil and 5-alpha reductase inhibitors are widely used⁸. Dutasteride 0.5 mg was recently added on the treatment options. Several studies proved that 0.5 mg of dutasteride improved hair growth and was relatively well tolerated for the treatment of AGA⁹⁻¹¹. However, concerns on the safety and tolerability remain.

The objective of this study was to explore adverse events of dutasteride in Korean patients with AGA as per the requirement of Korea Ministry of Food and Drug Safety.

MATERIALS AND METHODS

Subjects

Men 18 to 41 years of age diagnosed as AGA were eligible for this study if they will be treated with dutasteride 0.5 mg on the physician's medical judgement. Patients who previously treated with minoxidil or finasteride were eligible for this study but they must never have used dutasteride before for any reasons. Subjects who could not comply with the requirements of the protocol and follow the administration regimen were not enrolled. The institutional review boards approved the study protocol. The study was carried out from July 2009 to July 2013 at 21 centers in Korea (Ajou University Hospital, Asan Medical Center, Chonnam National University Hospital, Chung-Ang University Hospital, Chungbuk National University Hospital, Chungnam National University Hospital, Dankook University Hospital, Dong-A University Hospital, Inha University Hospital, Keimyung University Dongsan Medical Center, Konkuk University Medical Center, Korea University Ansan Hospital, Kyung Hee University Hospital at Gangdong, Kyungpook National University Hospital, Myongji Hospital, Samsung Medical Center, SMG-SNU Boramae Medical Center, Seoul National University Bundang Hospital, Seoul National University Hospital, Severance Hospital, Wonju Severance Christian Hospital). Approximately 900 subjects planned to be enrolled in order to provide 600 evaluable subjects for the primary analysis (according to Guideline for Korean New Drug Re-Examination¹²) in consideration of an expected 30% drop out rate.

Study design

In the open-label, multi-center, observational study, dermatologists in Korea were asked to document on case report forms their observations for the contracted number of AGA subjects who were to receive dutasteride 0.5 mg daily on the physician's medical judgement.

Treatment

The subjects received dutasteride as monotherapy or as part of a combination therapy, based on the physician's medical judgement. In accordance with the prescribing information, dutasteride 0.5 mg once a day was prescribed. The treatment duration was not pre-specified.

Subject evaluation

Each physician decided visit schedules based on their routine practices. At the initial consultation, demographic information (including age, height, and weight), medical history (including allergy history, family history, concomitant diseases, and AGA treatment history), modified Norwood-Hamilton classification, and concomitant medications were recorded. Physicians were guided to record any treatment-emergent adverse events during the follow up. At the last treatment visit, the effectiveness was additionally evaluated as "improved", "no change", "worsened" and "not assessed." The overall effectiveness assessment will depend on the physician's medical judgement.

Definitions

An adverse event (AE), which was coded based on World Health Organization Adverse Reactions Terminology 092, was defined as any untoward medical occurrence in a subject temporally associated with the use of a dutasteride, whether or not considered related to the medicinal product. Serious adverse event (SAE) is any untoward medical occurrence that at any dose; 1) results in death, 2) is life-threatening, 3) requires inpatient hospitalisation or prolongation of existing hospitalisation, 4) results in persistent or significant disability/incapacity, or 5) is a congenital anomaly/birth defect. An adverse drug reaction (ADR) was defined as all noxious and unintended responses related to dutasteride 0.5 mg. Physicians classified the relatedness into 6 category; "certain", "probable/likely", "possible", "unlikely", "conditional/unclassified," and "unassessable/unclassifiable." If the causality between dutasteride and AEs are considered "certain", "probable/likely", "possible" "conditional/unclassified," and "unassessable/unclassifiable," AEs were classified as ADRs.

