

EFFECT OF LONG-TERM ADMINISTRATION OF FINASTERIDE (MK-906), AN INHIBITOR OF 5 α -REDUCTASE, IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA

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We evaluated the effect of long-term administration of finasteride (MK-906), a potent inhibitor of 5 α -reductase in patients with benign prostatic hyperplasia (BPH). The effect of an increase in dose was also assessed.

Finasteride was administered to 61 patients with BPH at the dose of 1 mg/day for 48 weeks. Thirty three of these patients subsequently received finasteride at the dose of 5 mg/day for further 24 weeks in an open extension study. Urinary symptoms, urinary flow rate, residual urinary volume, prostatic volume and serum concentrations of dihydrotestosterone and prostate-specific antigen were examined periodically during the treatment.

The size of the prostate and total urinary symptom scores decreased progressively during the first 16 weeks of treatment. The patients who received finasteride had a significant increase in the maximal urinary flow rate and a significant decrease in residual urinary volume. After 72 weeks of treatment, finasteride at an increased dose of 5 mg did not provide additional benefit to patients, although the effects of the drug at a dose of 1 mg were well maintained. Treatment with finasteride was well tolerated at both doses.

In conclusion, the treatment of BPH with 1 mg of finasteride per day for 48 weeks results in a significant increase in maximal urinary flow rate, and a decrease in prostatic volume, symptoms of obstruction and residual urinary volume, with minimal toxicity.

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Key words: Anti-androgen therapy, Finasteride, MK-906, 5 α -reductase inhibitor, Benign prostatic hyperplasia

INTRODUCTION

Benign prostatic hyperplasia (BPH) is common in aged men, and results in enlargement of the prostate gland and urinary obstruction^{1,2)}. This enlargement is directly due to cellular hyperplasia of both the glandular and stromal elements of the gland. Although most older men have either histologic or clinical BPH, the majority of cases do not progress to

a state warranting treatment³⁾. Nevertheless, BPH is the most common disease treated by urologists today. Many forms of treatment for BPH are palliative, and an important aspect of treatment should be improvement of the patient's symptoms and his quality of life⁴⁾.

Androgens are required to maintain the size and function of the prostate. The prostate does not become enlarged in boys castrated before puberty, and androgen withdrawal therapy results in shrinkage of the prostate with relief of obstructive symptoms^{5,6)}. The androgen primarily responsible

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for prostatic growth and enlargement is dihydrotestosterone. Men who have 5 α -reductase deficiency and who therefore cannot convert testosterone to dihydrotestosterone have poor prostatic growth, although some other tissue are responsive to testosterone^{7,8)} Therefore, a compound that selectively inhibits 5 α -reductase could provide effective treatment for BPH.

Finasteride (MK-906), a 4-azasteroid, is a competitive inhibitor of 5 α -reductase. It possesses no androgenic, estrogenic, or progestational properties and has no affinity for androgen receptor⁹⁾ Administration of this agent for short periods results in decreased serum dihydrotestosterone levels, a reduction in the size of the prostate and improvement in urinary flow rate¹⁰⁻¹²⁾ The optimal dose of finasteride has been reported to be 5 mg per day^{13,14)}. Our early phase II study also demonstrated that treatment of BPH patients with 1 mg of finasteride per day for 12 weeks decreased the serum level of dihydrotestosterone and the size of the prostate without serious side effects. Since finasteride needs to be administered for a long period, the purpose of this study was to evaluate the efficacy and safety of long-term administration of finasteride. We also evaluated the effect of an increase in dose from 1 mg to 5 mg.

PATIENTS AND METHODS

1. Subjects

This study was conducted at 15 centers in Japan from May 1992 to August 1994, and was approved by the institutional review board at each center. We explained the objectives and contents of the study and the meaning of participating in the study to the patients. Their informed consent was obtained before the study. A total of 61 patients ranging in age from 54 to 83 years (mean: 69.5 years) who had BPH were enrolled (Table 1). All patients had some symptoms of urinary obstruction, an enlarged prostate gland on digital examination, and maximal urinary-flow rates of less than 15 ml per second with a voided volume of 150 ml or more. Patients with prostatic cancer, prostatitis, urethral stricture,

neurogenic bladder, mental diseases, renal dysfunction or serious cardiovascular disorders were excluded. Patients whose past history included serious allergy, drug or alcohol abuse, transurethral resection of the prostate, balloon dilation of the prostatic urethra, insertion of urethral stent, transurethral hyperthermia treatment or anti-androgen medication were also excluded.

