(fig. 3C) was significantly increased in OLETF rats compared to LETO rats at 30 weeks of age.

Immunoperoxidase Staining

The immunohistochemical study for Smad3 showed that cells showing predominantly nuclear immunostaining for Smad3 were more abundant in glomeruli from OLETF rats (fig. 4D) than from LETO rats (fig. 4C) at 30 weeks of age. Positive immunostaining for Smad3 was observed in glomerular epithelial cells, mesangial cells, proximal tubular cells, and endothelial cells. Smad3 is one of the receptor-regulated Smads, which translocate from the cytoplasm into the nucleus after phosphorylation by a receptor complex activated by TGF-β stimulus. Therefore, we studied whether the Smad-mediated pathway was activated in glomeruli by calculating the ratio of cells with nuclei immunostained for Smad3 to the total component cells in a glomerulus. The glomerular cells with accelerated nuclear accumulation of Smad3 significantly increased in glomeruli from diabetic OLETF rats aged 30 weeks compared with age-matched LETO rats (fig. 5). At 12 weeks of age, Smad3 localization in the nucleus did not differ in glomeruli between both strains (fig. 4A, B, fig. 5). Incubation with rabbit IgG substituted for a primary antibody showed negative staining in renal tissue (data not shown).

Western Blot Analysis

Western blot analysis revealed that Smad2 and Smad3 in protein extracted from isolated glomeruli of OLETF rats were increased compared with control LETO rats at 30 weeks of age (fig. 6A, B). There were found more increased glomerular amounts of TGF-β_1 in OLETF rats than in LETO rats at the age of 39 weeks (fig. 6C). At 12 weeks of age, no differences were found between both rat strains (data not shown).

Discussion

In this study, we sought to elucidate whether the TGF-β/Smad signaling pathway was functional in the progression of nephropathy in OLETF rats, a genetic model of type 2 diabetes. Our results indicated that OLETF rats aged 30 and 39 weeks developed diabetes mellitus and excreted massive urinary albumin. Mesangial expansion specific to diabetic nephropathy was found in their renal tissue. Our immunofluorescence study showed that glomerular TGF-β_1 protein was increased in 30-week-old OLETF rats compared with age-matched LETO rats. This finding was consistent with the report by Yagi et al. [25].

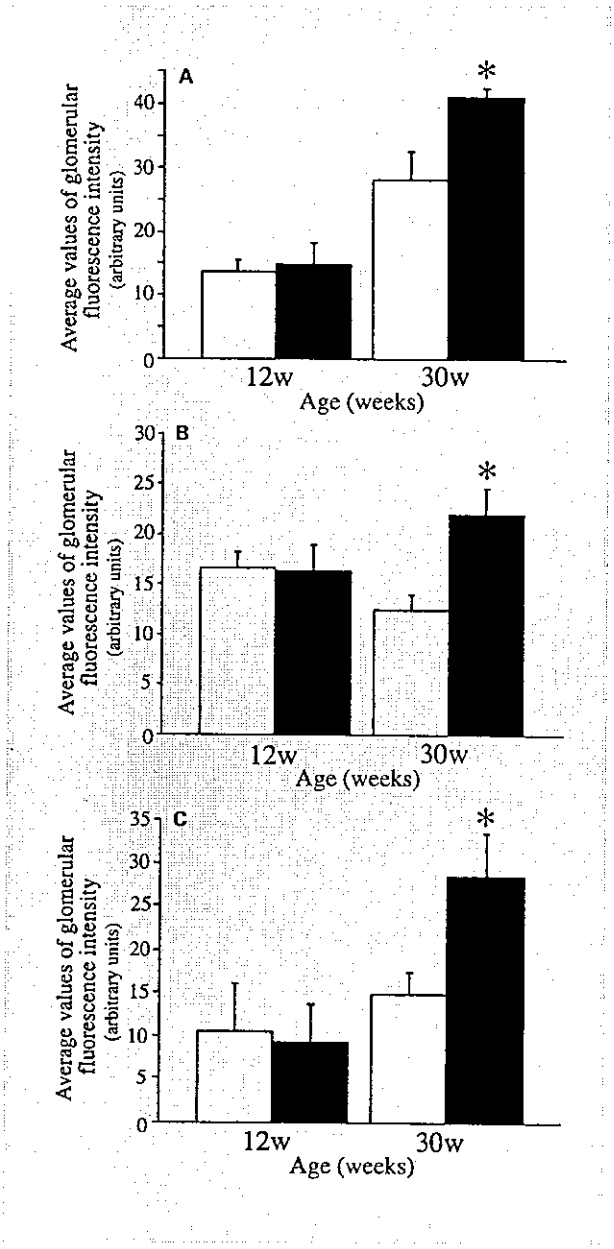

Fig. 3. Expression of TGF-β_1 (**A**), fibronectin (**B**) and Smad2 (**C**) proteins in glomeruli from OLETF (black bars) and LETO (white bars) rats was quantified as described in the Materials and Methods section. Data are summarized as mean ± SE. * $p < 0.05$ vs. LETO rats at the same age.