After dutasteride treatment, the effectiveness was evaluated by treating physicians as "improved", "no change",

“worsened”, or “not evaluable”. “Improved” is defined as an improvement or maintenance of the treating condition. Patients are classified as “improved” if the patient experienced hair growth or if the patient experienced comparable hair growth from prior treatment or if the patient experienced less hair loss. “No change” is defined as no improvement of the condition after treatment. Patients are classified as “no change” if the patient is on treatment and experiences the no improvements of hair loss compared to baseline or without any treatment. “Worsened” is defined as worsening of the condition after treatment. Patients are classified as “worsened” if the patient on treatment and experiences worsening of hair loss compared to baseline or without any treatment.

Statistical analysis

Continuous variables are expressed as the mean with one standard deviation and discrete variables are expressed as the frequency and rate. The primary objective was to evaluate the frequency and cases of AE after dutasteride administration. After all AEs were classified by preferred terms and system-organ classes, frequency and percent of each AE were estimated. Chi-square test or Fisher’s exact test were used in order to check whether ADRs are associated with specific factors. Multivariate logistic regression was used to predict the factors affecting the frequency of ADR. The potential factors were initially evaluated separately, then all the factors with a p -value smaller than 0.2 were tested simultaneously in the multivariate logistic regression model. p -value less than 0.05 was considered statistically significant. Statistical calculation was carried out using SAS ver 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Subject characteristics

During the study period, 712 subjects were enrolled and exposed to dutasteride for 204.7 ± 161.5 days. The mean age of subjects was 29.3 ± 6.0 years and 56.4% of subjects were less than 30 years old. The mean height and weight were 173.9 ± 5.0 cm and 71.5 ± 9.0 kg, respectively. The number of subjects with the AGA treatment history was 292 (41.0%). The number of subjects classified by modified Norwood-Hamilton classification is described in Table 1. Of the treatment experienced subjects, 109 subjects (37.3%) were treated with combination of finasteride and minoxidil, 104 subjects (35.6%) with finasteride, and 55 subjects (18.8%) with minoxidil. It is reported that 488 subjects (68.6%) had family history of AGA and 52 subjects (7.3%) had allergic history. In all, 436 subjects (61.2%) took other medicines with dutasteride and 55

Table 1. Number of subjects with baseline modified Norwood-Hamilton classification

Classification	Total subjects	Treatment naive	Treatment experienced
1	111 (15.6)	63 (15.0)	48 (16.4)
2, 2A	226 (31.7)	135 (32.1)	91 (31.2)
3, 3A, 3 vertex	254 (35.7)	165 (39.3)	89 (30.5)
4, 4A	65 (9.1)	33 (7.9)	32 (11.0)
5, 5A	46 (6.5)	19 (4.5)	27 (9.2)
6	10 (1.4)	5 (1.2)	5 (1.7)
7	0	0	0
Total	712 (100.0)	420 (100.0)	292 (100.0)

Values are presented as number (%).

subjects (7.7%) used minoxidil as well. The average treatment duration was 204.7 ± 161.5 days.

Safety and tolerability

Of 712 subjects, 110 subjects (15.4%) reported 138 AEs. Dyspepsia (11 subjects, 1.5%) was most frequent AE, followed by decreased libido (9 subjects, 1.3%), pruritus (7 subjects, 1.0%), rash (7 subjects, 1.0%), and impotence (7 subjects, 1.0%). The number AEs reported to be resolved was 106 (76.8%).

Four subjects (0.6%) reported 5 SAEs. Twenty-six years old subject taking dutasteride for about 3.5 months had surgery for right distal radius fracture. Thirty-one years old subject taking dutasteride for 2 months admitted for influenza infection. Thirty-five years old subject admitted on the day dutasteride was prescribed and had tonsillectomy for chronic follicular tonsillitis. After a few days he had chronic follicular tonsillitis again and underwent medical treatment. Twenty-five years old subject taking dutasteride for 8 months had appendectomy for acute appendicitis. All these SAEs were recovered and considered not to be associated with treatment.

Sixty-six subjects (9.3%) reported 80 ADRs (Table 2). Most frequent ADR was libido decreased (9 subjects, 1.3%), followed by dyspepsia (8 subjects, 1.1%), impotence (7 subjects, 1.0%), and fatigue (5 subjects, 0.7%). Other interested ADRs were sexual function abnormality (4 subjects, 0.6%), gynecomastia (2 subjects, 0.3%) and ejaculation disorder (1 subject, 0.1%). No subject reported prostate cancer, breast cancer or heart failure.