2. Study protocol

Finasteride [N-(2-methyl-2-propyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide] is a 5 α -reductase inhibitor. After a two-week period during which the patients were given lactose placebos, they received 1 mg tablet of finasteride daily for 48 weeks. Subsequently, each patient was offered the opportunity to continue with a 5 mg tablet of finasteride daily for further 24 weeks. The tablets were apple-shaped and film coated, and were orally taken once daily after breakfast.

Each patient was evaluated monthly, at which time side effects and the degree of compliance with the treatment regimen were assessed. Prostatic volume was measured at baseline and at 16, 32, 48 and 72 weeks. Urinary symptoms were assessed every 4 weeks. The urinary flow rate and residual urinary volume were measured at baseline and after 4, 16, 32, 48 and 72 weeks of treatment. Laboratory tests and serum hormone values were also examined at these times. Other antiandrogens, α -receptor blockers or drugs which affect micturition were not used in combination. In the event of serious urinary obstruction, urethral catheterization, intermittent self-catheterization or indwelling catheter were allowed.

Patients withdrawn from the study were examined as much as possible. Handling of these patients was finally determined at case study conferences. During the study, 17 patients receiving 1 mg of finasteride and 5 patients receiving 5 mg withdrew from the study for some reasons such as side effects.

3. Evaluation procedures

Prostatic volume was measured by transrectal ultrasonography. Measurements were made in the axial, sagittal and coronal planes, and the volume of

Table 1. Baseline characteristics of patients with BPH

Characteristics	No. of patients	Mean $\pm$ SD
Age (years)	61	69.5 $\pm$ 6.7
Prostatic volume (ml)	49	45.6 $\pm$ 22.9
International prostate symptom score	41	14.9 $\pm$ 6.3
Maximal urinary flow rate (ml/sec)	48	9.0 $\pm$ 3.2
Average urinary flow rate (ml/sec)	48	4.2 $\pm$ 1.9
Residual urinary volume (ml)	33	83.8 $\pm$ 59.0
Serum DHT (ng/ml)	34	0.62 $\pm$ 0.27
Serum testosterone (ng/ml)	35	5.80 $\pm$ 1.64
Serum PSA (ng/ml)	38	4.0 $\pm$ 3.9

the prostate was calculated according to the following formula: $\text{volume} = (4/3)\pi(\text{axial value}/2)(\text{coronal value}/2)(\text{sagittal value}/2)$. With the use of this approach, the mean prostatic volume in patients with BPH was 45.6 cm^3 .

The patients' symptoms were assessed on the basis of their responses to a questionnaire modified from that of Gormley, et al¹³⁾. The total symptom score (international prostate symptom score) was calculated from the responses to seven questions about nocturia, dysuria, interruption of urination, impairment of size and force of the urinary stream, bladder emptying, urgency, and urination within two hours. Each symptom was scored according to a six-point scale, with a score of 0 indicating the absence of a symptom and a score of 5 presence of a severe symptom, so that the worst possible score was 35.

Urinary outflow obstruction was measured with a urinary flow-meter. Measurements of maximal and mean urinary flow rates were used in the analyses only if at least 150 ml of urine was voided. Patients were instructed to drink about 270 ml of water before the examination. Residual urinary volume was measured by transabdominal ultrasonography or by catheterization.

Serum testosterone and dihydrotestosterone (DHT) were measured by radioimmunoassay at Endocrine Sciences (Tarzana, CA, USA). Serum prostate-specific antigen (PSA) was measured by the Ohtsuka Assay Institute (Tokushima, Japan).

4. Statistical analysis

Statistical significance was determined by the signed rank sum test. All P values of 0.05 or less were considered to indicate significance.

