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Voiding Dysfunction

The Different Reduction Rate of Prostate-Specific Antigen in Dutasteride and Finasteride

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Purpose: To compare and analyze the therapeutic effects and changes in the prostate-specific antigen (PSA) level with treatment with finasteride or dutasteride for benign prostatic hyperplasia (BPH) for 1 year.

Materials and Methods: We retrospectively investigated patients who suffered from BPH for 1 year between January 2005 and December 2008. For treatment groups, we divided the patients into two groups: one was treated with alfuzosin and finasteride and the other was treated with alfuzosin and dutasteride. At the beginning of treatment, the patients underwent transrectal ultrasonography and measurement of urine flow rate, residual urine volume, PSA, and International Prostate Symptom Score (IPSS). Patients with diseases affecting urinary function were excluded. We not only analyzed the data at the time of initial treatment, but also after 1 year of treatment. A total of 219 patients were able to be evaluated for 1 year.

Results: Both finasteride and dutasteride reduced PSA and prostate volume significantly. The comparison between groups showed a more significant reduction of PSA (p=0.020) and prostate volume (p=0.052) in the dutasteride group. Other parameters did not differ significantly between the groups.

Conclusions: 5-α Reductase inhibitors for BPH treatment reduced PSA and prostate volume significantly when the patients were treated for 1 year. Administration of dutasteride is considered to be more effective in reducing PSA and prostate volume. Therefore, dutasteride should not be considered equivalent to finasteride in the reduction rate of PSA. The intensity of dutasteride must be reevaluated in comparison with finasteride.

Key Words: *Dutasteride; Finasteride; Prostate-specific antigen; Prostatic hyperplasia*

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a disease in which lower urinary tract symptoms are concurrently present while the prostate is gradually enlarged. It has been reported to occur in more than approximately 50% of males aged 60 years or older. Due to the increased mean life expectancy, the importance of BPH has increased [1]. Accordingly, in recent years, drug therapy has been used as a mainstream modality in most patients [2]. α-blockers and 5-α-reductase inhibitors (5ARIs) are representative of these treatment agents. In particular, useful treatment outcomes have been reported after long-term use of 5ARIs.

5AR is classified into type I and type II. Both types are increasingly expressed in cases of BPH compared with normal tissue. However, in cases of primary prostate cancer, type I 5AR is increased. By contrast, type II 5AR is decreased or remains unchanged as compared with BPH [3]. In addition, type II is increased when local prostate carcinoma progresses to metastatic cancer. Both types I and II are increased in high-grade carcinoma compared with low-grade carcinoma [4].

Of the 5ARIs that are currently used in Korea, finasteride selectively inhibits type II. By contrast, dutasteride

inhibits both types I and II. Of the studies that have been conducted to date, not many have made comparisons between the two drugs. Some studies have reported that there are no great discrepancies in the effects and side effects. Other studies have reported that the concentration of serum dihydrotestosterone (DHT) was suppressed more powerfully by dutasteride than by finasteride after a 6-month administration [5].

Regarding the effects of each treatment agent, many studies have been conducted to evaluate a single treatment or a concomitant treatment with α-blocker during a certain length of time or a long-term period. However, no clinical studies have been conducted to compare these two drugs, whose effects are based on totally different modes of action. We therefore compared the clinical effects of finasteride and dutasteride in BPH patients after 1 year of treatment.

MATERIALS AND METHODS

We retrospectively investigated patients who were more than 50 years old with lower urinary tract symptoms between January 2005 and December 2008. The patients had been taking medication for treatment of BPH (alfuzosin 10 mg, finasteride 5 mg, dutasteride 0.5 mg) for 1 year. The patients were classified into the alfuzosin+finasteride combination therapy group and the alfuzosin+dutasteride combination therapy group. At the early stage outpatient visit, all patients underwent transrectal ultrasonography and measurement of urine flow rate, residual urine volume, prostate-specific antigen (PSA), and International Prostate Symptom Score (IPSS). BPH was defined as cases in which the prostate volume exceeded 20 cc, the maximal flow rate was lower than 15 ml/s, and IPSS was higher than 8 points in patients with lower urinary tract symptoms. A past history was also evaluated. Then, patients with any diseases affecting their voiding functions were excluded, such as vertebral diseases, cerebrovascular diseases, or diabetic peripheral diseases. Patients who had pyuria or infections detected in urine chemistry and microbial tests were also excluded. Only patients who could be reevaluated after a 1-year period were enrolled.

A total of 219 patients were enrolled in this study. To assess the treatment effect between the groups, at the initial outpatient visit and after a 1-year period, a comparative analysis was performed for prostate volume, PSA, maximal flow rate, residual urine volume, and IPSS. The proportion of each parameter was also examined. PSA was measured by electrochemiluminescence (ECLA, Modula, Roche Inc., Indianapolis, IN, USA). Statistical analysis was performed by using the SPSS ver. 10.0 (SPSS Inc., Chicago, IL, USA), for which an independent t-test was used. Statistical significance was set at $p<0.05$.

