

Evaluating the effects of switching from dutasteride to tadalafil in benign prostatic hyperplasia patients with lower urinary tract symptoms: A randomized, open-label, multicenter study

下部尿路症状を伴う前立腺肥大症患者におけるデュタステリドからタダラフィルへの切り替えによる影響を評価するための無作為化非盲検多施設研究

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There are several treatment options for lower urinary tract symptoms (LUTS) with benign prostatic hyperplasia (BPH) such as an α -blocker, a phosphodiesterase type 5 inhibitor (PDE5I), a 5- α reductase inhibitor (5ARI).¹⁻³ However, there has been limited evidence on how long a man should take these agents for LUTS and on whether men with BPH/LUTS can discontinue one agent from the combination therapy. Therefore, we conducted a randomized trial to compare the treatment outcomes of discontinuing dutasteride alone with a switch to tadalafil.

A prospective, randomized, open-label, multicenter trial was conducted to evaluate the efficacy of switching from dutasteride to tadalafil in patients with LUTS/BPH. Patients underwent dutasteride discontinuation or were switched to tadalafil 5 mg. The primary outcome measure was the change in International Prostate Symptom Score (IPSS) from baseline to 12 weeks. The secondary end points included changes in IPSS subscore, peak urinary flow rate, postvoid residual urine volume, blood pressure, testosterone, serum 8-hydroxy-2-deoxyguanosine (8OHdG) level, erectile function, and patient preference. This study was approved by the institutional ethics committee of Hirosaki University School of Medicine (K11H27001) and registered as a clinical trial (UMIN000020369). All participants provided written informed consent. Differences were considered

statistically significant at $P < 0.05$.

Participants were randomly assigned 5 mg of tadalafil daily (TAD group, $n = 34$) or underwent dutasteride discontinuation (Ctrl group, $n = 34$). Patient's background is shown in the supplemental file. There were no significant differences in the baseline between the two groups (**Table S1**). Twelve weeks after dutasteride discontinuation, IPSS (**Fig. 1A, B**) and sexual function (**Fig. 1C, D**) were not significantly different between the Ctrl and TAD groups. Furthermore, there were no significant differences in the other secondary endpoint measures between the groups (**Fig. S1**). For both groups, a severe adverse event and a significant worsening of LUTS were not observed. In a patient preference questionnaire, the majority (70%) of patients responded "neither satisfied nor dissatisfied" for postdutasteride therapy (**Fig. 1E**).

This study investigates the short-term effect of dutasteride discontinuation and the effect of switching from dutasteride to tadalafil in men with BPH/LUTS. Our results suggest that there is no significant difference in IPSS, prostate volume, uroflowmetry parameters, testosterone concentration, and sexual function between the groups. Small sample size and inclusion of older men (median age: 77 years) might reduce the efficacy of tadalafil in this study. Considering that the long-term discontinuation of dutasteride may have a harmful effect,^{4, 5} our observation suggests that the short-term discontinuation (≤ 12 weeks) of dutasteride is not harmful for LUTS in men with BPH and that tadalafil does not provide an additional effect in these patients.

The efficacy of tadalafil on sexual function and serum testosterone concentration in elderly population needs further studies. Considering that the median age of 77 years in this study is remarkably higher than that in

most previous prospective trials (50–60s), the marginal improvement ($P = 0.051$) may suggest the potential benefit of this treatment for sexual function in older patients with BPH/LUTS.

In this study, tadalafil 5 mg did not demonstrate the protective effect on serum 8OHdG concentration. Based on significant association among LUTS, oxidative stress, and PDE5I,^{6,7} we hypothesized the protective efficacy of tadalafil on oxidative stress. However, the impact of tadalafil 5 mg on 8OHdG may be limited. Further long-term studies may necessary to address this association in men with BPH/LUTS. The major limitation of this study was a small sample size with lower statistical power, short-term duration, and lack of placebo arms. A further long-term study is necessary to investigate the discontinuation effect of dutasteride and switching effect of tadalafil.