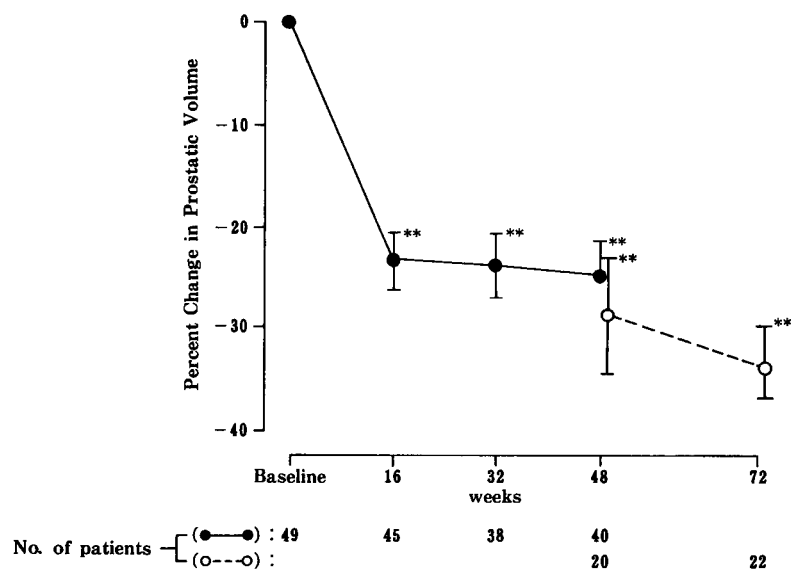


Fig. 1. Mean ($\pm$ SE) percent change in prostatic volume in patients with BPH during treatment with 1 mg (●—●) or 5 mg (○--○) of finasteride. ** $p < 0.01$ vs. baseline.

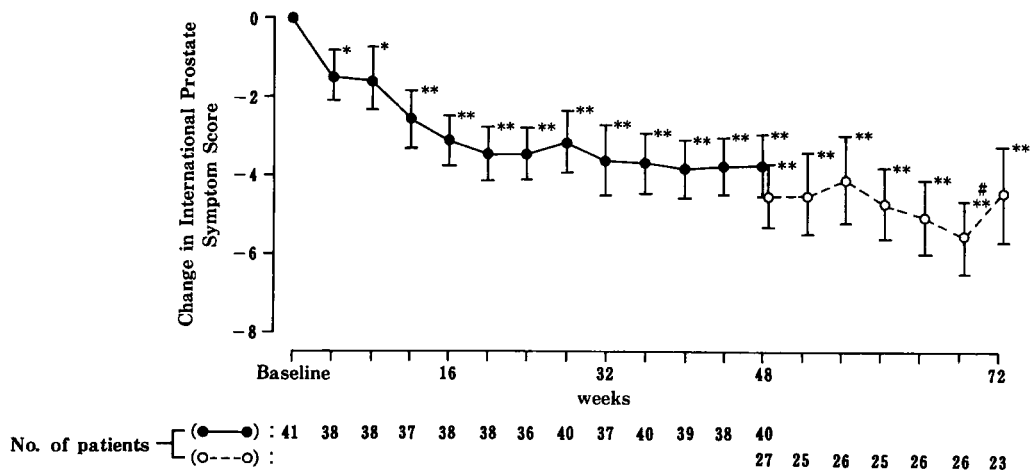


Fig. 2. Mean ($\pm$ SE) change in international prostate symptom score in patients with BPH during treatment with 1 mg (●—●) or 5 mg (○--○) of finasteride. * $p < 0.01$, ** $p < 0.01$ vs. baseline, # $p < 0.05$ vs. week 48.

RESULTS

1. Effect of finasteride on prostate size

During the first 16 weeks, the mean size of the prostate decreased progressively, after which it did not change significantly (Fig. 1). At 48 and 72 weeks of treatment, the prostate shrunk by 22.5% and 29.3% from baseline, respectively. The prostatic volume decreased by at least 25% in 46.9% of patients given 1 mg of finasteride at 48 weeks of treatment and

in 80.8% of patients given 5 mg of finasteride at further 24 weeks.