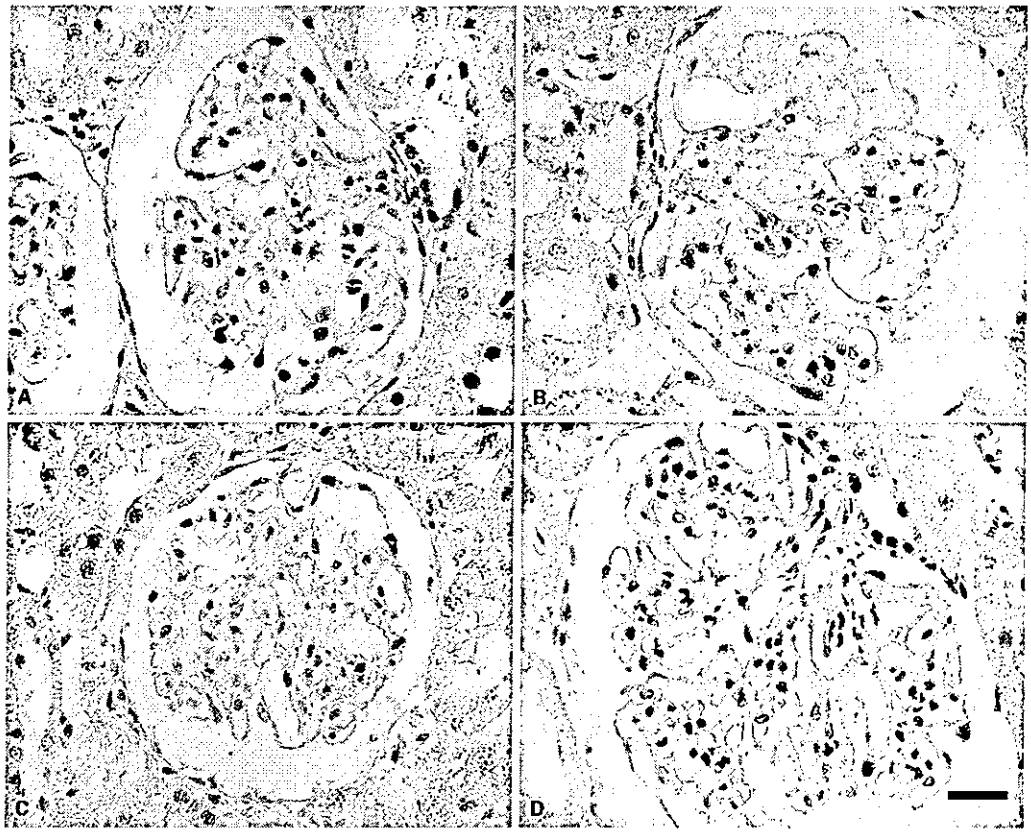

Fig. 4. Nuclear accumulation of Smad3 protein in glomeruli by immunohistochemistry. Light micrographs of glomeruli from LETO (**A**, **C**) and OLETF (**B**, **D**) rats at the age of 12 weeks (**A**, **B**) and 30 weeks (**C**, **D**) immunostained for Smad3. Note the promoted nuclear accumulation of Smad3 in glomeruli from diabetic OLETF rats at 30 weeks of age (**D**). Bar: 20 μm.

We have found increased fibronectin accumulation in the glomeruli of OLETF rats compared with LETO rats at 30 weeks of age by the immunofluorescence method. Kushiro et al. [26] reported that an increase in glomerular fibronectin was observed in 12-month-old, but not in 6-month-old OLETF rat. According to their findings and our results, glomerular fibronectin in OLETF rats was supposed to increase between about 25–30 weeks of age. The Smad pathway mediating TGF-β responses has been shown to participate in the transcriptional activation of the fibronectin gene by Isono et al. [27]. Therefore, we sought to assess the protein expression and the activation of Smad proteins in glomeruli from OLETF rats aged 30 weeks.

Indirect immunofluorescence staining showed significantly increased glomerular expression of Smad2 in diabetic OLETF rats than in LETO rats at 30 weeks of age. Moreover, Western blot analysis revealed that Smad2 and Smad3 were increased in the glomeruli of OLETF rats compared with LETO rats at the same age. Immunoperoxidase staining revealed that Smad3 localization in the nucleus was significantly increased in glomeruli of OLETF rats compared with LETO rats at this age. There were no differences in protein expression of Smad2 and Smad3 and nuclear localization of Smad3 in glomeruli between both strains at 12 weeks of age when OLETF rats were not diabetic.

These data suggest that TGF-β signaling pathway mediated by Smad proteins may be accelerated not only through TGF-β induced by high blood glucose levels but also by increased expression of Smad2 and Smad3 proteins in glomeruli from OLETF rats, and that this may

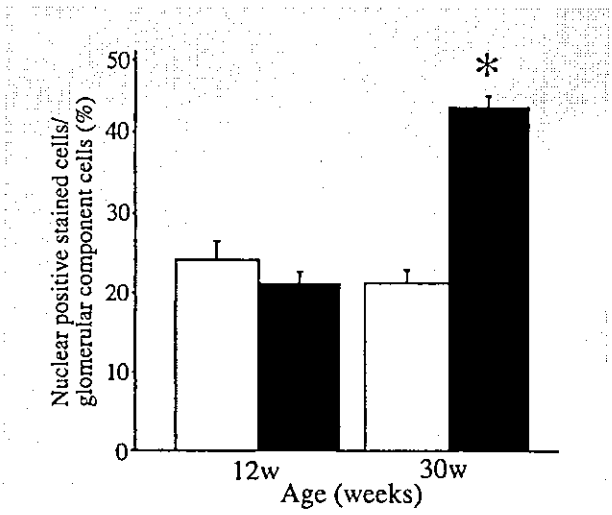

Fig. 5. Quantification of nuclear immunostain for Smad3 in glomeruli revealed significantly increased activated Smad3 in glomeruli from OLETF rats (black bars) compared to control LETO (white bars) rats at 30 weeks of age. Data are mean ± SE. * $p < 0.05$ vs. LETO rats at the same age.

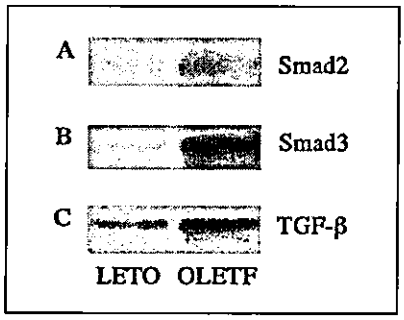

Fig. 6. Western blot analyses of glomerular proteins from OLETF and LETO rats at the age of 30 weeks with anti-Smad2 antibody (**A**) or anti-Smad3 antibody (**B**) and at the age of 39 weeks with anti-TGF-β_1 antibody (**C**). Glomerular Smad2, Smad3 and TGF-β_1, were increased in OLETF rats compared with LETO rats at 30 and 39 weeks of age when OLETF rats were diabetic.

play an important role in progression of diabetic nephropathy. Smad3 activation can be explained by the augmented expression and activation of TGF-β induced by high blood glucose concentrations in OLETF rats. Isono et al. [27] have reported that Smad3 activation was induced by TGF-β in diabetic mice kidneys, but we found not only augmented activation of Smad3 but also increased glomerular expression of Smad2 and Smad3 proteins in this spontaneously diabetic animal model. These results suggest that the total TGF-β signaling may be enormously enhanced in glomeruli of diabetic OLETF rats.

