Evaluation of Alpha 1 Adrenoceptor Antagonist Dose Increase Therapy: An Essential Strategy for Patients with Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia

Masaki Watanabe\textsuperscript{a} Satoshi Yamaguchi\textsuperscript{b} Hidehiro Kakizaki\textsuperscript{c} Naoki Hirabayashi\textsuperscript{d} Hironori Ishida\textsuperscript{b}

\textsuperscript{a}Department of Urology, Hokkaido Social Welfare Association Furano Hospital, Furano; \textsuperscript{b}Department of Urology, Kitasaito Hospital; \textsuperscript{c}Department of Renal and Urologic Surgery, Asahikawa Medical University, Asahikawa; \textsuperscript{d}Medical Affairs Department, Asahi Kasei Pharma Corporation, Tokyo, Japan

Key Words
Lower urinary tract symptoms • Dose increase therapy • Benign prostatic hyperplasia • Naftopidil • Tamsulosin • Alpha 1 adrenoceptor antagonist

Abstract

Introduction: There have been a number of reports on dose increase therapy (DI-T) with the alpha 1 adrenoceptor antagonists (α1-blockers) naftopidil and tamsulosin for lower urinary tract symptoms associated with benign prostatic hyperplasia. Methods and Results: The reports on DI-T (naftopidil 75 mg/d, tamsulosin 0.4 mg/d) in non-responders to low-dose initial therapy (LI-T, naftopidil 50 mg/d, tamsulosin 0.2 mg/d) were summarized. In each study, a non-responder was defined as a patient without sufficient improvements on the International Prostate Symptom Score (IPSS), IPSS Quality of Life, maximum flow rate of urine, or treatment satisfaction. These reports showed that 22.4–76.1% of patients were non-responders to LI-T, indicating that a novel treatment strategy for such patients is important. Moreover, 22.5–90.0% of non-responders to LI-T showed a response to DI-T, which achieved the same level of efficacy as low-dose maintenance therapy. Specifically, the improvements of the IPSS voiding symptom sub-score and maximum flow rate of urine were superior. The predictive factors for non-response to α1-blockers LI-T were insufficient improvement of subjective symptoms and objective findings during LI-T. These patients require high-dose initial therapy or DI-T at an early stage, since adverse events associated with naftopidil and tamsulosin do not show a dose-response relationship. Conclusions: DI-T with α1-blockers has high potential as an essential treatment strategy for lower urinary tract symptoms associated with benign prostatic hyperplasia.

Introduction

Lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH) are progressive and common in elderly men [1]. Alpha 1 adrenoceptor antagonists (α1-blockers) are among the first-line drugs for the treatment of LUTS/BPH [2–5]. In Western countries, α1-blockers in common use are the uro-selective drugs, tamsulosin and silodosin [5–7]. Naftopidil is a uro-selective α1-blocker launched in 1999 in Japan, which is widely used for LUTS/BPH treatment.
in Japan, Korea, China, and India. The dosage of naftopidil is 25–75 mg/d, with the optimal dose being 50 or 75 mg/d [8–10]. Naftopidil has a 3-fold higher affinity for the α1D adrenoceptor subtype than for the α1A adrenoceptor subtype. In contrast, tamsulosin has a high affinity for the α1A adrenoceptor subtype [11]. There are reports that the α1D adrenoceptor subtype contributes to bladder function [12, 13]. Naftopidil has been reported to be effective for storage symptoms through inhibition of the α1D adrenoceptor subtype in the bladder [14, 15].

There are many reports that α1-blockers do not improve symptoms in some patients. Switch therapy to another α1-blocker or additional therapy with drugs that have other mechanisms of action have been reported for non-responders to α1-blockers [16–20]. However, polypharmacy is a problem with additional therapy because LUTS/BPH is a disease of elderly persons [21].

There have been several reports on the efficacy of α1-blocker dose increase therapy (DI-T) [22–29]. In naftopidil DI-T, the dose was increased to 75 mg/d in non-responders to naftopidil 50 mg/d low-dose initial therapy (LI-T), because of the wide dosage range of naftopidil [10, 22–26]. A dosage of 0.2 mg/d tamsulosin is commonly used in Japan and Korea, but the most common dosage in Western countries is 0.4 or 0.8 mg/d [30]. In non-responders to tamsulosin 0.2 mg/d LI-T, there have been a few reports that the dosage was increased from 0.2 to 0.4 mg/d as tamsulosin DI-T in Korea [27–29].

