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Natural course of lower urinary tract symptoms following discontinuation of alpha-1-adrenergic blockers in patients with benign prostatic hyperplasia

Teruhiko Yokoyama* Toyohiko Watanabe† Takashi Saika‡
Yasutomo Nasu** Hiromi Kumon††
Yoshiyuki Miyaji‡‡ Atsushi Nagai§

*Department of Urology, Kawasaki Medical School, uroyoko@med.kawasaki-m.ac.jp
†Okayama University
‡Okayama University
**Okayama University
††Okayama University
‡‡Department of Urology, Kawasaki Medical School
§Department of Urology, Kawasaki Medical School

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TERUHIKO YOKOYAMA,[1] TOYOHIKO WATANABE,[2] TAKASHI SAIKA,[2] YASUTOMO NASU,[2] HIROMI KUMON,[2] YOSHIYUKI MIYAJI,[1] AND ATSUSHI NAGAI[1]

[1]*Department of Urology, Kawasaki Medical School, Kurashiki, Japan and* [2]*Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan*

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Correspondence:

Teruhiko Yokoyama. Department of Urology
Kawasaki Medical School
577 Matsushima Kurashiki, Okayama, Japan
Phone:+81(86)462-1111
Fax :+81(86)462-7879
E-mail address: uroyoko@med.kawasaki-m.ac.jp

Abstract

***Aim*:** Alpha 1-adrenergic blocker (α b) remains the first line therapy in men with lower urinary tract symptoms (LUTS). ~~The current literature advocates continued use of α b for their effect to be maintained.~~ However, some patients decide to discontinue use of the medication after their symptoms~~ are relieved and can keep good conditions~~. In this study, we investigated the natural course of LUTS after the discontinuation of successful treatment of α b.

***Patients and methods*:** Among 75 patients with LUTS who stopped α b medication once their symptoms improved, 60 patients (aged 50 to 87 years old, with a median of 70) who could be followed for at least 12 months after discontinuation of α b were ~~enrolled~~ analyzed in this study. Evaluations included a clinical determination of the International Prostate Symptom Score (IPSS), peak flow rate (Qmax), and post-void residual urine volume (PVR). Upon patient request or in cases of PVR more than 100ml, administration of α b was resumed.

***Results*:** Eighteen out of the 60 patients (30%) asked for re-treatment within 12 months after discontinuation (re-treatment group). Other 42 patents could maintain the good condition without medication (discontinuation group). IPSS was 15.9, 8.7, 10.1, 10.2, 9.7, 8.8, 9.0, on the first visit, just before discontinuation, and 1, 3, 6, 9 and 12 months

after stopping treatment among the discontinuation group, respectively. ~~Similarly, Qmax was 10.6, 14.8, 14.2, 14.3, 14.7, 13.2, 13.6 ml/sec., respectively.~~ Treatment periods, prostatic volume and peak flow rates just before discontinuation of medication differed significantly between the re-treatment and discontinuation group.

***Conclusions*:** In spite of the short follow-up periods, these results suggest that selected patients with relatively small prostatic volume and good flow rates after therapy can discontinue α b medication after their symptoms improve.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a major problem for many elderly men. An enlarged prostate associated with moderate to severe lower urinary tract symptoms (LUTS) and / or a decreased urine flow occurs in approximately 25% of men at 55 years old and this incidence increases linearly to 50% in men at 75 years old.[1,2] It has been widely accepted that α 1-adrenergic blockers are useful in the treatment of BPH because they reduce urethral resistance by relaxation of the prostate smooth muscle, acting on the dynamic component of obstruction.[3,4] The median probability for symptomatic improvement with α 1-adrenergic blocker therapy was found to be 74%.[5] The current literature advocates continued use of α 1-adrenergic blockers for their

effect to be maintained.[6] However, some patients decide to discontinue use of the medication after their symptoms are relieved. Verhamme et al. reported that a quarter of patients discontinued α1-adrenergic blockers very rapidly.[7] To our knowledge, the point at which to discontinue α 1-adrenergic blockers and the time for which sustained therapeutic efficacy remains after discontinuation have not yet been determined. In this study, we assessed the natural course of lower urinary tract symptoms (LUTS) suggestive of BPH following discontinuation of α 1-adrenergic blockers.