In conclusion, the discontinuation of dutasteride for 12 weeks did not worsen LUTS in men with BPH. The benefits of switching from dutasteride to tadalafil for LUTS may be limited in older men with LUTS/BPH.

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status and prolidase activities in men with erectile dysfunction. *Clinics (Sao Paulo)*. 2010; **65**: 1311-4.

Figure legends

Fig. 1. Primary and secondary outcomes from baseline to 12 weeks

Twelve weeks after the withdrawal of dutasteride, IPSS was not significantly different between the Ctrl and TAD groups (**A**, $P = 0.827$). The median change of IPSS was not significantly different between the Ctrl and TAD groups (**B**, $P = 0.283$). No significant difference was observed in IIEF-EF score between the groups (**C**, $P = 0.795$). The change in International Index of Erectile Function-Erectile Function Domain (IIEF-EF) score did not reach statistical significance between the Ctrl and TAD groups (**D**, $P = 0.051$). In the patient preference questionnaire, 80% of patients in the Ctrl group and 50% of patients in the TAD group responded “neither satisfied nor dissatisfied” in this study. Only 20% of patients in the TAD group responded “posttherapy (tadalafil) better,” whereas 30% of patients in the TAD group responded “dutasteride better.” (**E**)

Fig. S1. Secondary outcome measures of parameter changes from baseline to 12 weeks

The IPSS voiding score (**A**, $P = 0.805$) and storage score (**B**, $P = 0.766$) were not significantly different between the Ctrl and TAD groups. No significant differences between the Ctrl and TAD groups were observed in prostate volume (**C**, $P = 0.177$), peak urinary flow rate (**D**, $P = 0.961$), residual urine volume (**E**, $P = 0.168$), mean BP (**F**, $P = 0.830$), testosterone concentration (**G**, $P = 0.223$), and 8-OHdG (**H**, $P = 0.199$).

Table S1. Background of patients

There were no significant differences in the baseline between the Ctrl and TAD groups.

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	Ctrl group	TAD group	P value
n	34	34	
Age, years (IQR)	77 (68-80)	77 (71-79)	<i>0.328</i>
Diabetes mellitus, n	6 (18%)	7 (21%)	<i>0.758</i>
Hypertension, n	23 (68%)	18 (53%)	<i>0.215</i>
Prostate volume, mL (IQR)	34 (23-58)	34 (24-69)	<i>0.764</i>
PSA, ng/mL (IQR)	1.5 (0.6-3.5)	1.4 (0.6-3.6)	<i>0.992</i>
testosterone, ng/dL (IQR)	648 (482-840)	519 (382-683)	<i>0.152</i>
Uroflowmetry, mL/sec. (IQR)			
Maximum flow rate	9.7 (5.0-14)	8.6 (5.5-14)	<i>0.952</i>
Average flow rate	5.7 (3.5-8.7)	4.6 (3.0-7.0)	<i>0.266</i>
Residual volume (mL)	0.0 (0.0-38)	21 (0.0-93)	<i>0.054</i>
Blood pressure, mmHg (IQR)			
Systolic	146 (132-157)	141 (129-159)	<i>0.843</i>
Diastolic	79 (70-92)	82 (71-87)	<i>0.670</i>

IPSS (IQR)

Total	13 (9-19)	13 (10-21)	<i>0.739</i>
Voiding score	8 (5-11)	8 (5-13)	<i>0.797</i>
Storage score	6 (4-9)	6 (4-9)	<i>0.925</i>
Alpha-1-adrenoceptor blocker	21 (62%)	23 (68%)	<i>0.478</i>
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IIEF-EF Domain score (IQR)	7 (5-12)	5 (5-8)	<i>0.160</i>
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IQR: interquartile range, IIEF-EF: International Index of Erectile Function-Erectile Function Domain