RESULTS

In the total group of 219 patients, the patients' mean age was 69 years (range, 45-85 years), their mean prostate volume was 35.5±17.6 g, and their mean PSA level was 2.08±2.38 ng/ml. A comparison of the treatment effect between the alfuzosin+finasteride group and the alfuzosin+dutasteride group showed no significant differences in the abso-

TABLE 2. Comparison of parameter ratios according to patient group after 1 year of treatment

	Group 1 (n=136)	Group 2 (n=83)	p-value
Prostate volume ratio	0.87±0.14	0.83±0.16	0.052
PSA ratio	0.85±0.62	0.67±0.39	0.019[a]
Qmax ratio	1.14±0.57	1.41±2.07	0.163
Voided volume ratio	1.46±3.13	1.26±0.95	0.575
Residual urine volume ratio	1.05±1.08	1.00±0.89	0.724
IPSS			
Total score ratio	1.02±0.78	0.98±0.47	0.764
Quality of life score ratio	0.97±0.35	0.91±0.32	0.247

Group 1: alfuzosin+finasteride group, Group 2: alfuzosin+dutasteride group, ratio: value of pre-medication/value of post-medication, PSA: prostate-specific antigen, Qmax: urine peak flow rate, IPSS: International Prostate Symptom Score, [a]: significant difference ($p<0.05$) between the two groups

TABLE 1. The comparison of medication effect parameters according to patient group

	Basement		1 year later		Differences between basement and 1 year later		p-value
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	
Prostate volume (g)	37.3±21.7	38.5±14.2	32.4±19.8	31.9±12.8	4.9±6.9	6.6±7.5	0.084
PSA (ng/ml)	2.32±2.93	2.27±2.15	1.48±1.60	1.47±1.79	0.80±2.30	0.80±1.10	0.886
Qmax (ml/s)	14.2±6.8	13.5±6.3	14.5±7.2	14.8±7.5	0.3±6.7	1.3±6.5	0.299
Voided volume (ml)	206.7±131.5	207.1±130.7	213.0±243.6	207.1±130.7	6.6±223.6	1.3±116.0	0.851
Residual urine volume (ml)	42.2±45.0	48.7±56.6	27.3±28.9	28.7±25.4	14.8±39.9	20.0±52.7	0.409
IPSS							
Total score	14.5±8.0	15.7±7.6	11.1±7.6	11.6±7.1	3.4±6.3	4.1±6.2	0.430
Quality of life score	2.7±0.6	2.8±0.7	2.5±1.0	2.4±1.0	0.2±0.9	0.4±0.8	0.083

Group 1: alfuzosin+finasteride group, Group 2: alfuzosin+dutasteride group, PSA: prostate-specific antigen, Qmax: urine peak flow rate, IPSS: International Prostate Symptom Score

lute changes in each parameter between the two groups (Table 1). However, the degree of PSA reduction was relatively higher in the dutasteride combination therapy group (p= 0.020). The volume of the prostate gland was reduced, but this was not statistically significant (p=0.052) (Table 2).

DISCUSSION

BPH is the most common cause of lower urinary tract symptoms in male patients, and it is a chronic, progressive disease. At present, long-term drug treatment is the first-line treatment of choice, commonly with α-blockers. In addition, 5ARIs are both concomitantly administered or used as the sole treatment. 5ARI suppresses type I reductase, which is mainly present in the skin and liver, and type II reductase, which is specific to organs such as the prostate and male reproductive organ. By blocking the enzymatic conversion to DHT, it reduces the concentration of DHT within the prostate and thereby induces the degeneration of the prostatic gland. Finasteride, which is mainly specific to type II, reduces serum DHT by 70% and prostate DHT by 80-90% within 2 weeks after administration. Following a 12-month administration with a dose of 5 mg, the volume of the prostate has been reported to be reduced by approximately 20% [6]. Dutasteride, which is specific to both types I and II, has also been reported to be effective in reducing prostate volume by approximately 23% after a 1-year administration. Moreover, dutasteride has been reported to be effective in improving lower urinary tract symptoms such as IPSS or the maximal flow rate in male patients [7]. Some studies have suggested that dutasteride was more effective in suppressing DHT within the prostate as compared with finasteride (94-97% vs. 68-85%) [8-10]. Debruyne et al performed an open marker test during a 2-year period after a 2-year double-blind study [7]. According to those authors, following a comparison of IPSS between a 4-year dutasteride treatment group and a 2-year placebo treatment group, IPSS was significantly higher in the former group [7]. According to studies on prostate volume, in the finasteride group, there was an 18% decrease during a 4-year period. In the dutasteride group, however, there was a 23.6% decrease during a 1-year period and a 27.3% decrease during a 4-year period [7,11]. In addition, there have also been studies that compared other aspects of finasteride and dutasteride treatment. For example, Fenter et al reported that dutasteride was effective in reducing medical expense by approximately 20% as compared with finasteride [12,13]. According to Roehrborn et al and O'Leary et al, dutasteride showed a higher degree of effect in improving symptoms [14,15]. Issa et al reported that the proportion of acute urinary retention and that of surgical management were 5.3% vs. 8.3% and 1.4% vs. 3.4% after a 5-month drug treatment with dutasteride vs. finasteride, respectively [16]. These results indicate that both parameters were relatively lower in the dutasteride group than in the finasteride group. In our study, prostate volume and IPSS were relatively lower in the alfuzosin+dutasteride group, but there were no statistically significant differences between the two groups (Table 1).

