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LETTER TO EDITOR

# Outcomes of dutasteride discontinuation in patients with benign prostatic hypertrophy

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To the Editor,

Benign prostatic hyperplasia (BPH) is a common cause of *lower urinary tract symptoms* (LUTS) in elderly males. The current guidelines recommend the use of a 5-alpha reductase inhibitor (5ARI) to treat males with moderate-to-severe LUTS and an enlarged prostate (1). Combination therapy with an alpha blocker and a 5ARI has proven effective at ameliorating LUTS and reducing the *total prostate volume* (TPV) and the risk of the disease progression (2-5).

With the aging of the Japanese population, it is expected that the frequencies of various chronic diseases will increase, and as a result, it is assumed that the number of oral medications being taken by older people will rise. It has been reported that the incidence of adverse drug events is higher among the elderly than among younger patients, and adverse drug event rates of 15-20% per year have been reported in nursing homes in the United States (6). The higher adverse drug event rates seen in elderly patients are caused by greater drug sensitivity due to age-related changes in pharmacokinetics and the higher number of drugs being taken by each patient.

As mentioned above, elderly people are prone to polypharmacy, as they have many comorbidities. In a multicenter study, it was reported that the elderly subjects were taking an average of 4.5 different medications (7). Polypharmacy is associated with increases in drug costs and drug interactions. In addition, it has been reported that the risk of adverse drug events was increased in patients taking ≥ 6 drugs (8), and furthermore, that the incidence of falls was high among patients taking ≥ 5 drugs (9). Therefore, among elderly people, even if only one type of medication is discontinued, the risk of adverse drug events can be expected to decrease, which may help to reduce healthcare costs in the long term.

It has been reported that when an alpha-1 blocker is combined with dutasteride, symptom relief can be maintained with dutasteride alone after the discontinuation of the alpha-1 blocker (10). However, it has also been reported that 60% of patients who stop taking dutasteride resume taking it within 1 year (11). Recently, it was suggested that 5ARI may induce suicidal behavior and depression and that the discontinuation of 5ARI should be considered (12). However, there are no studies involving a follow-up period of 2 years after discontinuation of dutasteride.

The purpose of this study was to investigate the predictors of restarting dutasteride in a real-world setting in the era of polypharmacy. At the beginning of 2016 a shortage of the drug forced us to stop dutasteride treatment in a group of patients. The drug returned to be available after four months. Nevertheless, some patients did not restart dutasteride but remained on treatment with alpha-blockers alone. We aimed to evaluate reasons for restarting or not dutasteride after a period of discontinuation.

## MATERIAL AND METHODS

### *Study subjects*

We retrospectively reviewed the medical records of patients with LUTS secondary to BPH who were treated with an alpha-1 blocker and dutasteride (0.5 mg/d) from September 2010 to December 2015. From January 2016, dutasteride was discontinued, and the patients were only prescribed an alpha-1 blocker. A total of 39 patients were included in this study.

The patients were divided into two groups: patients who restarted *dutasteride* (DR) and patients who remained on discontinuation of dutasteride (DD) group. In both groups, age, *body mass index* (BMI), *International Prostate Symptom Score* (IPSS), *quality-of-life* (QoL) score, *Overactive Bladder Symptom Score* (OABSS), duration of dutasteride treatment before

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discontinuation, number of different types of medications being taken by the patients, prostate volume, rate of reduction in prostate volume, *post-void residual volume* (PVR), and presence or absence of comorbidities were evaluated.
Prostate volume and the PVR were evaluated by using transabdominal ultrasound. All data were collected prior to the discontinuation of dutasteride.
The follow up period after the discontinuation of dutasteride lasted 24 months. Alpha-1 blocker monotherapy was continued during this period.
IPSS, OABSS, *prostate volume* (PV), and PVR were evaluated at 1, 3, 6, 12, 18, and 24 months after the discontinuation of dutasteride.
Patients were allowed to restart dutasteride during the follow-up period according to their desires and the judgement of the attending physician.

### *Statistical analysis*

Statistical analyses were carried out to identify clinical parameters that differed significantly between the DR and DD groups. The results are shown as the mean ± *standard error* (SE). The Mann-Whitney U test and Chi-squared test were used for the statistical analyses. The Cox proportional hazards model was used to estimate the relative risk of dutasteride being restarted associated with each parameter. Rate estimates were calculated using the Kaplan-Meier method. The log-rank test was used to evaluate differences in rates between the groups. All analyses were performed with JMP version 10 (*SAS Institute Inc., Cary, NC, USA*). Probability values of $< 0.05$ were considered statistically significant.

### *Ethical approval*

The institutional review board of Teikyo University approved this study (TUIC-COI 21-179).