The mechanism underlying the increased expression of Smad2 and Smad3 proteins in the glomeruli of OLETF rats remains unclear. One possibility is that TGF-β itself may induce Smad protein expression. The levels of Smad2 mRNA have been observed to increase following TGF-β treatment in certain cell lines [28]. Expression of Smad7 mRNA was induced by TGF-β [18]. However, there have been no reports about the regulation of Smad3 and Smad protein production by TGF-β in the kidney or other tissues. The other possibility is that factors other than TGF-β might induce overexpression of Smad proteins in the kidney. For example, platelet-derived growth factor (PDGF) may be one such candidate. PDGF-β receptors are overexpressed in the medial smooth muscle cells from the aorta of OLETF rats before the onset of diabetes mellitus, suggesting that a genetic factor may contribute not only to atherosclerosis but also to diabetic nephropathy in these animals [29]. To that end, microalbuminuria has been reported to be clinically correlated with atherosclerosis [30–32]. The third possibility is that Smad proteins may be genetically overexpressed with increasing age in OLETF rats. However, further investigation is required for elucidation of the mechanism underlying increased expression of Smad2 and Smad3 proteins in glomeruli of OLETF rat.

In summary, we demonstrated that the Smad proteins might play an important role in the development of diabetic nephropathy in OLETF rats. Further analyses of this rat model would provide new insights into the mechanism of progression of diabetic nephropathy as well as potential treatment related to the modulation of Smad proteins.

Acknowledgment

We thank Dr. Kubosawa (Department of Pathology, Chiba Municipal Hospital, Chiba, Japan) for helpful advice.

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Eur J Dermatol 2004; 14: 247-54

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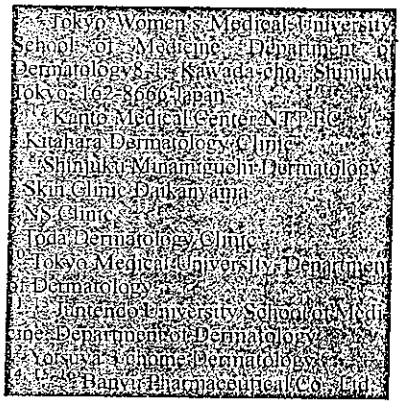

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Article accepted on 14/05/2004
This study was supported by a grant from Banyu Pharmaceutical Co., Ltd., Tokyo, Japan.

Finasteride in the treatment of Japanese men with male pattern hair loss

Finasteride is a type 2 5α-reductase inhibitor that inhibits conversion of testosterone to dihydrotestosterone, a key mediator of male pattern hair loss (androgenetic alopecia).
The objective of this study was to identify the optimal dosage of finasteride and to evaluate its efficacy and safety in the treatment of Japanese men with male pattern hair loss. In this double- blind randomized study, 414 Japanese men with male pattern hair loss received finasteride 1 mg (n = 139), finasteride 0.2 mg (n = 137), or placebo (n = 138) once daily for 48 weeks. Efficacy was evaluated by global photographic assessment, patient self-assessment, and investigator assessment. All efficacy endpoints showed significant improvement with finasteride therapy by 12 weeks ($p < 0.05$ *versus* placebo). At 48 weeks, 58%, 54%, and 6% of men in the finasteride 1 mg, finasteride 0.2 mg, and placebo groups, respectively, had improved based on assessments of global photographs. All efficacy endpoints were numerically superior for the 1 mg dose over the 0.2 mg dose at 48 weeks. Finasteride treatment was generally well tolerated. Finasteride 1 mg/day slows hair loss and improves hair growth in Japanese men with male pattern hair loss.

Key words: androgenetic alopecia, dihydrotestosterone, finasteride, male pattern hair loss, type 2 5 α-reductase inhibitor

Male pattern hair loss, or androgenetic alopecia, is an androgen-mediated condition that is characterized by the gradual thinning of scalp hair, particularly in the frontal, temporal, and vertex regions. The incidence of this common condition increases with age and is approximately 50% among Caucasian men by the age of 50 [1-3]. Among Japanese men, the development of male pattern hair loss occurs at later ages, with an incidence at a given age similar to that among Caucasians 10 years younger [4, 5].
Hair thinning in men with androgenetic alopecia occurs secondary to the progressive miniaturization of hair follicles and shortening of the anagen (active growth) phase of the hair- growth cycle. Dihydrotestosterone is implicated as one of the principal mediators of this condition because of the fact that male pattern hair loss does not occur in men with genetic deficiency of type 2 5α-reductase, the enzyme that converts testosterone to dihydrotestosterone [6].
Finasteride is a type 2 5α-reductase inhibitor and thus inhibits the conversion of testosterone to dihydrotestosterone (DHT), lowering levels of DHT in serum and scalp [7]. Administered at 1 mg once daily, finasteride increases hair weight, promotes the conversion of hairs into the anagen phase, and can reverse hair miniaturization in men with androgenetic alopecia [8-10]. Finasteride at this dosage is generally well tolerated and has been shown to produce long-lasting improvement in scalp hair growth for up to 5 years in men with male pattern hair loss [11-13]. The objectives of this multicenter, double-blind, placebo-controlled, randomized clinical trial were to identify the optimal dosage of finasteride and to evaluate its efficacy and safety in the treatment of Japanese men with male pattern hair loss.

Methods

Patients

Patients enrolled were Japanese men, 20 to 50 years of age, with male pattern hair loss. Eligible patients were in good

Table I. *Hair growth questionnaire*

Question	Possible responses
1. Since the start of the study, I can see my bald spot getting smaller.	Strongly agree (1) → Strongly disagree (5)
2. Because of the treatment I have received since the start of the study, the appearance of my hair is :	A lot better (1) → A lot worse (7)
3. Since the start of the study, how would you describe the growth of your hair ?	Greatly increased (1) → Greatly decreased (7)
4. Since the start of the study, how effective do you think the treatment has been in slowing down your hair loss ?	Very effective (1) → Not effective at all (4)
5. Compared to the beginning of the study, which statement best describes your satisfaction with the appearance of :	
a) the hairline at the front of your head ?	Very satisfied (1) → Very dissatisfied (5)
b) the hair on top of your head ?	Very satisfied (1) → Very dissatisfied (5)
c) your hair overall ?	Very satisfied (1) → Very dissatisfied (5)

physical and mental health and had mild to moderate hair loss classified as modified Norwood-Hamilton grade II vertex, III vertex, IV, or V balding [1, 2, 4]. Patients had to agree not to change their hairstyle or use hair color throughout the study or to use other drugs for promoting hair growth.