Since PSA was disclosed to have a specificity for the prostate in 1979, it has been used as a useful marker for the detection of prostate cancer. However, PSA has also been shown to have a tendency to increase in other cases, such as prostatitis or BPH. Therefore, particularly in patients whose PSA level is 4-10 ng/ml, measurement of the PSA level does not have sufficient sensitivity and specificity to be a screening test for prostate diseases. Besides, the PSA level has also been reported to be affected by drugs that are commonly used to treat prostate diseases in the field of urology. Milam et al reported a lack of significant change in PSA in a study on α-blockers, especially terazosin [17]. In addition, Brown et al reported that the PSA level was decreased following a 2-month drug treatment [18]. As described here, there were no definite effects on the PSA level. Bozeman et al and Potts reported that the PSA level was decreased after treatment with quinolone antibiotics. Meanwhile, these authors maintained that unnecessary prostate biopsy should be reduced [19,20]. Fowke et al also reported that nonsteroidal antiinflammatory agents have been reported to significantly reduce the PSA level after treatment [21].

Many studies have reported that 5ARI is effective in lowering the PSA level. In association with this, Guess et al reported that the PSA level was decreased by 50% after a 1-year administration of finasteride 5 mg. After a 12-month period, however, there were no further effects in reducing the PSA level. Therefore, these authors maintained that the dose of finasteride should be determined to be twice the PSA level after a 1-year period [22]. In addition, Espana et al also advocated the "multiply by 2" principle, in which the dose should be multiplied by two based on the PSA level [23]. In Korea, Hong and Hong also reported that the PSA level was decreased by approximately 45% following a 6-month administration of finasteride and by approximately 50% following a 12-month administration [24]. Brawer et al reported that the PSA level was decreased by approximately 30-60% after a 54-week concomitant treatment with α-blockers and 5ARI [25]. The Proscar Long-term Efficacy and Safety Study (PLESS) is a 4-year study of finasteride therapy with the application of the "multiply by 2" principle. It tried to analyze the diagnostic rate for prostate cancer based on a PSA level of 4 mg/ml. According to this study, there was a similar profile of sensitivity (66% vs. 70%) and specificity (82% vs. 74%) as compared with the placebo-controlled group when the actual PSA level was applied [26]. Regarding dutasteride, Andriole et al reported that the PSA level was increased by 8.3% in year 2 in the placebo-controlled group [27]. However, the PSA level was decreased by 59.5% in year 2 and by 66.1% in year 4 in the dutasteride group. Based on these findings, the application of the "double PSA (multiply by 2)" principle to treatment with finasteride should be effective, as shown for treatment with dutasteride, considering the sensitivity and specificity for the diagnosis of prostate cancer [27].

In our study, when we compared the proportion of PSA

alterations between the finasteride group and the dutasteride group, the degree of PSA reduction was significantly higher in the dutasteride group (0.85 vs. 0.67, $p<0.05$) (Table 2). As for the reasons for these findings, no definite study results have been provided except that dutasteride has a dual effect, as compared with finasteride, and is more effective in suppressing DHT. However, according to Andriole et al, it has been theoretically hypothesized that dutasteride has an effectiveness in suppressing and necrotizing the proliferation of prostate cancer [28]. Also, in our series, in cases in which potential patients with prostate cancer were included, it can be presumed that this might cause a difference between tumor necrosis and the PSA level [28]. In the above studies, both finasteride and dutasteride were mentioned to be in need of application of the "multiply by 2" principle. According to our studies, however, it was questionable to consistently apply the "multiply by 2" principle in making a diagnosis of prostate cancer in all patients who were treated with dutasteride. At present, ongoing efforts are being made to examine the effects of long-term administration of 5ARI in preventing prostate cancer. It would therefore be notable to determine whether there is an optimal method for monitoring the PSA level in cases in which 5ARI is administered long-term. In our study, we found that the PSA level can vary depending on the use of two different types of drugs. According to this, it is presumed that a precise measure rather than the simple application of the "multiply by 2" principle would be mandatory.

There are several limitations to our study. First, the number of cases enrolled in each group was small. Second, we could not perform a head to head study for each pure 5ARI because of the limitations of a retrospective study. Therefore, to establish more precise criteria for prostate biopsy in patients treated with 5ARI, an adequate number of cases and a well-designed prospective study are required.

CONCLUSIONS

The degree of PSA reduction was significantly higher in the dutasteride group than in the finasteride group. It is therefore assumed that criteria for a screening test for prostate biopsy could be established on the basis of the degree of PSA reduction in patients whose PSA level was elevated. The difference between the two drugs should be clarified, and prostate biopsy should be performed accordingly with a consideration of the changes in the PSA level depending on the characteristics of the two different drugs. This would be helpful in the development of a screening test for prostate cancer by reducing the number of unnecessary tests and raising the sensitivity and specificity.

Conflicts of Interest

The authors have nothing to disclose.

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