Frequency of adverse drug reactions by subject profiles are described in Table 3. The results of multivariate analysis for significant factors affecting the rate of ADR are Table 4. Age was found to be significantly associated with the frequency of ADR after controlling for potential confounders. Older subjects experienced more frequent ADR.

Table 2. The frequency of adverse drug reactions

Adverse drug reaction	Subjects (n = 712)	Total events	Resolved events	Unresolved events	Unknown results
Skin and appendages disorders	18 (2.5)	18	13	1	4
Rash	4 (0.6)	4	3	1	0
Pruritus	3 (0.4)	3	3	0	0
Acne	2 (0.3)	2	2	0	0
Alopecia	2 (0.3)	2	1	0	1
Folliculitis	2 (0.3)	2	2	0	0
Other skin disorder	2 (0.3)	2	1	0	1
Dermatophytosis	1 (0.1)	1	1	0	0
Seborrhea	1 (0.1)	1	0	0	1
Verruca	1 (0.1)	1	0	0	1
Gastro-intestinal system disorders	9 (1.3)	10	8	0	2
Dyspepsia	8 (1.1)	8	6	0	2
Diarrhea	2 (0.3)	2	2	0	0
Psychiatric disorders	13 (1.8)	13	11	1	1
Libido decreased	9 (1.3)	9	9	0	0
Depression	2 (0.3)	2	1	0	1
Insomnia	1 (0.1)	1	1	0	0
Somnolence	1 (0.1)	1	0	1	0
Reproductive disorders, male	12 (1.7)	12	5	3	4
Impotence	7 (1.0)	7	3	3*	1 [†]
Sexual function abnormality	4 (0.6)	4	1	0	3 [‡]
Ejaculation disorder	1 (0.1)	1	1	0	0
Liver and biliary system disorders	5 (0.7)	9	9	0	0
SGPT increased	4 (0.6)	5	5	0	0
SGOT increased	2 (0.3)	3	3	0	0
Bilirubinaemia	1 (0.1)	1	1	0	0
Body as a whole, general disorders	5 (0.7)	5	5	0	0
Fatigue	5 (0.7)	5	5	0	0
Resistance mechanism disorders	1 (0.1)	1	1	0	0
Pharyngitis	1 (0.1)	1	1	0	0
Respiratory system disorders	1 (0.1)	1	1	0	0
Epistaxis	1 (0.1)	1	1	0	0
Metabolic and nutritional disorders	2 (0.3)	2	1	1	0
Hypertriglyceridaemia	1 (0.1)	1	1	0	0
Weight increase	1 (0.1)	1	0	1	0
Central and peripheral nervous system disorders	2 (0.3)	2	2	0	0
Paraesthesia	1 (0.1)	1	1	0	0
Dizziness	1 (0.1)	1	1	0	0
Endocrine disorders	3 (0.4)	3	1	1	1
Gynaecomastia	2 (0.3)	2	1	1	0
Testosterone decreased	1 (0.1)	1	0	0	1
Heart rate and rhythm disorders	2 (0.3)	2	2	0	0
Palpitation	2 (0.3)	2	2	0	0
Special senses other, disorders	1 (0.1)	1	0	0	1
Taste perversion	1 (0.1)	1	0	0	1
Secondary terms	1 (0.1)	1	1	0	0
Surgical intervention [§]	1 (0.1)	1	1	0	0

Values are presented as number (%) or number only. SGPT: serum glutamic-pyruvic transaminase, SGOT: serum glutamic oxaloacetic transaminase. *After the end of the study, 2 impotence events were resolved even under dutasteride treatment. Another patient who discontinued dutasteride was unreachable after the end of the study. [†]One event with the unknown prognosis of sexual dysfunction continued to take dutasteride. [‡]Three events with the unknown prognosis of sexual dysfunction continued to take dutasteride 0.5 mg and didn't take any medicine to treat sexual dysfunction. [§]Posterior tooth extraction. ^{||}Gynaecomastia was reported only after 4 days of treatment with dutasteride, which was stopped after 1 month and was finally resolved after the end of the study.