These reports on naftopidil and tamsulosin DI-T, including our report, were summarized, and this review shows the re-analysis of our data for the new clinical questions related to DI-T.

**Purpose and Definition of Efficacy in These Studies**

A prospective study of DI-T was first performed by Yoshida et al. [22]. Naftopidil 50 mg/d as LI-T was administered for 4 weeks in 45 patients. For a further 4 weeks, the dose was increased to 75 mg/d as DI-T for non-responders, defined as patients with an improvement of less than 1 point in the International Prostate Symptom Score (IPSS) Quality of Life (IPSS-QoL) at weeks 4 and 8.
Table 2. Response rates to LI-T, LM-T, and DI-T

| Author            | Drug     | Response rate to LI-T | Rate (%) | Response rate to LM-T or DI-T | Rate (%) |
|-------------------|----------|-----------------------|----------|-----------------------------|----------|
|                   |          |                       |          | Therapy                     |          |
|                   |          |                       |          |                             |          |
| Yoshida et al. [22]| naftopidil |                     |          |                             |          |
|                   |          | responders             | 66.7% (20/30) | –                          | –        |
|                   |          | non-responders        | 33.3% (10/30) |                             |          |
| Funahashi et al. [23]| naftopidil |                     |          |                             |          |
|                   |          | responders             | 52.5% (64/122) | DI-T                       | responders |
|                   |          | non-responders        | 47.5% (58/122) | non-responders             | –        |
| Mizusawa et al. [24]| naftopidil |                     |          |                             |          |
|                   |          | responders             | 23.9% (11/46) | DI-T                       | responders |
|                   |          | non-responders        | 76.1% (35/46) | non-responders             | –        |
| Tanuma et al. [25]| naftopidil |                     |          |                             |          |
|                   |          | responders             | 55.4% (46/83) | DI-T                       | responders |
|                   |          | non-responders        | 44.6% (37/83) | non-responders             | –        |
| Yamaguchi et al. [26]| naftopidil |                     |          |                             |          |
| and re-analyzed data |          | responders             | 68.6% (59/86) | LM-T                       | responders |
|                   |          | non-responders        | 31.4% (27/86) | non-responders             | –        |
| Chung et al. [27]| tamsulosin |                     |          |                             |          |
|                   |          | responders             | 77.6% (90/116) | LM-T                       |             |
|                   |          | non-responders        | 22.4% (26/116) | DI-T                       |             |
| Kim et al. [28]| tamsulosin |                     |          |                             |          |
|                   |          | responders             | 61.3% (95/155) | LM-T                       |             |
|                   |          | non-responders        | 38.7% (60/155) | DI-T                       |             |
| Park et al. [29]| tamsulosin |                     |          |                             |          |
|                   |          | responders             | 31.2% (29/93) | DI-T                       | responders |
|                   |          | non-responders        | 68.8% (64/93) | non-responders             | –        |

To evaluate the efficacy of naftopidil DI-T in non-responders to LI-T, Funahashi et al. [23] gave naftopidil 50 mg/d as LI-T for 12 weeks to 122 patients. The dose was increased to 75 mg/d as DI-T for non-responders to LI-T for a further 12 weeks. Non-responders were defined as patients with an improvement of less than 5 points in IPSS at weeks 12 and 24.

Mizusawa et al. [24] compared the efficacy of naftopidil DI-T for non-responders to LI-T with naftopidil low-dose maintenance therapy (LM-T) that was maintained at 50 mg/d for responders to LI-T [24]. Naftopidil LI-T was used for 4 weeks. The non-responders and responders to LI-T were treated with DI-T and LM-T for a further 4 weeks, respectively. Non-responders were defined as patients who were not satisfied with their urinary status at week 4.

The predictors of the efficacy of naftopidil DI-T were evaluated in the INFORM study [25]. There were 92 patients who were treated with naftopidil LI-T for 4 weeks. All patients were increased to 75 mg/d for a further 4 weeks. Non-responders were defined after 4 and 8 weeks based on the criteria in the Japanese Urological Association Clinical Guidelines for BPH [3].