## Results

Out of 39 eligible patients, 36 were analyzed at 24 months, and 13 patients (13/36, 36%) restarted dutasteride.
The remaining 23 patients (64%) discontinued dutasteride within 24 months as shown by the Kaplan-Meier curve in Figure 1.
Neither the type nor dose of alpha-1 blocker was changed during the follow-up period in any patient.
The mean number of different types of medications being taken by the patients in the DR and DD groups was 6.5 and 5.7, respectively. The mean number of nocturia events experienced per day before the discontinuation of dutasteride was significantly higher in the DR group than in the DD group (2.8 *vs* 1.8, respectively; p = 0.005). The mean duration of dutasteride treatment prior to discontinuation was significantly longer in the DR group (37 months) than in the DD group (25 months) (p = 0.0261) (Table 1).

***Figure 1.***
*Dutasteride discontinuation rate during the 2-year follow-up period as determined using a Kaplan-Meier curve.*
*The discontinuation rates at 6, 12, 18, and 24 months were 87%, 74%, 64%, and 64%, respectively.*

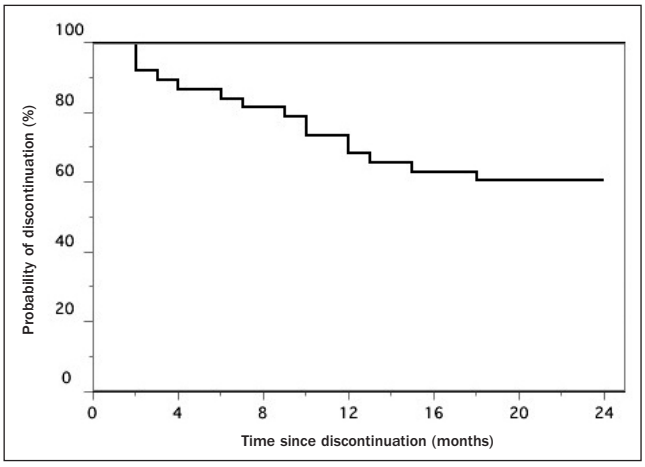


***Table 1.***
*Patient characteristics.*

| Variables | DR group (n=13) | DD group (n=23) | P-value |
|---|---|---|---|
| Age (mean ± SE), years | 79 ± 2.2 | 76 ± 1.3 | 0.2283 |
| BMI (mean ± SE), kg/m$^2$ | 23.3 ± 0.9 | 23.3 ± 0.6 | 0.6523 |
| Prostate volume (mean ± SE), ml | 46.3 ± 7.3 | 45 ± 3.6 | 0.781 |
| Hypertension, n (%) | 9 (75%) | 12 (52%) | 0.1907 |
| Diabetes mellitus, n (%) | 2 (17%) | 2 (9%) | 0.4817 |
| Dyslipidemia, n (%) | 0 (0%) | 6 (26%) | 0.0519 |
| No. of types of medications being taken (mean ± SE) | 6.5 ± 2.2 | 5.7 ± 2.2 | 0.3334 |
| Duration of dutasteride treatment (mean ± SE), months | 37 ± 4.6 | 24 ± 3.5 | 0.0261 |
| No. of nocturia events per night (mean ± SE) | 2.8 ± 0.3 | 1.7 ± 0.2 | 0.0050 |
| Total IPSS (mean ± SE) | 14.3 ± 1.7 | 11.7 ± 1.3 | 0.1294 |
| Urinary symptom score (mean ± SE) | 6.0 ± 1.0 | 5.5 ± 0.7 | 0.7005 |
| Irritative symptom score (mean ± SE) | 5.5 ± 1.2 | 4.4 ± 0.6 | 0.31 |
| QOL score (mean ± SE) | 2.8 ± 0.6 | 3.2 ± 0.3 | 0.6329 |
| Total OABSS (mean ± SE) | 5.3 ± 1.5 | 4.2 ± 0.6 | 0.7391 |
| PVR (mean ± SE), ml | 59 ± 16 | 35 ± 7.3 | 0.0868 |
| Reduction rate (mean ± SE), % | 12.4 ± 4.3 | 14.4 ± 4.1 | 0.8894 |

*Overactive Bladder Symptom Score; PVR: Post-void residual volume; SE: Standard error.*

The PVR before the discontinuation of dutasteride was not significantly different in the DR group (59 ml) compared to the DD group (35 ml) (p = 0.0868). Total IPSS and total OABSS were also not significantly higher in the DR group than in the DD group.
Multivariate analysis showed statistically significant differences in the duration of dutasteride treatment before discontinuation and the frequency of nocturia between the groups.
In DD group, the change from baseline of mean IPSS values (Δ-IPSS) at 1, 3, 6, 12, 18, and 24 months were ±0, +0.6, +0.3, +0.6, +0.9, and +0.6, respectively (p = 0.9985), the Δ-OABSS values at 1, 3, 6, 12,18, and 24

months were +0.1, +0.5, +0.4, +0.1, ±0, and +0.6, respectively (p = 0.9927), and the mean Δ-PVR values at 1, 3, 6, 12,18, and 24 months were -6.4, -3.0, -6.3, -1.4, +0.3, and -3.3, respectively (p = 0.9920). In DD group, the mean ΔPV values at 1, 3, 6, 12, 18, and 24 months were +4.1, +2.7, +5.7, +9.2, +11.7, and +8.9 respectively (p = 0.3945).
The reasons why dutasteride was restarted were as follows: choice of the patient in 4 cases, macrohematuria in 2 cases, nocturia in 1 case, symptom exacerbation in 4 cases, and the judgment of the physician in 2 cases.