2. Effect of finasteride on symptom scores

Patients treated with 1 mg of finasteride showed a significant decrease in total symptom scores from week 4 through week 48 (Fig. 2). Scores continued to decrease through week 72 of treatment. In the 24-week open extension study, the scores fell significantly only at week 68 compared with the scores at week 48. The frequency of nocturia decreased

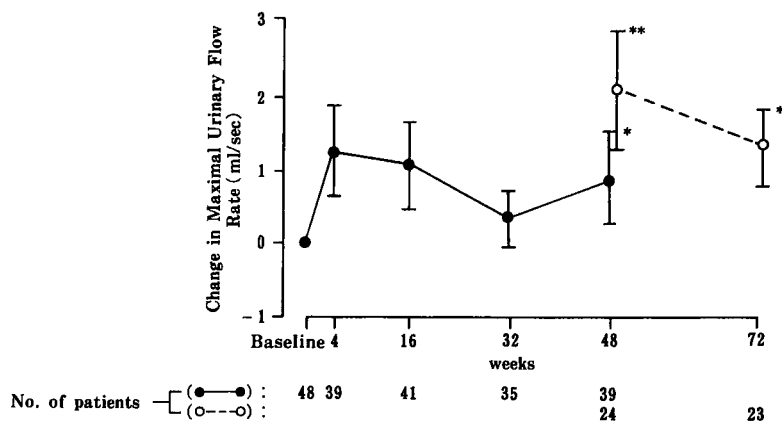


Fig. 3A

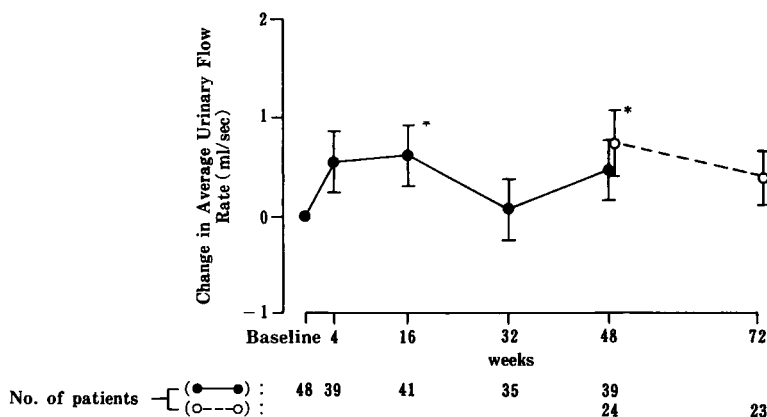


Fig. 3B

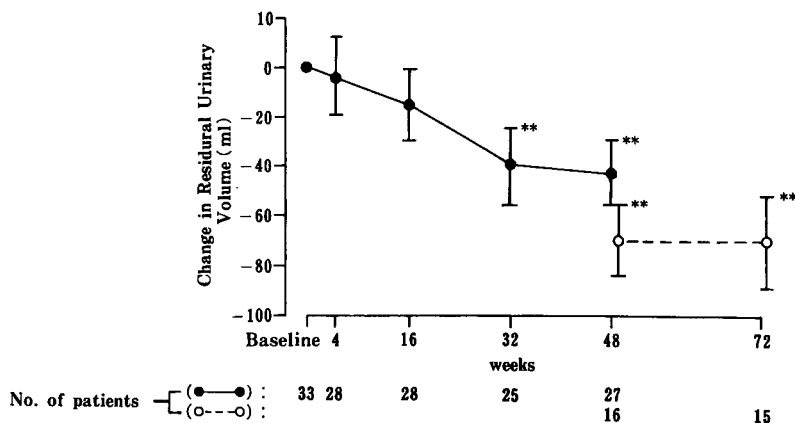


Fig. 3A

Fig. 3. Mean ($\pm$ SE) change in maximal urinary flow rate (Fig. 3A), average urinary flow rate (Fig. 3B) and residual urinary volume (Fig. 3C) in patients with BPH during treatment with 1 mg (●—●) or 5 mg (○--○) of finasteride. * $p < 0.05$, ** $p < 0.01$ vs. baseline.

during the first 16 weeks, but then increased gradually toward baseline level. The symptom score decreased by at least 10 points or 37% in 43.1% of patients who received 1 mg of finasteride for 48 weeks of treatment and in 55.6% of patients who received 5 mg of finasteride for a further 24 weeks.

3. Effect of finasteride on urinary flow rate and residual urinary volume

Maximal urinary flow rates showed a significant increase from week 48 to week 72 (Fig. 3A). The

finasteride-treated patients showed a significant increase in mean urinary flow rate at week 16 (Fig. 3B), but there were no significant changes from baseline after 32 weeks of treatment. The residual urinary volume, compared to baseline, significantly decreased at each measurement from 32 to 48 weeks (Fig. 3C), and the decrease was well maintained at 72 weeks.