Naftopidil LI-T was given for 8 weeks to 95 patients to evaluate the efficacy of naftopidil DI-T [26]. The non-responders and responders to naftopidil LI-T were treated with DI-T and LM-T, respectively, for a further 8 weeks. Non-responders were defined as patients with IPSS-QoL scores ≥ 4 at week 8, or patients whose improvement of the IPSS-QoL from baseline to week 8 was < 2.

In 133 patients, Chung et al. [27] administered tamsulosin 0.2 mg/d as LI-T for 8 weeks to compare the efficacies of tamsulosin LM-T and DI-T. Tamsulosin 0.4 mg/d as DI-T and 0.2 mg/d as LM-T were given to the non-responders and responders to LI-T, respectively, for a further 8 weeks. Non-responders to LI-T were defined as patients with changes in the IPSS total score < 20% and in the maximum flow rate of urine (Qmax) < 20%, aggravation of the IPSS-QoL score, or development of clinically significant complications at week 8.

With 174 patients, Kim et al. [28] conducted a similar study comparing tamsulosin DI-T in the non-responders and LM-T in the responders to LI-T. Tamsulosin LI-T was administered for 12 weeks, and DI-T in the non-responders and LM-T in the responders to LI-T were given.

[–]: The response rate was not evaluated.

*Chi-squared test: p = 0.409; **4/64 non-responders lost to follow-up.
for a further 26 weeks. Non-responders were defined as patients who desired DI-T or needed DI-T based on an objective assessment at week 12.

Park et al. [29] administered tamsulosin LI-T to 120 patients for 8 weeks to evaluate the efficacy of tamsulosin DI-T. In non-responders to LI-T, DI-T was administered for a further 8 weeks. Non-responders were defined as patients with improvement in the IPSS total score < 3 at weeks 8 and 16. These studies are shown in table 1.

It is a problem that each of the reports on DI-T differed in the definition of the response and the treatment period. Thus, it is necessary to standardize the criteria of the evaluation method and the period in LUTS/BPH therapy.

Response Rate

In 30 patients who could be evaluated, Yoshida et al. [22] reported that 33.3% were non-responders to naftopidil LI-T, and the response rate to DI-T was 90.0%. Funahashi et al. [23] reported that 58/122 patients (47.5%) were non-responders to naftopidil LI-T, and 9/40 patients (22.5%) available for evaluation showed improvement with naftopidil DI-T. Tanuma et al. [25] showed that 37/83 patients (44.6%) who could be evaluated were non-responders to naftopidil LI-T, and DI-T was effective in 17 (45.9%) of the non-responders.

Because there are few reports on the number of responders to DI-T, we re-analyzed the data from our previous paper on naftopidil DI-T [26]. It was found that naftopidil LM-T was given to 59/86 responders to LI-T who could be evaluated for naftopidil LI-T, and 52 patients (88.1%) were improved. On the other hand, there were 27 (31.4%) non-responders to naftopidil LI-T, and 22 patients (81.5%) were improved with DI-T. The response rate showed no significant difference between DI-T in the non-responding group and LM-T in the responder group (p = 0.409, unpublished data).

Park et al. [29] reported that non-response to tamsulosin LI-T was seen in 64/93 patients (68.8%), and 31/60 patients (51.7%) who could be evaluated were improved with DI-T. Mizusawa et al. [24], Chung et al. [27], and Kim et al. [28] reported that the percentages of non-responders to naftopidil or tamsulosin LI-T were 76.1, 22.4, and 38.7%, respectively. However, the response rate to DI-T was not evaluated. These studies are shown in table 2.

Thus 22.5–90.0% of non-responders to LI-T could benefit from DI-T, though the individual study designs showed a different result. DI-T was concluded to be a useful and important treatment strategy for non-responders, since it achieved approximately the same response rate as LM-T. Conversely, the response rate to LI-T was 23.9–77.6%. It is important that α1-blockers should be started with LI-T to establish an effective dose that is as low as possible for safety reasons and to avoid unnecessary overdosage, because LI-T improves many patients.

**Subjective and Objective Efficacy of DI-T**

At the end of naftopidil LI-T (week 4), Mizusawa et al. [24] reported a significantly improved IPSS total score (IPSS-TS) and IPSS voiding symptom (IPSS-VS) sub-score in the LM-T group compared with the DI-T group (p = 0.041, p = 0.016, respectively). However, similar levels of improvement were seen in the 2 groups at the study endpoint (week 8).