Effectiveness

Effectiveness was evaluated based on the treating physicians' clinical opinion in 332 subjects. The number of subjects who was evaluated as "improved" was 261 (78.6%). Sixty-nine subjects (20.8%) were classified as "no change" and only two subjects (0.6%) "worsened." Older subjects were more classified as "improved." Subjects in modified Norwood-Hamilton classification 4, 4A benefited most with 100% "improved."

DISCUSSION

Dihydrotestosterone (DHT) plays a key role in the patho-

genesis of AGA. Although testosterone is a major circulating androgen, DHT, which is converted by 5-alpha reductase from testosterone, is more active in scalp hair follicles.

The role of type 2 5-alpha reductase in AGA has been supported by the men with a congenital deficiency of type 2 5-alpha reductase¹³ and by the finasteride, a selective type 2 5-alpha reductase inhibitor¹⁴. Type 1 5-alpha reductase is the major isoenzyme in sebaceous and sweat glands in skin¹⁵⁻¹⁷ and liver¹⁷. However, the virilization at puberty of pseudohermaphrodites without type 2 5-alpha reductase associates with increasing type 1 5-alpha reductase expression in skin, suggesting that DHT can have paracrine effects¹⁷. As a result, this suggests that the inhibition of both the type 1 and 2 5-alpha reductases may be needed to control DHT effectively.

Dutasteride inhibits both type 1 and 2 5-alpha reductases, eventually suppressing DHT in circulation and the target organ. In phase II trial, dutasteride from 0.05 mg to 2.5 mg suppressed serum and scalp DHT concentrations, which were inversely correlated with target area hair count, in a dose-related manner¹¹. Considering the fact that there was no dose-response relationship among finasteride groups¹⁸, dutasteride's type 1 5-alpha reductase inhibition is likely to lead to the difference in dose-response of serum and scalp DHT inhibition. In the Olsen et al.'s report¹¹, dutasteride 0.5 mg suppressed DHT concentrations in serum by 92% and in scalp by 51%, while finasteride 5 mg in serum by 73% and in scalp by 41%. Recent study with bigger number of subjects showed the close dose response in hair count increase across dutasteride 0.02 mg, 0.1 mg and 0.5 mg¹⁰ and added that dutasteride 0.1 mg was non-inferior to finasteride 1 mg and dutasteride 0.5 mg was superior to finasteride 1 mg.

In addition to the efficacy, it is believed that the AE is related to the DHT suppression. As a result, physicians perceive that the more potent DHT suppression by dutasteride, the more hair growth but the more AEs. Though this study does not have control group, the result on the safety in the real world can give some insights on safety information of dutasteride 0.5 mg in AGA.

In this observational study, decreased libido was reported

Table 3. Frequency of adverse drug reactions by subject profiles

Category	Total subjects	Subjects	p-value
Age (yr)			0.027*
18~19	23	1 (4.3)	
20~29	379	25 (6.6)	
30~39	262	33 (12.6)	
40~41	48	7 (14.6)	
Concomitant diseases			<0.001 [†]
Yes	220	24 (10.9)	
No	492	42 (8.5)	
Concomitant medications			0.493 [†]
Yes	436	43 (9.9)	
No	276	23 (8.3)	
Alopecia treatment history			0.986 [†]
Yes	292	27 (9.2)	
No	420	39 (9.3)	
Allergic history			0.283 [†]
Yes	52	7 (13.5)	
No	658	59 (9.0)	
Dutasteride treatment duration (mo)			0.572 [†]
<3	175	15 (8.6)	
3~6	146	17 (11.6)	
6~9	197	14 (7.1)	
9~12	71	8 (11.3)	
≥12	97	11 (11.3)	

Values are presented as number only or number (%). *Fisher's exact test, [†]chi-square test.