Improvement was regarded as an increase in maximal urinary flow rate by at least 3 ml per

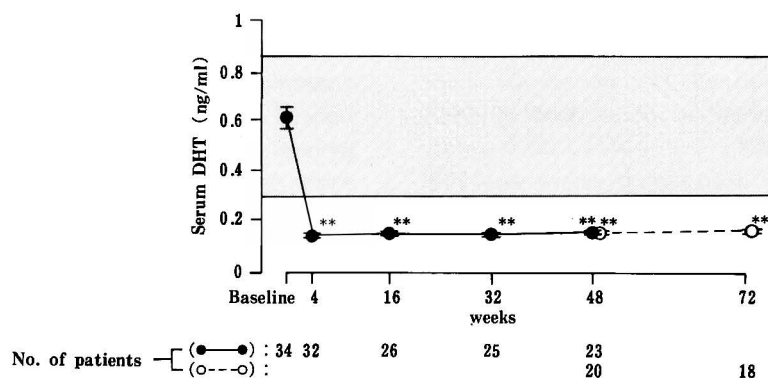


Fig. 4A

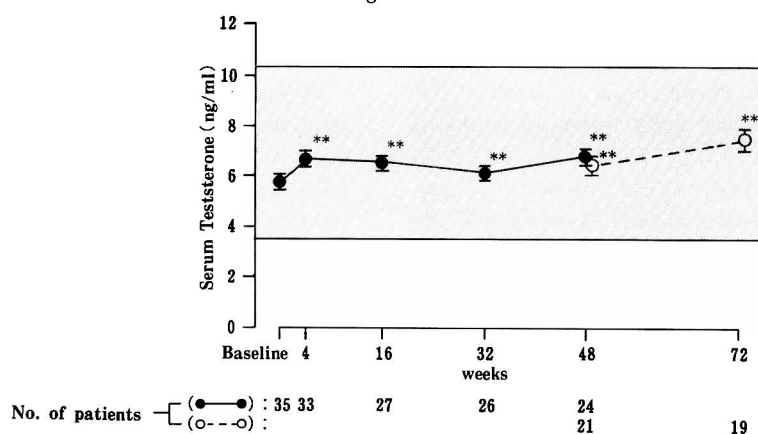


Fig 4B

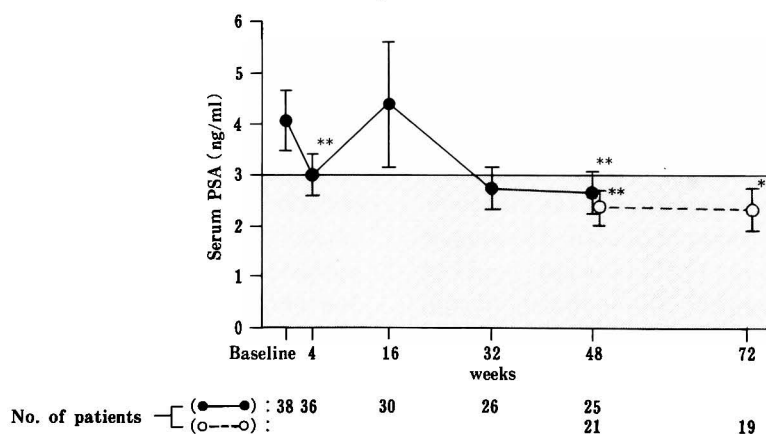


Fig 4C

Fig. 4 Effects of treatment with 1 mg (●—●) or 5 mg (○---○) of finasteride on mean ($\pm$ SE) serum levels of DHT (Fig. 4A), testosterone (Fig. 4B) and PSA (Fig. 4C) in patients with BPH. The stippled area in figure indicates the normal range in men. * $p < 0.05$, ** $p < 0.01$ vs. baseline.

second, increase in mean urinary flow rate by at least 1 ml per second, or decrease in residual urinary volume by at least 50%. These criteria were met by 35.4% patients who received 1 mg of finasteride for 48 weeks and 42.3% who received 5 mg of finasteride for further 24 weeks.

In total, these findings suggest that patients with BPH may respond with prostatic shrinkage, improvement in symptoms, an increase in maximal flow rate and a decrease in residual urinary volume after long-term therapy with 1 mg of finasteride per day, and that even if the dose of finasteride is increased from 1 mg to 5 mg, no additional effect may be seen.