The INFORM study showed that the changes in IPSS-TS, IPSS-VS, and IPSS storage symptoms (IPSS-SS) at the study endpoint (week 8) were significantly improved in responders to naftopidil LI-T compared with non-responders (p < 0.001, p = 0.001, p < 0.001, respectively). This suggested that DI-T was more effective in responders to LI-T. The change in Qmax of responders to LI-T was significantly improved in comparison to non-responders at the end of LI-T (week 4, p < 0.001). However, the change in Qmax showed no significant difference between the groups at the study endpoint (week 8). Naftopidil DI-T was effective for objective findings in the non-responders to LI-T [25].

At the end of naftopidil LI-T (week 8), we reported that changes in IPSS-TS, IPSS-VS and IPSS-SS were significantly improved in the LM-T group compared to the DI-T group (p = 0.004, p = 0.013, p = 0.038, respectively). However, these showed similar efficacy in the 2 groups at the study endpoint (week 16). Change in Qmax was significantly improved at the study endpoint (week 16) compared with the end of LI-T (week 8) in the DI-T group (p = 0.015). In contrast, it was significantly increased between the baseline and the end of LI-T (week 8, p < 0.01), but not significantly improved between the end of LI-T (week 8) and the study endpoint (week 16) in the LM-T group [26].

At the end of tamsulosin LI-T (week 8), Chung et al. [27] reported significantly improved IPSS-TS and Qmax in the LM-T group compared with the DI-T group (p < 0.001, p < 0.001 respectively). However, both groups showed similar levels of improvement at the study endpoint (week 16).
Table 3. Changes in IPSS and Qmax

| Author          | Drug    | Group           | IPSS-TS               | Qmax               | Baseline | End of LI-T | Endpoint | Intragroup* |
|-----------------|---------|-----------------|-----------------------|--------------------|----------|-------------|----------|-------------|
| Mizusawa et al. | naftopidil | LM-T (n = 11)  | 14.2 ± 5.1 (0.01)     | NS                 | 7.6 ± 3.0 | 7.4 ± 4.5   | NS       | -           |
|                 |         | DI-T (n = 35)  | 18.1 ± 7.2 (0.041)    | NS                 | 12.4 ± 7.3 | 10.3 ± 7.3  | 0.019    | -           |
|                 |         | intragroup      | NS                    | NS                 | NS       | NS          | NS       | -           |
| Tanuma et al.   | naftopidil | responders at week 4 (n = 46) | 0 ± 80.0 ± 5.5 | 0.040             | NS       | 9.0 ± 6.4   | NS       | -           |
|                 |         | non-responders at week 4 (n = 37) | 0 ± 0.3 ± 5.5 | -2.4 ± 6.1       | 0.023    | NS          | NS       | -           |
| Yamaguchi et al. | naftopidil | LM-T (n = 89)  | 0 ± 9.6 ± 4.7 (0.001) | NS                 | 0 ± 10.0 ± 5.3 | 0 ± 10.0 ± 3.9 | 0.001 | NS          |
|                 |         | (n = 59)        | (n = 59)             | NS                 | (n = 59) | (n = 27)    | NS       | -           |
| Chung et al.    | tamsulosin | LM-T (n = 90)  | 23.8 ± 7.0 ± 0.004   | NS                 | 17.1 ± 3.7 | 16.8 ± 4.5  | NS       | -           |
|                 |         | (n = 27)        | (n = 27)             | NS                 | (n = 27) | NS          | NS       | -           |
| Kim et al.      | tamsulosin | LM-T (n = 95)  | 18.3 ± 7.6 ± 0.004   | NS                 | 13.3 ± 6.6 | 10.3 ± 5.0  | NS       | -           |
|                 |         | (n = 60)        | (n = 60)             | NS                 | (n = 60) | (n = 27)    | NS       | -           |

*End of LI-T versus end point; NS = not significant; <: no evaluation.

The amount of change in Qmax was significantly increased between before and after LI-T in the LM-T group (p < 0.01); **the amount of change in Qmax was significantly increased in the DI-T group compared to the LM-T group (p = 0.01).