## Discussion

In the present study, it was suggested that nocturia and a long period of dutasteride treatment prior to the discontinuation of dutasteride are predictors of restarting dutasteride in the real-world setting. Consequently, in patients that do not exhibit nocturia before the discontinuation of dutasteride, the withdrawal of dutasteride should be considered feasible.

### *Discontinuation of drugs for BPH treatment*

There have been a few prospective studies on the discontinuation of dutasteride. *Shindo et al.* evaluated the possibility of discontinuing dutasteride after it was used in combination with an alpha-1 blocker for BPH (11). After 6 months of combination therapy, 60% of the patients in whom dutasteride was discontinued restarted taking dutasteride within 12 months. The degree of prostatic enlargement seen after the discontinuation of dutasteride differed among patients. According to this study, rapid regrowth of the prostate leads to the deterioration of storage symptoms and a tendency to restart dutasteride and the baseline intraprostatic architecture may be a predictor of whether a patient is a good candidate for dutasteride discontinuation.
*Victor et al.* investigated the outcomes of discontinuing one medication after 2 years of combined alpha-blocker and 5ARI therapy for BPH/LUTS in a randomized multicenter study (13). They concluded that the discontinuation of either drug caused the progression of BPH. However, they suggested that the risk of resuming medication or undergoing transurethral resection of the prostate was greater in patients who discontinued 5ARI.
*Jeong et al.* reported that the discontinuation of 5ARIs during combination therapy induced prostate regrowth and symptom aggravation in males with BPH (14). Therefore, they suggested that the life-long use of 5ARIs should be considered to prevent BPH progression.
In the current study it was demonstrated that the temporary discontinuation of dutasteride was feasible, and in selected cases it was possible to discontinue dutasteride for 2 years.

### *Polypharmacy*

Regarding polypharmacy in the elderly, it was suggested that the temporary discontinuation of medications could be a good option, and it is expected that reducing the number of medications being taken could potentially reduce healthcare costs. In the present study, the number of different types of oral medications being taken by the patients was higher in the DR group. Basically, it is assumed that patients want to reduce the number of different types of oral medications they are taking, and hence, to maintain discontinuation. However, when the number of different types of oral medications being taken exceeds a certain level, one less medication does not really change the patient's condition. In fact, the restarting of oral medications may be related to the types of oral medications being taken, rather than the number of medications being taken by itself.

### *Length of previous treatment*

This study suggested that a longer period of dutasteride treatment before discontinuation was associated with a greater likelihood of restarting dutasteride, whereas previous administration of dutasteride for a shorter period (approximately 2 years) was associated with persistent discontinuation of dutasteride. A longer dutasteride treatment before discontinuation could be associated with a greater effect of prostate shrinkage that could be maintained for a longer period after dutasteride discontinuation so delaying restarting of dutasteride treatment, on the contrary we observed the opposite in this study. It has been reported that the main reason for restarting dutasteride is the regrowth of the prostate due to the discontinuation of the drug (11) although in this study dutasteride was mainly restarted because of hematuria or the choice of the patient.

### *Nocturia*

Nocturia before the discontinuation of dutasteride was identified as another predictor of restarting dutasteride treatment. In a recent study involving a follow-up period up to 21 years, it was reported that males with BPH have a persistently higher risk of Alzheimer's disease and all-cause dementia compared with males in the general population (15). The study identified BPH (and associated sleep disturbances) as a common, potentially curable, disorder associated with dementia risk. Therefore, it seems that controlling nocturia is an important issue for urologists.

### *Risk of depression*

Moreover, it is important to prescribe appropriate medication. Associations between 5ARIs and suicidality and depression have been reported. In a large cohort of males aged ≥ 66 years, it was found that the risk of self-harm and depression were higher than in males that were treated with 5ARIs. Therefore, it was suggested that the discontinuation of 5ARIs in these circumstances may be appropriate (12).

***Limitations***

We would like to emphasize several limitations of our study. Firstly, it was a retrospective cohort study, which involved the extraction of electronically stored clinical data, and it had a small sample size. Secondly, we could not assess the effects of the discontinuation of dutasteride on QoL.

Thirdly, we examined the types of other medications (in general) the patients were taking, but we should also have examined the actual daily amounts of other medications that they were taking. It was suggested that if the daily amounts of other medications being taken by a patient is high, the patient may not restart taking discontinued medications because they may want to reduce the daily amounts of other medication that they are taking.

## Conclusions

The present study suggested that the temporary discontinuation of dutasteride can be considered in cases who present a low frequency of nocturia and a relatively short period of dutasteride treatment before discontinuation. In addition, temporary discontinuation of dutasteride may be useful for dealing with polypharmacy in the elderly.

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