4. Effect of finasteride on serum level of DHT, testosterone and PSA

Serum DHT level decreased by more than 70% from baseline during the first 4 weeks of treatment (Fig. 4A). This decrease was maintained, through 72 weeks. In contrast, serum testosterone concentrations increased approximately 20% after 4 weeks of treatment, and remained unchanged thereafter (Fig. 4B). However, all values remained within the normal range at all times. Serum PSA concentration significantly decreased from week 48 through week 72 of treatment (Fig. 4C). The serum PSA levels were abnormally high at baseline and decreased to the normal range after 32 weeks of treatment.

5. Side effects

Symptoms considered by the investigators to be possibly drug-related were observed in 4 of 61 (6.6%) patients who received 1 mg finasteride for 48 weeks. No drug-related symptom were seen in patients given 5 mg of finasteride. The symptoms were gynecomastia, anorexia, general malaise, nausea and stomachache, but were not serious. Gynecomastia spontaneously disappeared about one month after onset. The other symptoms also disappeared after the discontinuation of finasteride.

Eight of 61 (13.1%) patients had mild abnormalities in laboratory values during the study. One patient had an increase in activity of serum lactic dehydrogenase, one patient an increase in serum total cholesterol and triglyceride, and a third an increase in serum triglyceride. Three patients had a decrease in red blood cell count. Other changes were an increase in serum potassium and in urinary sugar in one patient each. These findings suggest that finasteride is generally well tolerated.

DISCUSSION

This study was undertaken to evaluate the efficacy and safety of long-term administration of finasteride (MK-906), a 5 α -reductase inhibitor, in patients with BPH. Results showed that finasteride was effective for a significant proportion of patients with BPH with

minimal toxicity. Serum DHT concentrations decreased to the castration levels soon after the initiation of finasteride therapy. Serum testosterone levels increased only slightly and remained well within the normal range throughout the study. These findings suggest that suppression of DHT formation leads to regression of the hyperplastic prostate gland in the majority of patients with BPH, although the ultimate biochemical mechanisms responsible for prostatic hyperplasia has not been fully elucidated.

Prostatic volume decreased significantly within 16 weeks in finasteride-treated patients. Mean reductions in prostatic volume were 22.5% in patients given 1 mg of finasteride daily for 48 weeks and 29.3% in patients given 5 mg of finasteride daily for further 24 weeks. Approximately 50% of patients who received 1 mg of finasteride daily had a decrease of 25% or more in the size of the prostate. This response is similar to that reported in patients treated with an analogue of gonadotropin-releasing hormone⁶⁾ or surgical castration⁵⁾. The reduction in prostatic volume in the finasteride-treated patients was consistent with the significant decreases in serum PSA levels in these patients, and thus were indicative of a decreased activity of glandular cells of the prostate¹⁵⁾.

The present study demonstrates that patients who received 1 mg of finasteride daily had a significant decrease in total urinary symptom scores. However, previous studies revealed no significant difference in total symptom scores between patients treated with 1 mg of finasteride and placebo^{13,14)}. Since there was no placebo group in this study, a control group may be necessary to evaluate the effect of finasteride precisely.

Maximal urinary flow rate increased significantly during finasteride treatment. The increase in the maximal urinary flow rate occurring after transurethral resection of the prostate (TUR-P) is 8 to 9 ml per second¹⁶⁾. The maximal urinary flow rate has been reported to be significantly higher in finasteride-treated BPH patients than in patients who received placebo (1 to 2 ml per second)^{13,14)}. Study of the natural history of BPH indicates that the mean decrease in maximal urinary flow rate is approximately 0.2 ml per second per year¹⁷⁾. In the current study, the increase in maximal urinary flow rate in finasteride-treated patients was small (1.3 ml per second), but this modest improvement may represent a shift of several years in the natural course of the disease. Despite this only slight improvement in maximal urinary flow rate, the residual urinary volume significantly decreased in these patients.

Previous studies demonstrated that a daily dose of 5 mg of finasteride was more effective than a 1 mg dose^{13,14)}. However, the present study showed no additional effect even after the dosage increase of

finasteride from 1 mg to 5 mg. This might be caused by the shorter period of treatment with 5 mg than that with 1 mg. These findings suggest that finasteride at an increased dose of 5 mg might not confer greater clinical benefit to patients with BPH.