Table 4. Changes in IPSS-VS and IPSS-SS

| Author          | Drug    | Group           | IPSS-SS               | IPSS-TS              | Baseline | End of LI-T | Endpoint | Intragroup* |
|-----------------|---------|-----------------|-----------------------|----------------------|----------|-------------|----------|-------------|
| Mizusawa et al. | naftopidil | LM-T (n = 11)  | 5.0 ± 3.5             | 0.016                | 2.1 ± 1.4 | 4.2 ± 4.1   | NS       | -           |
|                 |         | DI-T (n = 35)  | 7.9 ± 4.3             | NS                   | 5.3 ± 4.1 | 2.3 ± 1.9   | 0.047    | -           |
|                 |         | intragroup      | NS                    | NS                   | NS       | NS          | NS       | -           |
| Tanuma et al.   | naftopidil | responders at week 4 (n = 46) | 0 ± 5.2 ± 4.3 | -4.2 ± 4.4       | NS       | -3.5 ± 4.2  | NS       | -           |
|                 |         | non-responders at week 4 (n = 37) | 0 ± 0.6 ± 3.8 | -0.8 ± 3.6      | 0.017    | NS          | NS       | -           |
| Yamaguchi et al. | naftopidil | LM-T (n = 59)  | 0 ± -4.9 ± 2.9         | NS                   | -3.5 ± 3.2 | -5.3 ± 3.2  | NS       | -           |
|                 |         | (n = 27)        | (n = 27)             | NS                   | (n = 27) | (n = 27)    | NS       | -           |
| Kim et al.      | tamsulosin | LM-T (n = 95)  | 8.8 ± 4.8             | NS                   | 6.1 ± 3.9 | 5.0 ± 3.2   | NS       | -           |
|                 |         | (n = 60)        | (n = 60)             | NS                   | (n = 60) | (n = 27)    | NS       | -           |

*End of LI-T versus end point; NS = not significant; <: no evaluation.

In the tamsulosin LM-T group, Kim et al. [28] reported significant improvement of the change in IPSS-TS compared with the DI-T group at the study endpoint (week 24, p < 0.01). In addition, tamsulosin DI-T caused a greater change in IPSS-VS, and this led to a greater change in IPSS-TS for patients receiving tamsulosin 0.4...
mg/d. However, these levels at the baseline were significantly different between the groups. The evaluation of DI-T by subjective symptoms is difficult. The changes of subjective symptoms and objective findings are shown in table 3, 4.

DI-T was thus improved to a similar level in comparison with LM-T in responders to LI-T, with particularly high rates of improvement suggested in IPSS-VS and Qmax. In Japan, however, it is necessary to be careful about the normal approved dosage of naftopidil, which is initially 25 mg/d, and the normal approved dosage of tamsulosin, which is 0.2 mg/d.

Adverse Events

The adverse event incidence rate of naftopidil was reported to be 8.9% (4/45) in patients given 75 mg/d by Yoshida et al. [22], 0.6% (1/181) and 6.9% (4/58) in patients given 50 and 75 mg/d, respectively, by Funahashi et al. [23], 9.4% (5/53) and 5.4% (2/37), respectively, by Mizusawa et al. [24], and only 1.1% (1 patient) at 50 mg/d in our study [26].

Adverse events with tamsulosin were reported in 11.1% (10/90) and 19.2% (5/26) of patients given 0.2 and 0.4 mg/d, respectively, by Chung et al. [27], and 21.6% (13/60) in patients given 0.4 mg/d by Park et al. [29].

In one report, the adverse event incidence rate in 286 patients given 25 to 75 mg/d of naftopidil did not differ with the dosage [10]. Adverse events resulting in withdrawal of tamsulosin 0.2 mg/d were reported in 5.7% (11/192) and 1.0% (1/103) by Kawabe et al. [32] and Lee et al. [33], respectively. In a study that compared 0.4 with 0.8 mg/d of tamsulosin via an oral controlled absorption system, adverse events resulting in withdrawal were reported in 3.9% (14/360) and 3.9% (28/722), respectively, by Chapple et al. [34]. Adverse events associated with naftopidil or tamsulosin showed no dose-response relationship in these reports. DI-T should therefore be actively considered for non-responders to LI-T.