Patients with a history of multifactorial or serious drug allergy were excluded from study participation, as were those with a history of or ongoing thyroid disease, a history of or suspected malignancy, or elevated plasma concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin. Also excluded were patients with severe seborrheic dermatitis of the scalp and those who had undergone hair transplant surgery, scalp reduction surgery, or hair weaving.

Prior use of finasteride or any other 5 α-reductase inhibitor was cause for exclusion from the trial. The use of systemic corticosteroids or anabolic steroids, or topical corticosteroids on the area of hair loss, was not permitted during the study. Other medications were required to be withdrawn 3 to 12 months before the study and were not permitted during the study ; these included drugs known to cause hypertrichosis or hair loss as an adverse reaction (for example, zidovudine, cyclosporine, tamoxifen) for 1 year before, antiandrogenic drugs (for example, progesterone and ketoconazole) for 6 months before, minoxidil and carpronium chloride for 4 months before, and any investigational drug for 3 months before study drug administration.

The study protocol was approved by the appropriate institutional review board, and each patient signed a written consent form before participating in the study.

Study design

This 1-year, double-blind, randomized study was conducted at nine centers in Japan from June 2001 to September 2002. After the initial screening visit, patients eligible to enter the study were randomly assigned to finasteride 1 mg, 0.2 mg or placebo once daily in the morning for 48 weeks. The three types of film-coated tablets were identical in appearance. Follow-up visits were scheduled at weeks 2 and 4 and then every 4 weeks until week 48. At each visit, adverse experiences were recorded, and a medical examination was performed. Standardized clinical photographs of the head (global photographs) for clinical assessment were taken at weeks 12, 24, and 48. Patients completed a hair growth questionnaire, and investigators rated the change in hair appearance compared with baseline, at weeks 12, 24, 36, and 48.

Efficacy assessments

Global photographic assessment

The vertex and superior-frontal areas of the scalp were photographed using a standardized technique [14]. Photographs were assessed in blinded fashion by three independent dermatologists (E. Olsen, R. Savin and D. Whiting) in the United States (US) who compared the pre- and post-treatment appearance of the scalp using a 7-point scale as follows : greatly decreased (score of − 3), moderately decreased (− 2), slightly decreased (− 1), unchanged (0), slightly increased (+ 1), moderately increased (+ 2), and greatly increased (+ 3) [11]. The dermatologists in this expert panel were experienced in photographic assessments of hair growth, and this technique has been shown to have excellent reproducibility and inter-rater agreement [15].

Patient self-assessments

Every 12 weeks, patients completed a validated, self-administered hair growth questionnaire [11, 16] comprising seven questions, four relating to efficacy of treatment and three to satisfaction with appearance of scalp hair *(Table I)*. The translation of the questionnaires and the responses from English into Japanese were cross language validated by CoreMed Corp., Osaka, Japan. Responses were scored on 4 to 7 point scales, with a score of 1 assigned to the most positive response. For the statistical analysis, scores were centered on 0 (neutral response), and improvement was assigned the positive numbers.

Investigator assessments

The investigators rated change relative to baseline in hair growth in the vertex area (a global photograph of the area at baseline was used for reference), using the standardized 7 point scale described above. Investigator assessments of hair growth were made every 12 weeks after the start of study drug administration.

Safety assessments

At the screening visit, the medical history was recorded and a complete physical examination was performed. Safety assessments included physical examination and nonleading questioning about adverse experiences at each visit, as well as periodic laboratory evaluations.

Laboratory evaluations

Hematology, serum biochemical analysis, and urinalysis were performed at screening, baseline, and weeks 2, 4, 12,

Table II. *Baseline characteristics of men enrolled in the study*

	Placebo (n = 138)	Finasteride 1 mg (n = 139)	Finasteride 0.2 mg (n = 137)
Age (mean ± SD)	40 ± 6	40 ± 6	40 ± 6
No. (%) of patients with family history*	127 (92%)	122 (88%)	120 (88%)
No. (%) of patients with hair loss pattern†			
II vertex	35 (25%)	39 (28%)	43 (31%)
III vertex	40 (29%)	37 (27%)	36 (26%)
IV	44 (32%)	36 (26%)	32 (23%)
V	19 (14%)	27 (19%)	26 (19%)

** Family history = parents or siblings with history of male pattern hair loss.*
† According to modified Norwood-Hamilton scale.

24, 36, and 48. Serum prostate-specific antigen (PSA) concentrations were measured at screening and weeks 24 and 48. In addition, serum concentrations of DHT and testosterone were determined at baseline and weeks 24 and 48, while those of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured at baseline and 48 weeks. These assays, except DHT, were performed at the central laboratory in Japan (BML, Saitama, Japan). Serum DHT concentrations were assayed at Esoterix laboratory (Calabasas Hills, CA, USA).

Statistical analysis

Efficacy analyses were prespecified for all endpoints and were performed using the full analysis set (FAS) patient population that included all randomized patients who had a baseline and at least one post-treatment assessment. In the case of missing values, the last measured value was carried forward in the place of missing data ; data from week 24 or later were carried forward in place of missing 48-week data.

The primary efficacy endpoint was the global photographic assessment of the change in hair growth in the vertex area of the scalp at 48 weeks (final assessment) as compared with baseline. The median value of the three dermatologists' assessments was used for the global photographic endpoints score for each patient at each time point. Secondary efficacy assessments included global photographic assessment of the vertex area at weeks 12 and 24 and of the superior/frontal area at weeks 12, 24, and 48 compared with baseline, and the patient self-assessments and investigator assessment of scalp hair growth at weeks 12, 24, 36 and 48.

The presence of a dose response was tested by linear regression analysis (including study center effect) for all efficacy endpoints. Doses were log-transposed and placebo (0 mg) was assigned a value of 0.01 mg. An analysis of co variance (ANCOVA) was used for pairwise between-group comparisons (finasteride 1 mg vs placebo, finasteride 0.2 mg vs placebo, and finasteride 1 mg vs 0.2 mg). The ANCOVA model included factors for both treatment and study center. The incidence of adverse experiences and laboratory abnormalities was compared between treatment groups using Fisher's exact test.