Not all patients with BPH responded to finasteride therapy. The variation in the response to finasteride may be due to the heterogeneous nature of the disease or to the multifactorial process of the pathogenesis¹⁸⁾.

Symptoms considered by the attending physicians to be possibly finasteride-related was observed in 4 of 61 patients during administration of 1 mg finasteride. In endocrinological symptom, gynecomastia was observed in only one patient. This symptom disappeared spontaneously about one month after the onset. The other symptoms were anorexia, general malaise, nausea and stomachache, all of which disappeared within four weeks after discontinuation of administration. No additional symptoms were seen in the 33 patients in whom the dose of finasteride was increased to 5 mg. Eight of 61 patients had mild abnormalities in laboratory values during the study. These findings suggest that finasteride is well-tolerated during long-term administration, and that the excellent safety and tolerability of finasteride is attributed to its specific mode of action and the limited role of 5 α -reductase in male reproductive tissues. Moreover, finasteride at 5 mg/day was as safe as that at 1 mg/day.

Surgical treatment is clearly indicated for complete urinary retention, renal functional damage caused by obstruction, recurrent urinary tract infection, bladder stones and recurrent gross hematuria, if the patient is fit for surgery. The results in experienced hands have been excellent, and any alternative invasive procedure must approach its level of efficacy, namely symptomatic improvement of 88–95%, death rate of less than 1%, morbidity of 16%, incontinence of 0.8%, impotence in 5–10%, and reoperation in 6–15% over 8 years¹⁹⁾. Generally, however, the clinical diagnosis of BPH is not regarded as an immediate threat to the upper urinary tract or to survival of the patients. In addition, TUR-P is by no means perfect, although it is an effective treatment for most patients with symptomatic BPH. Follow-up data suggested that approximately 20–25% of patients undergoing this procedure do not obtain a satisfactory long-term outcome¹⁶⁾. There are sound reasons to accept alternative choices including careful observation of the patients. Since the development of BPH is clearly linked to the presence of functioning testes, androgen receptor antagonists, progestin-estrogen combinations and LH-RH analogues have been tested in patients with BPH^{6,20,21)}. Although the reduction in prostatic volume obtained with any of these therapies was comparable to that obtained following surgical castration⁵⁾, they all had significant

side effects such as impotence, decreased libido, lack of energy, gynecomastia and an increased risk of osteoporosis. The present study shows the efficacy and the safety of finasteride as a treatment for symptomatic BPH, and suggests that finasteride is acceptable as an alternative treatment for BPH.

In conclusion, long-term finasteride therapy in patients with BPH led to a sustained decrease in serum DHT concentrations, followed by a decrease in prostatic volume. These changes were accompanied by an increase in maximal urinary flow rate and decreases in symptom scores and residual urinary volume. The treatment with a daily dose of 5 mg of finasteride did not increase the incidence of adverse events, compared with a daily dose of 1 mg. The present findings showed that treatment with a daily dose of 1 mg of finasteride (MK-906) may modify the natural history of BPH favorably and may be beneficial in patients with BPH, and the most attractive feature of finasteride may be its excellent toxicity profile.

APPENDIX

This study was carried out in accordance with the notification of the Pharmaceutical Affairs Bureau in the Japanese Ministry of Health and Welfare (PAB notification No. 874), "Good Clinical Practice"

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和文抄録

前立腺肥大症に対する 5α 還元酵素阻害剤
フィナステリド (MK906) の長期投与効果

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前立腺肥大症患者61例を対象に 5α 還元酵素阻害剤であるフィナステリド (MK906) の 1 mg/day を48週間, そのうち33例には引き続き 5 mg/day を24週間投与し, 前立腺体積, 尿流動態, 自覚症状などについて定期的に検討した. フィナステリドの投与により投与開始後16週で前立腺は著明に縮小し, 自覚症状も改善した. また最大尿流率も有意に増加し, 残尿も減

少した. フィナステリド投与量を 5 mg/day へ増加してもさらなる効果は認められず, 1 mg/day 投与時と同様な効果であった. 副作用は4例に出現したが, 重篤なものは認められなかった.

前立腺肥大症に対し, フィナステリド 1 mg/day, 48週間の長期投与にて高い有効性をえることができた. フィナステリドは前立腺肥大症に対する治療の1つのオプションであると考えられた.

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