An anti-muscarinic is often added for the α1-blocker non-responders who have BPH with an overactive bladder. The most common side-effect of anti-muscarinics is xerostomia, and increased postvoid residual urine may be seen [2–4, 35]. The additional anti-muscarinic therapy has the possibility of increasing the risk of adverse events such as xerostomia and increased postvoid residual urine. Furthermore, taking multiple medications is related to not only an increased risk of side effects, but also greater health care costs, as well as increased risks of drug-interactions, medication non-adherence, reduced functional capacity, and multiple geriatric syndromes. In the examination of patients who took one or more drugs for chronic diseases for 3 months and were 65 years or older, 54.7% of patients took 5 or more different medicines, and 45.0% took 12 or more [36]. Such polypharmacy is a serious problem for LUTS/BPH patients, many of whom are elderly. For example, if switching from naftopidil 50 to 75 mg or tamsulosin 0.2 to 0.4 mg is possible, the risk of polypharmacy decreases compared to that with additional therapy.

Discussion

Yoshida et al. [22] reported that the differences in patient characteristics between responders and non-responders to naftopidil LI-T were unknown, because no significant difference in each IPSS sub-score was seen at the baseline between the 2 groups. However, respond-

### Table 5. PV at the baseline of responders and non-responders to LI-T

| Author         | Drug    | PV at the baseline, ml | Intergroup |
|----------------|---------|------------------------|------------|
|                |         | Responders             | Non-responders |           |
| Yoshida et al. [22] | naftopidil | 35.2 ± 16.7 (n = 20) | 33.4 ± 8.9 (n = 10) | NS         |
| Mizusawa et al. [24] | naftopidil | 25.0 ± 24.8 (n = 35) | 34.6 ± 24.9 (n = 11) | NS         |
| Tanuma et al. [25] | naftopidil | 38.4 ± 24.3 (n = 44) | 43.9 ± 24.6 (n = 37) | NS         |
| Yamaguchi et al. [26] | naftopidil | 26.9 ± 10.4 (n = 56) | 36.7 ± 14.5 (n = 26) | < 0.01     |
| Chung et al. [27] | tamsulosin | 27.1 ± 7.1 (n = 90) | 28.1 ± 4.4 (n = 26) | NS         |
| Kim et al. [28]  | tamsulosin | 30.6 ± 12.0 (n = 95) | 32.8 ± 11.9 (n = 60) | NS         |

NS = Not significant.
ers showed improvements of changes in IPSS-TS and IPSS-QoL during LI-T, whereas non-responders did not. In contrast, Kim et al. [28] showed that the predictors of non-response to tamsulosin LI-T were higher age, lower Qmax, and a higher IPSS frequency sub-score at the baseline. Mizusawa et al. [24] reported that a higher IPSS-VS at the baseline and less improvement in IPSS-QoL and nocturia during naftopidil LI-T were characteristic of non-responders to LI-T. In non-responders to naftopidil LI-T, the INFORM study showed that patients for whom DI-T was effective showed improvement of Qmax during LI-T [25]. Chung et al. [27] showed that IPSS-TS, IPSS-QoL, and Qmax at the baseline were not significantly different between responders and non-responders to tamsulosin LI-T. In responders to LI-T, however, changes in them during LI-T showed significant improvements in comparison with non-responders to LI-T. Thus, the appropriate use of DI-T should be considered based on changes in subjective symptoms and objective findings during LI-T.

Prostate volume (PV) does not affect α1-blockers efficacy in studies with follow-up periods < 1 year, but α1-blockers do seem to be more efficacious in patients with smaller prostates (< 40 ml) in longer-term studies [2]. In a systematic review, Malde et al. [31] showed that PV had low diagnostic accuracy for bladder outlet obstruction in men with LUTS. Also, we reported that PV at the baseline was significantly greater in non-responders than in responders to naftopidil LI-T (p < 0.01) [26]. Mizusawa et al. [24], Tanuma et al. [25], and Kim et al. [28] reported a similar result, but without a significant difference (table 5). Accordingly, we re-analyzed our previously reported data using receiver operating characteristic curve analysis and found the cut-off level for PV to be 29.7 ml (table 6, unpublished data). We probably need to recognize beforehand that patients with an enlarged PV are more likely to receive DI-T, and thus α1-blockers DI-T might be considered for patients with an enlarged PV in addition to combination therapy of α1-blockers and 5α-reductase inhibitors.