Sample size calculations

Assuming a total of 100 patients per treatment group, we calculated that this study had approximately 90% power to demonstrate a dose response and the superiority of finasteride 1 mg over placebo as well as the superiority of finasteride 0.2 mg over placebo. This calculation was based on data from a previous 24-week study (phase II dose range study [17]) to estimate the following scores for the primary endpoint (global photographic assessment scores for the vertex area at 48 weeks) : finasteride 1 mg group, 0.647 ; finasteride 0.2 mg group, 0.427 ; placebo group, 0.010. The current study randomized approximately 125 patients per treatment group to account for a projected discontinuation rate of 20%.

Results

Baseline patient demographics and accounting

A total of 414 patients were enrolled in the study. Baseline characteristics of enrolled patients were not significantly different among the three treatment groups and are summarized in *Table II*. The mean age of enrolled patients was 40 years, and most (89-92%) had a family history of hair loss.

Patient accounting is summarized in *Fig. 1*. All patients were included in the safety analyses, and one patient in the finasteride 0.2 mg treatment group was excluded in all FAS efficacy analyses because of ineligibility (hair weaves) for study.

Global photographic assessment

At 48 weeks, over half of the patients in the two finasteride treatment groups demonstrated improvement relative to baseline in global photographic assessment of the vertex area *(Fig. 2)*. Rates of improvement (vertex scalp hair slightly, moderately, or greatly increased) in hair growth relative to baseline were 58%, 54%, and 6% in the finasteride 1 mg, finasteride 0.2 mg, and placebo groups, respectively, whereas rates of deterioration (vertex scalp hair slightly, moderately, or greatly decreased) in hair growth relative to baseline were 2%, 5%, and 22%, respectively. The mean scores at 48 weeks *(Fig. 3A)* demonstrated a significant dose response ($p < 0.001$). Moreover, the mean score for each of the finasteride treatment groups was significantly better ($p < 0.001$) than that for the placebo group. Although the study was not designed to detect a significant difference between the two finasteride doses, the mean score (mean ± standard error) for the 1 mg finasteride group (0.7 ± 0.1) was numerically but not significantly superior to that for the 0.2 mg group (0.6 ± 0.1). Scores were similar for patients with different grades of hair loss at baseline (data not shown).

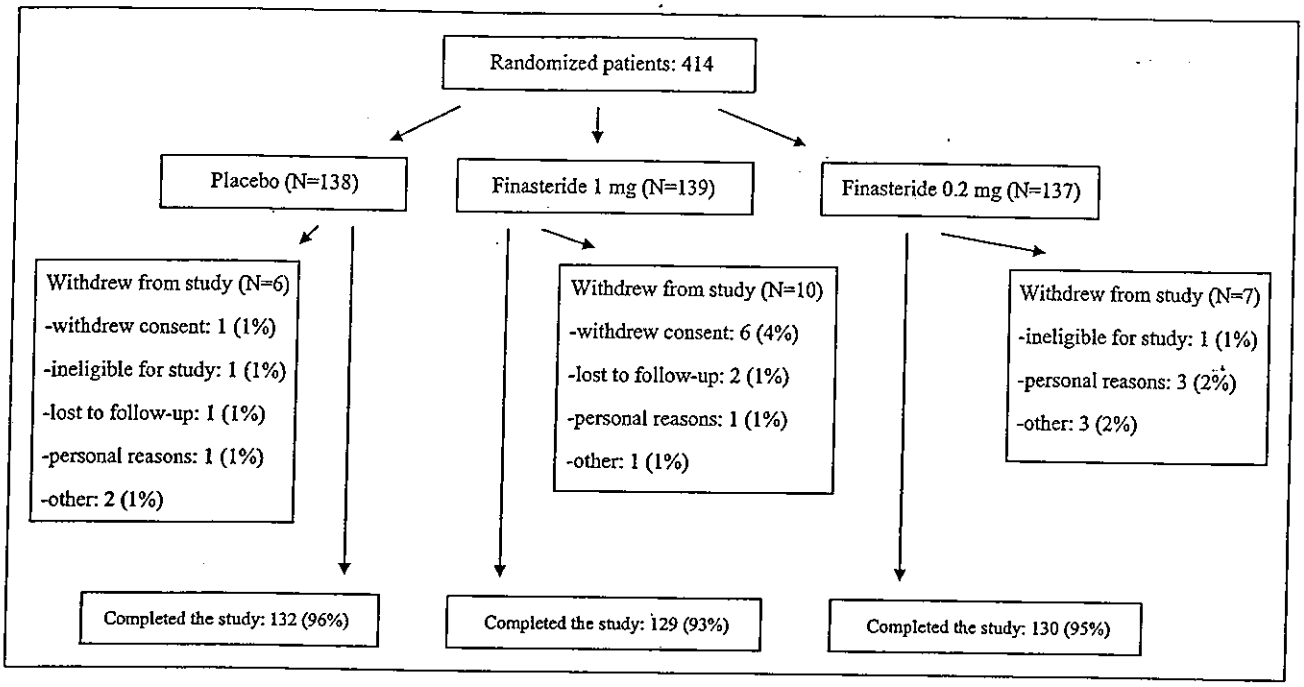


Figure 1. *Patient accounting.*

Vertex global photographic assessment scores for finasteride-treated patients showed improvement at 12 and 24 weeks and then remained stable, while those for patients in the placebo group gradually declined *(see Fig. 3A)*. These scores were significantly better for the finasteride groups compared with the placebo group ($p < 0.001$), and a statistically significant dose response ($p < 0.001$) was evident at 12 and 24 weeks.