PATIENTS AND METHODS

This study was performed between October 2002 and June 2004. Seventy five men with LUTS who reported improvement in subjective symptoms and post-voided residual urine volume (PVR) lower than 50ml after α 1-adrenergic blockers treatment and wanting to discontinue medication were enrolled.

~~Inclusion criteria included post-voided residual urine volume (PVR) lower than 50ml and the patient wanting to discontinue medication after their symptoms were relieved.~~ Among the 75 patients with BPH who accepted to stop α 1- adrenergic blocker medication once their symptoms improved, 60 patients (aged 50 to 87 years old, with a median of 70) who could be followed for at least 12 months after discontinuation of the

medication were investigated in this study (Table 1). The medication period just before discontinuation ranged from 2 to 200 months (median 14 months). Treatment at the time of discontinuation consisted of 25 or 50 mg naftopidil daily in 32 patients, 0.2 mg tamsulosin in 21 patients and 30 mg urapidil two times daily in 7 patients. Estimation of prostatic volume was used transabdominal ultrasonography. The prostate was scanned in the transverse and sagittal directions with the patient in supine position. Prostate volume was determined using the following formula: width×length ×height×0.52. Patients who had an elevated serum PSA level were confirmed as BPH before the treatment by transrectal ultrasonography guided prostate sextant biopsies. Evaluations included clinical determination of the International Prostate Symptom Score (IPSS), peak flow rate (Qmax), and PVR measured before and 1, 3, 6, 9, and 12 months after treatment had ended. When patients wanted medication or PVR was more than 100ml, administration of α1-adrenergic blocker was resumed. All patients provide informed consent before joining the study.

All results are expressed as the mean ± SD. The Wilcoxon signed rank test was used to evaluate intra-group differences and the Mann-Whitney *U* test was used for inter-group comparisons. *P* values of less than 0.05 were considered significant.

RESULTS

Eighteen out of 60 patients (30%) reported worsening of symptoms after the discontinuation of treatment and they asked for treatment to be resumed: 10, 3, and 5 patients restarted medication within 1, 6, and 12 months after discontinuation, respectively (re-treatment group). *No patients were found to have PVR more than 100ml during the follow-up period in the re-treatment group. Other 42 out of 60 patents (70%) could maintain the good condition without medication (discontinuation group). IPSS was 15.9±6.8, 8.7±4.3, 10.1±6.1, 10.2±6.1, 9.7±5.6, 8.8±5.3, 9.0±5.4, on the first visit, just before discontinuation, and 1, 3, 6, 9 and 12 months after being stopped treatment respectively among the discontinuation group (Fig. 1). Similarly, Qmax was 10.6±4.5, 14.8±6.2, 14.2±6.3, 14.3±5.3, 14.7±7.7, 13.2±5.8, 13.6±5.0 ml/sec, respectively (Fig. 2). Symptom scores did not change significantly after use of the medication ceased during at least 12 months of follow-up. Qmax did not change significantly before the 6 month follow-up, but it was decreased 9 and 12 months after discontinuation. Treatment periods, prostatic volume, PSA and peak flow rates just before discontinuation of medication differed significantly between the re-treatment and discontinuation group: 51.2±13.7 versus 20.2±4.2 months (p=0.016), 32.3±2.8 versus 24.9±1.1 g (p=0.045), 3.55±0.7 versus 2.13±0.3 ng/ml (p=0.015) and 11.4±0.9 versus

16.4±1.0 ml/sec (p=0.007) (Table 2). However, other parameters including age, IPSS and QOL score (at first visit and just before discontinuation) did not differ between the two groups. Among the re-treatment group, each parameter was compared between the time just before discontinuation and the time when the patients wanted medication. Although the IPSS and QOL scores increased significantly, the parameter of uroflowmetry did not change even when the patients wanted to resume medication (Table 3). In this study, no patient with prostatic volume less than 25ml and Qmax at the time of discontinuation more than 15ml/s needed re-treatment at least during 12 months.