### Table 6. Cut-off level of PV

| Cut-off level of PV | Sensitivity | 1−Specificity (Specificity) | AUC       | p       |
|--------------------|-------------|-----------------------------|-----------|---------|
| 29.7ml             | 76.0%       | 37.5% (62.5%)               | 0.714     | 0.002   |

AUC = Area under the curve.

### Conclusion

In this paper, the efficacy and safety of α1-blockers DI-T were summarized, and new questions relating to DI-T were discussed based on a re-analysis of previous data.

1) Non-responders to LI-T were found to represent 31.4–53.3% of patients, and 22.5–90.0% of non-responders to LI-T showed a response to DI-T, which achieved the same level of efficacy as LM-T. DI-T is a good treatment strategy for non-responders to LI-T.

2) The predictors for non-responders to LI-T were insufficient improvements in subjective symptoms and objective findings during LI-T use. These patients need DI-T at an early stage.

3) Patients with an enlarged PV are probably the target for α1-blockers DI-T.

4) The adverse events associated with naftopidil and tamsulosin showed no dose-response relationship.

5) DI-T might decrease the risk of polypharmacy.

It was therefore concluded that DI-T has potential as an essential treatment strategy for LUTS/BPH.
References

1. Boyle P, Robertson C, Mazzetta C, Keech M, Hobbs FD, Fourcade R, Kiemeney L, Lee C: The prevalence of LUTS in men and women in four centres. The UrEpik study. BJU Int 2003;92:409–414.

2. Gravas S, Cornu IN, Drake MJ, Gacci M, Gratzke C, Herrmann TRW, Madersbacher S, Mamoulikis C, Tikkinen KAO, Kara-vitakis M, Kyrizias I, Malde S, Sakaklis V, Umbach B: EU guidelines on management of non-neurogenic male lower urinary tract symptoms (LUTS), incl. benign prostatic obstruction (BPO). European Association of Urology, 2018. https://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/

3. Homma Y, Gotoh M, Kawauchi A, Kojima Y, Masumori N, Nagai A, Saitoh T, Sakai H, Takahashi S, Ukimura O, Yamanishi T, Yokoyama O, Yoshida M, Maeda K: Clinical guidelines for male lower urinary tract symptoms and benign prostatic hyperplasia. Int J Urol 2017;24:716–729.

4. McVary KT, Roehrborn CG, Avisin AL, Barry MJ, Bruskewitz RC, Donnell RF, Foster HE Jr, Gonzalez CM, Kaplan SA, Penson DF, Ulicker JC, Wei JT: Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol 2011;185:1793–1803.

5. Fusco F, Palmieri A, Ficarra V, Giammarini G, Novara G, Longo N, Verze P, Creta M, Mirone V: α1-blockers improve benign prostatic obstruction in men with lower urinary tract symptoms: a systematic review and meta-analysis of urodynamical studies. Eur Urol 2016;69:1091–1101.

6. Montorsi F, Gandaglia G, Chapple C, Cruz F, Desgrandchamps F, Llorcete C: Effectiveness and safety of silodosin in the treatment of lower urinary tract symptoms in patients with benign prostatic hyperplasia: A European phase IV clinical study (SIRE study). Int J Urol 2016;23:572–579.

7. Ding H, Du W, Hou ZZ, Wang HZ, Wang ZP: Silodosin is effective for treatment of LUTS in men with BPH: a systematic review. Asian J Androl 2015;15:121–128.

8. Fukuta F, Masumori N: A review of naftopidi for treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Curr Bladder Dysfunct Rep 2015;10:160–169.

9. Masumori N: Naftopidil for the treatment of urinary symptoms in patients with benign prostatic hyperplasia. Ther Clin Risk Manag 2011;7:227–238.

10. Ishizuka O, Nishizawa O, Takeda M, Nomura T, Kagawa S: Early efficacy of an α1-adrenoceptor antagonist, naftopidil, against lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Lower Urin Tract Symptoms 2011;1:79–85.

11. Takei R, Ikagi K, Shibata K, Tsujimoto G, Asano T: Naftopidil, a novel α1-adrenoceptor antagonist, displays selective inhibition of canine prostatic pressure and high affinity binding to cloned human α1-adrenoceptors. Jpn J Pharmacol 1999;79:447–454.