Global photographic assessment scores for the superior-frontal view are depicted in *Fig. 3B*. As with the vertex view, scores for the superior-frontal view increased in the finasteride groups at both 12 and 24 weeks and then remained stable, while scores for the placebo group declined. Scores for both finasteride groups were significantly better

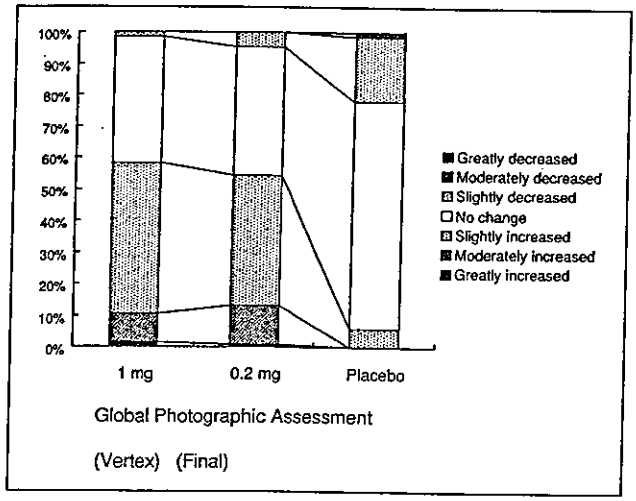
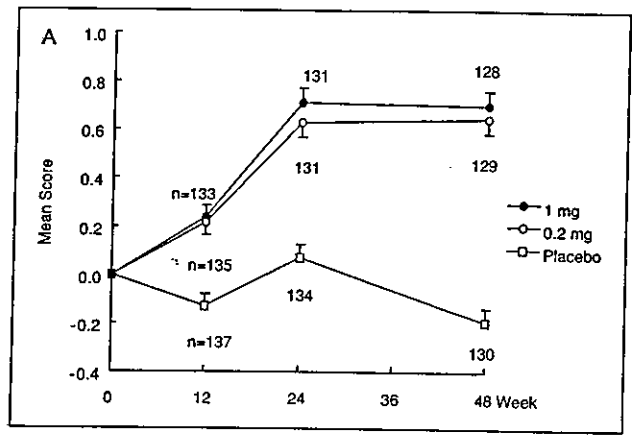


Figure 2. *Global photographic assessment of hair growth on the vertex area of the scalp, compared with baseline, after 48 weeks of treatment with finasteride 1 mg, finasteride 0.2 mg, or placebo once daily.*



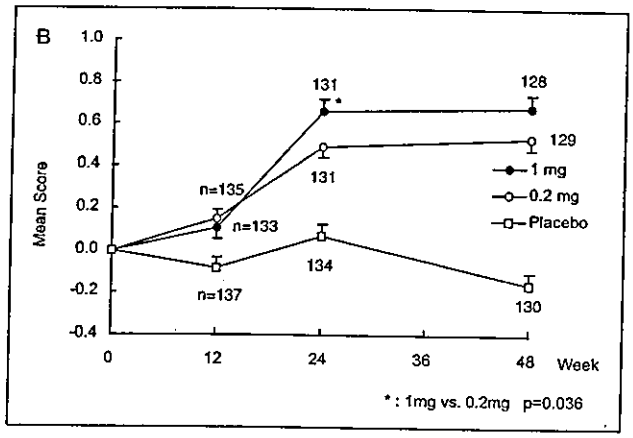


Figure 3. *Mean (± SE) global photographic assessment score for the vertex area (A) and superior-frontal area (B) of the scalp during 48 weeks of treatment (FAS population). $P < 0.001$ for the comparison between each finasteride treatment group and placebo at 12, 24, and 48 weeks. n in Fig means the number of statistically analyzed patients.*

($p \leq 0.006$) than that for the placebo group, and a significant dose response ($p \leq 0.002$) was evident at each time point. Representative global photographs of patients rated by the expert panel as having decreased or increased hair growth at 24 and 48 weeks are shown in *Fig. 4*.

Patient self-assessment

The mean scores for all seven patient self-assessment questions were significantly better for each of the finasteride treatment groups compared with the placebo group at each time point beginning at 12 weeks ($p \leq 0.007$ for all finasteride-placebo comparisons). Moreover, a significant dose response ($p \leq 0.003$) was found at each time point for each question. At 48 weeks, scores for the finasteride 1 mg group were numerically superior to those for the finasteride 0.2 mg group for each question.
A greater percentage of finasteride- than placebo-treated patients reported an improvement in each question at each time point. The proportion of men reporting improvement from baseline at Week 48 is depicted in *Fig. 5*.

Investigator assessment

The investigator assessment scores were significantly better for both the finasteride 1 mg ($p \leq 0.004$) and finasteride 0.2 mg ($p \leq 0.024$) groups compared with the placebo group at each time point from 12 weeks onward *(Fig. 6)*. Moreover, a significant ($p \leq 0.002$) dose response was found for each time point. At 48 weeks, investigators rated 60%, 61%, and 19% of patients in the finasteride 1 mg, finasteride 0.2 mg and placebo groups, respectively, as having improved.

Serum hormone and prostate-specific antigen concentrations

Pretreatment serum hormone and PSA concentrations were similar in the three treatment groups. Mean serum concentrations of DHT fell in the finasteride 0.2 and 1 mg groups from baseline concentrations. The percent change in DHT concentration was significantly larger ($p < 0.001$) in each of the finasteride groups compared with the placebo group. Serum testosterone concentrations increased in the finasteride 0.2 and 1 mg groups. Although the percent increases in serum testosterone at 48 weeks were significantly greater ($p = 0.014$ and $p = 0.028$, respectively) in the finasteride groups compared with the placebo group, serum concentrations of testosterone remained well within the normal range. Differences between the two finasteride groups were not significant for changes in serum DHT or testosterone concentrations.
There were no statistically significant differences between the finasteride and placebo groups in changes in LH or FSH concentrations during the study.
Pretreatment serum concentrations of PSA were 0.9 ng/ml in both finasteride treatment groups and 1.0 ng/ml in the placebo group (reference range, ≤ 4.0 ng/ml). As expected, the administration of finasteride was associated with a small decrease in serum PSA concentrations from baseline in the finasteride 1 mg group (– 0.3 ng/ml) and 0.2 mg group (– 0.2 ng/ml). There was no significant difference in the change in PSA level between the two finasteride groups.