DISCCUSION

As pharmacotherapies for LUTS associated with BPH, α1-adrenergic blockers have seen wide use in recent years, thanks to the fast action and safety of these agents. They remain the first-line therapy for the majority of patients today. The total symptom score following medication is improved by 30 to 45% and maximum urinary flow rate by 15 to 30% versus baseline.[8] Alpha1-adrenergic blocker is considered to be a rather safe drug. However, there are some shortcomings. The primary adverse events reported with α1-adrenergic blocker therapy are orthostatic hypotension,

dizziness, tiredness (asthenia), ejaculatory problems, and nasal congestion. These are probably related to the blockade of α1-adrenoceptors in blood vessels, and can limit the usefulness of these agents for LUTS. In addition, 15-20% of patients do not show any improvement.[9,10] The withdrawal rate due to such adverse events or insufficient treatment efficacy ranges from 14% to 38%.[7,11,12] In other studies the discontinuation rate of α1-adrenergic blockers was 60% to 64% after 3 years of follow-up.[6,13] The reasons for discontinuation were adverse events, persistence of complaints, or resolved complaints. Moreover, a MTOPS study showed that α1-adrenergic blocker (doxazosin) delayed the time of acute urinary retention but did not reduce the overall risk, at least not among patients at high risk of progression.[14]

The BPH guideline currently available proposes a watchful waiting strategy for patients with mild or moderate symptoms.[15] Watchful waiting is to be recommended for patients with minimal symptoms or moderate/severe symptoms with little impairment of quality of life. Several studies have been conducted regarding the natural course of patients after discontinuation of α 1-adrenergic blocker once their symptoms improved.[16-18] Debruyne reported that LUTS did not return to baseline after withdrawal of terazosin.[16] Kobayashi et al. also reported 68.9% patients could keep good condition at 24 weeks after discontinuation of tamslosin.[19] On the other hand, Kaplan et al. and

Yanardag et al. suggested that complete cessation of α1-adrenergic blocker led to relapse of both symptoms and impairment of urinary flow within 3 months.[17,18] Kaplan et al. presumed that a 3-month dosing regimen might have been insufficient to obtain a longer effect in their paper.[17] In our study, the medication period was 20.2 months among the discontinuation group. However, that of the re-treatment group was longer (51.2 months). The patients with a long-term medication period requested re-treatment significantly more frequently after discontinuation. Even in the re-treatment group, the objective parameters including uroflowmetry did not change at the time they wanted to resume medications. One of the reasons for requesting re-treatment might be anxiety about ~~discontinuation~~ stopping treatment after longer period medication.

The patients in our study had relatively mild symptom and responded well to α1-adrenergic blocker. Moreover, patients who did not want to discontinue were not entered in the study. There is thus a possibility of patient selection bias. We also stopped medication during some restricted periods. So the range of medication periods was very wide. These observations warrant further investigation. Even so, 70% of patients maintained their condition without medication during at least one year follow-up. Especially, all patients with prostatic volume less than 25ml and Qmax at the time of discontinuation more than 15ml/s could keep the good condition at least

during 12 months after stopping medication. We believe that these results represent useful information for patients who want to discontinue after their symptoms improve.

In conclusion, these results suggest that selected patients with relatively small prostatic volume and good flow rates with therapy can discontinue α1-adrenergic blocker medication after their symptoms improve.

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Figure Legends

Table 1: Background of the 60 patients enrolled in the study

Table 2: Comparison between re-treatment and discontinuation group
Asterisks, $p<0.05$

Table 3: Change of parameters in re-treatment group
Asterisks, $p<0.05$

Figure 1: Changes in mean IPSS in discontinuation group
Asterisks, $p<0.05$

Figure 2: Changes in mean Qmax in discontinuation group