Table 4. Results of multivariate analysis for significant factors affecting the frequency of adverse drug reaction

Variable	Description	Parameter estimate	Standard error	p-value	Odds ratio	95% confidence interval	
						Lower	Upper
Age	1 year	0.0720	0.0214	0.0008	1.075	1.030	1.121
Concomitant disease	yes	0.3030	0.2725	0.2662	1.354	0.794	2.310

Analysis with log odds regression models.

in 9 subjects (1.3%), impotence in 7 (1.0%), sexual function abnormality in 4 (0.6%), and ejaculation disorder in 1 subject (0.1%). In dose ranging phase II trial, 9 men (13%) in the 2.5-mg dutasteride group complained of decreased libido, compared with 1 man (1%) in the 0.5-mg dutasteride group and 3 men (4%) in the finasteride 5 mg group¹¹. In Eun et al.'s report⁹, sexually related AE was not different between dutasteride 0.5 mg group (4.1%) and placebo group (4.0%). Eun et al.⁹ added that sexual dysfunction, which occurred for 3 of 73 (4.1%) in dutasteride group and 2 of 75 (2.7%) in placebo group and that both erectile dysfunction and ejaculation disorder was noted in one subject in placebo group. More recently, sexual AEs in all active groups (including dutasteride 0.02 mg, 0.1 mg, 0.5 mg and finasteride 1mg) comparing placebo group showed no dose response relationship in dutasteride doses¹⁰. Gubelin Harcha et al.¹⁰ also reported that decreased libido was reported by 9 subjects (4.9%) in dutasteride 0.5 mg group and by 12 subjects (6.7%) in finasteride 1 mg group.

The reports on the prognosis of the AEs in alopecia subjects are not found. In the 4-year follow-up of the phase III trials in benign prostate hyperplasia (BPH), the incidence of the sexual AEs was low and tended to decrease over time¹⁹.

The reported sexually related AE in this observational study is relatively lower than other controlled studies. This difference might be from the age of study subjects. This observational study included male subjects from 18 to 41 years old per prescribing information while other studies enrolled up to 50 years old male.

Gynaecomastia is also one of the interesting AEs occurring after treatment with dutasteride. Gynaecomastia was reported in 2 subjects (0.3%) in this study. In phase II trial, the only subject to develop gynecomastia was in the placebo group and not in the dutasteride groups and finasteride groups¹¹. Gubelin Harcha et al.¹⁰ reported that 1 subject (0.5%) experienced gynecomastia in dutasteride 0.5 mg group and 1 subject (0.6%) in finasteride 1 mg group. The frequency is about 1% ~ 2% even in long term trials with thousands of older subjects for BPH¹⁸. The reason for the lower gynecomastia in trials for AGA may be from the shorter follow up period and the younger subjects.

Like other studies for AGA with dutasteride, this observational study showed no reports of prostate cancer, breast cancer, or cardiovascular AEs of special interest.

There are some limitations in this study in terms of assessment of the effectiveness and safety of the drug in a real practice with uncontrolled design. Firstly, though this study was designed to evaluate the safety and tolerability

of the dutasteride, all the other treatment was allowed and more than half of subjects had other treatment as well. These additional medicines might have caused biases. Secondly, 380 subjects out of 712 in the safety population could not be assessed for effectiveness due to effectiveness assessment being not documented or effectiveness being not evaluable. The incomplete result data due to those subjects who were not assessed for effectiveness may have induced withdrawal bias. Thirdly, although 78.6% of the subjects in the analysis set were assessed to have improved in this study, there were no objective variables and determined time to assess effectiveness and therefore the status in those subjects who indicated improvement could not be confirmed. However, this study can provide the information on safety and effectiveness in a clinical practice environment.

In this study, we evaluated AEs of dutasteride in Korean patients with AGA in the real world. However, we relatively more focused on the ADR in this article because information on ADRs rather than AEs are more useful to the clinicians. Further evidences for safety and effectiveness of dutasteride in AGA are needed.

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