Adverse experiences

There were no deaths or serious drug related adverse experiences and no drug related adverse experiences which resulted in discontinuation of the study medication during the trial. The incidence of drug related adverse experiences was not significantly different between groups (5%, 1.5% and 2.2% for the finasteride 1 mg, 0.2 mg and placebo groups, respectively, $p \geq 0.173$) ; of these, adverse experiences related to sexual function, particularly decreased libido, were most commonly reported (incidence of 2.9%, 1.5%, and 2.2%, respectively), and most resolved without discontinuation of therapy. These adverse experiences related to sexual function reported in the study were mild in intensity.
There were no significant differences between treatment groups in the overall incidence of laboratory abnormalities (16%, 12%, and 10%, respectively ; $p \geq 0.148$). The only abnormalities considered possibly related to treatment by the investigator were a mild increase in total cholesterol and a mild increase in ALT in two patients in the 1 mg finasteride group ; neither was considered to be clinically significant.

Discussion

We found that once daily treatment with finasteride at a dose of 0.2 or 1 mg for 48 weeks was effective in improving the appearance of scalp hair and slowing the loss of hair in Japanese men with male pattern hair loss. Significant improvement in hair growth with finasteride therapy relative to placebo was evident as early as 12 weeks for all measured endpoints. At 48 weeks, global photographs showed improvement from baseline for 58% of patients in the finasteride 1 mg group, while deterioration was recorded for only 2% of patients. These findings agree with those of previous US and multinational, non-Asian studies enrolling predominantly Caucasian men aged 18 to 41 years with male pattern hair loss [11, 17, 13].
Both finasteride doses were significantly more effective than placebo. Although the study was not designed to detect a significant difference between the two finasteride doses, a significant dose response was found, and the results for the 1 mg dose were significantly better than those for the 0.2 mg dose for some of the secondary endpoints. These data were well agreed with those in previous US study [17]. Moreover, at 48 weeks, all efficacy endpoints were numerically superior for the 1 mg dose. Thus, from the standpoint of efficacy, 1 mg appears to be the optimal dose for Japanese men with male pattern hair loss.
The 1 mg dose was selected as the optimal dose in prior non-Japanese, dose- ranging studies and is the dose marketed in over 60 countries for treatment of male pattern hair loss. Results of pharmacokinetic studies in healthy volunteers indicate that the pharmacokinetics of finasteride, as well as the effect of finasteride in lowering DHT concentrations, are similar in Japanese and non-Japanese male subjects (data on file, Banyu Pharmaceutical Co, Ltd, Tokyo, Japan). The findings of this study suggest that the beneficial clinical effects of finasteride are also similar in Japanese and non-Japanese men. Moreover, results of two recent open-label studies indicate that therapy with finasteride may be effective also for treating Taiwanese and Indian men with male pattern hair loss [18, 19].
The incidence of male pattern hair loss increases with age in both Japanese and Caucasian men ; however, the onset of male pattern hair loss occurs at later ages among Japanese men. The incidence of male pattern hair loss in Japanese

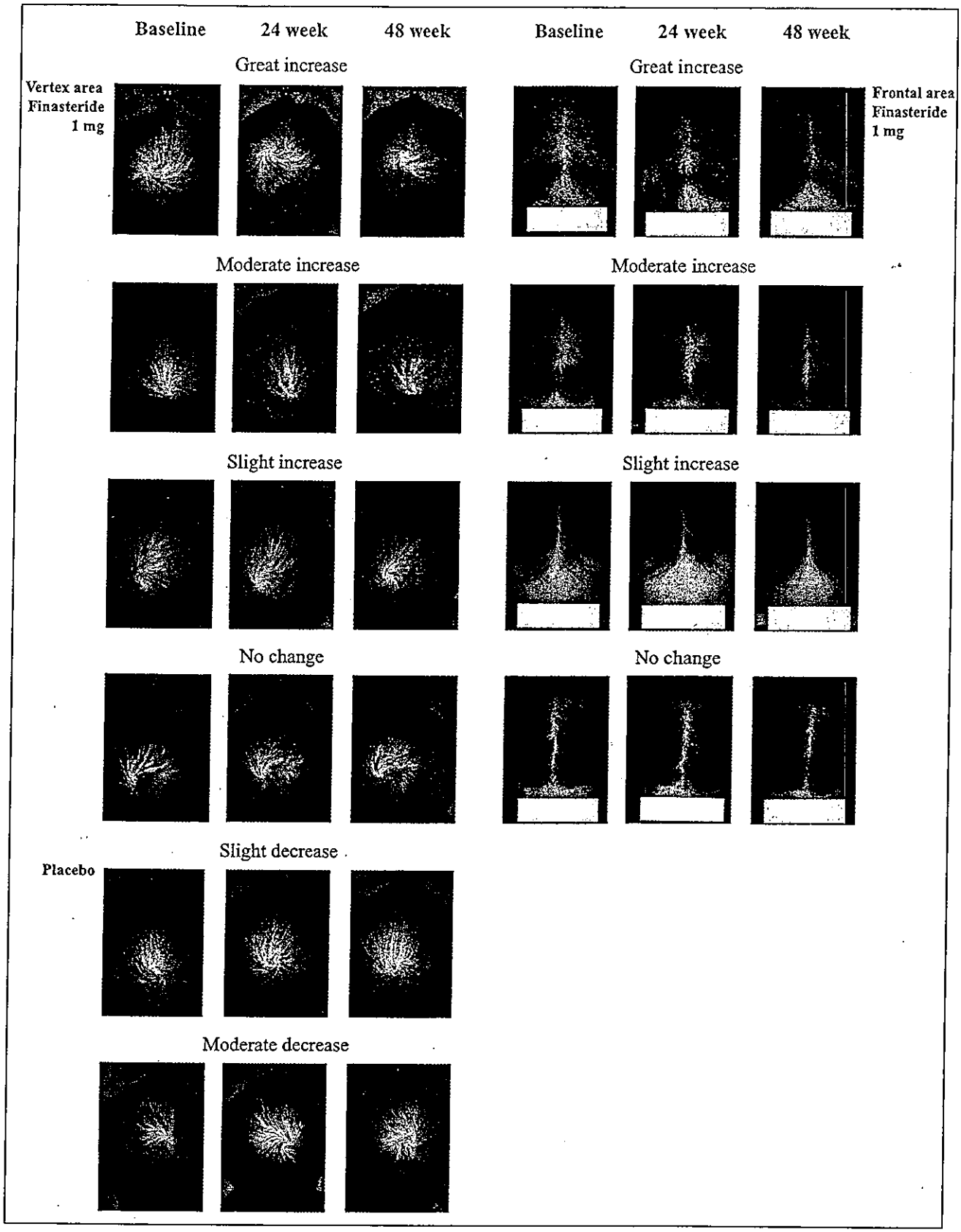


Figure 4. *Representative global photographs of patients at baseline and after 24 and 48 weeks of treatment with placebo and finasteride 1 mg. Changes in hair growth relative to baseline were rated by the expert panel.*

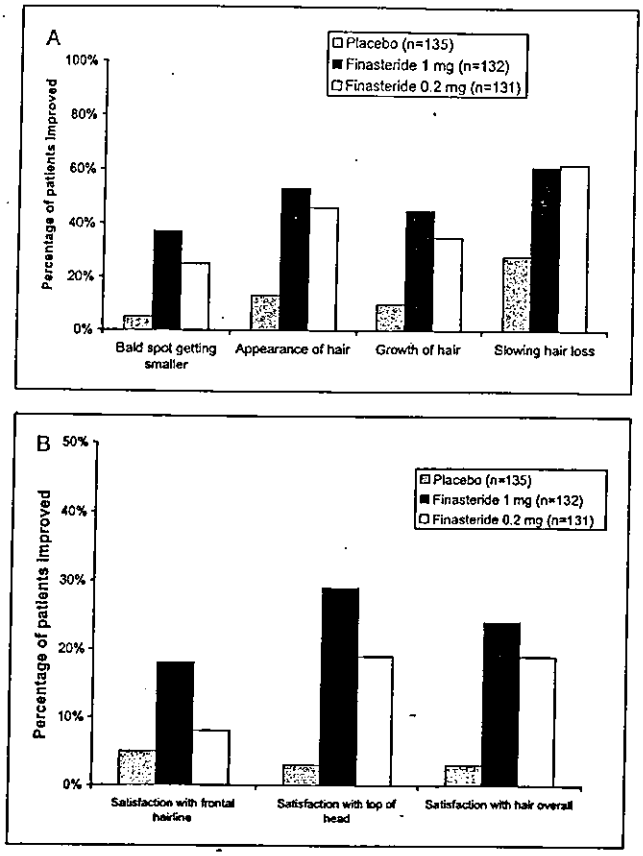


Figure 5. *Percentages of patients reporting improvement in hair growth (A) and satisfaction with appearance of hair (B) on final scoring of patient self assessment questionnaire (FAS).*

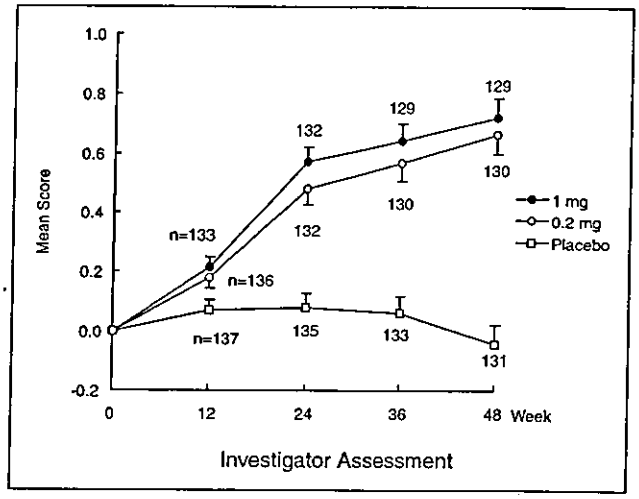


Figure 6. *Mean (± SE) investigator assessment score (FAS). $P \leq 0.024$ for the comparison between each finasteride treatment group and placebo at 12, 24, 36, and 48 weeks. n in Fig means the number of statistically analyzed patients.*

men in their 30s is about one third that in similarly aged Caucasian men. At later ages, the incidence in Japanese is about the same as that in Caucasians 10 years younger [4] ; hence our decision to include patients from 20-50 years of age in this study. Ishino and coworkers concluded that the progression of male pattern hair loss, as measured by the rate of increase in percentage of vellus hairs, is slower in Japanese than Caucasians. This led them to suggest that the detection of moderate changes in hair loss may be important when assessing the efficacy of treatments for hair loss in Japanese men.

Global photographic assessment at 48 weeks was the primary efficacy endpoint in this study. This endpoint assesses change in hair growth and scalp coverage with time. This reflects changes in both the number of hairs and the overall appearance of the hair, which includes changes in hair thickness and growth rate. We found that the results of global photographic assessments, demonstrating improvements in men treated with finasteride compared to placebo, were supported by the results of patient self-assessments and investigator assessments. Global photographic assessment also demonstrated that only 2% of patients treated with finasteride, compared with 22% of patients in the placebo group were rated as worsened at Week 48, demonstrating that finasteride treatment helped men maintain their scalp hair coverage.

Finasteride was generally well tolerated in this study. The incidence of drug related adverse experiences was not significantly different between treatment groups, and no patients stopped intake of the study drug because of a drug related adverse experience. The overall profile of drug related adverse experiences in our study was similar to that in previous US studies [11- 13].

In summary, we found that treatment with finasteride slows the progression of hair loss and improves hair growth in Japanese patients with male pattern hair loss. A dose of 1 mg given once a day is the optimal dose for treatment of this condition. Finasteride treatment is generally well tolerated in Japanese men with male pattern hair loss. ■

Acknowledgements. *Authors are grateful to : Emiko Akiyoshi, MD[1], Takeo Idezuki, MD[2], Etsuko Fujita, MD[3], Michiyasu Hamada, MD[4], Yuko Higaki, MD[5], Masami Ishida, MD[6], Naoko Ishiguro, MD[7], Kenzo Kaji, MD[8], Tami Kimura, MD[9], Satomi Kobayashi, MD[10], Etsuko Komiyama, MD[11], Mariko Kume, MD[12], Yuko Miura, MD[13], Junichi Mizushima, MD[14], Chitose Morita, MD[15], Noboru Nakamichi, MD[16], Hyota Saga, MD[17], Kumi Jin, MD[18], Takenori Takahashi, MD[19], Sunao Toda, MD[20], Minoru Tsuboi, MD[21], Shu Ueda, MD[22], Hironobu Ura, MD[23], and Kyoko Yanagisawa, MD[24] as cooperative investigators, and Katsuji Oguchi[25] as a controller.*

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This study was supported by a grant from Banyu pharmaceutical Co. Ltd. Tokyo, Japan.

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