12. Chen Q, Takahashi S, Zhong S, Hosoda C, Zheng HY, Ogushi T, Fujimura T, Ohha N, Tanoue A, Tsujimoto G, Kitamura T: Function of the lower urinary tract in mice lacking α1d-adrenoceptor. J Urol 2005;174:370–374.

13. Kurizaki Y, Ishizuka O, Namamura T, Ichino M, Ogawa T, Igawa Y, Nishizawa O, Andersson KE: Relation between expression of α1d-adrenoceptor mRNAs in bladder mucosa and urodynamical findings in men with lower urinary tract symptoms. Scand J Urol Nephrol 2011;45:15–19.

14. Nishino Y, Masue T, Miwa K, Takahashi Y, Ishihara S, Deguchi T: Comparison of two α1d-adrenoceptor antagonists, naftopidil and tamsulosin hydrochloride, in the treatment of lower urinary tract symptoms with benign prostatic hyperplasia: a randomized crossover study. BJU Int 2006;97:747–751.

15. Takahashi S, Tajima A, Matsushima H, Kawamura T, Tominaiga T, Kitamura T: Clinical efficacy of an α1a/α1d-adrenoceptor blocker (naftopidil) on overactive bladder symptoms in patients with benign prostatic hyperplasia. Int J Urol 2006;13:15–20.

16. Kojima Y, Sasaki S, Kubota Y, Hayase M, Hayashi Y, Shinoura H, Tsujimoto G, Kohri K: Expression of α1d-adrenoceptor subtype mRNA as a predictor of the efficacy of subtype selective α1d-adrenoceptor antagonists in the management of benign prostatic hyperplasia. J Urol 2008;179:1040–1046.

17. Ikemoto I, Kiyota H, Ohishi Y, Abe K, Goto H, Kishimoto K, Miki K: Usefulness of tamsulosin hydrochloride and naftopidil in patients with urinary disturbance caused by benign prostatic hyperplasia: a comparative, randomized, two-drug crossover study. Int J Urol 2003;10:587–594.

18. Lee KC, Kim JK, Cho SY, Jeon JS, Cho IR: Comparison of different α1-blocker combinations in male hypertensives with refractory lower urinary tract symptoms. Korean J Androl 2011;29:242–250.

19. Nishizawa O, Yamaguchi O, Takeda M, Yokoyama O: Randomized controlled trial to treat benign prostatic hyperplasia with overactive bladder using an α1-blocker combined with anticholinergics. Low Urin Tract Symptoms 2011;29:39–35.

20. Wada N, Kita M, Hashizume K, Matsumoto S, Kakizaki H: Urodynamic effects of dutasteride add-on therapy to α1-adrenergic antagonist for patients with benign prostatic enlargement: prospective pressure-flow study. Neurourology Urodyn 2013;32:1123–1127.

21. Maher RL, Hanlon J, Hajjar ER: Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf 2014;13:57–65.

22. Yoshida M, Miyamoto Y, Habu T, Kadoh J, Inadome A, Ishimatsu T, Fujisawa S, Otsuka Y, Nojiri A, Nabeura Y, Nakamura T, Mae-hara A: The therapeutic efficacy of naftopidil in patients with benign prostatic hyperplasia using a questionnaire for bothersomeness. Jpn J Urol Surg 2010;23:557–565.

23. Funahashi H, Hattori R, Matsuoka Y, Komatsu T, Sassa N, Gotoh M: Clinical efficacy of a loading dose of naftopidil for patients with benign prostatic hyperplasia. World J Urol 2011;29:225–231.

24. Mizusawa T, Hara N, Obara K, Isahaya E, Nakagawa Y, Takahashi K: Clinical feature of men who benefit from dose escalation of naftopidil for lower urinary tract symptoms: a prospective study. Adv Urol 2011:2011: 804583.

25. Tanuma Y, Tanaka Y, Takeyama K, Okamoto T: The predictive factors of α1-DA adrenoceptor antagonist, naftopidil, dose increase therapy for male lower urinary tract symptoms caused by benign prostatic hyperplasia: INFORM study. Urol Ann 2017;9:261–267.

26. Yamaguchi S, Otsane H, Namuta A, Watanabe M, Kakizaki H: α1D-α1A-adrenoceptor antagonist naftopidil for the male lower urinary tract symptoms associated with benign prostatic hyperplasia: efficacy of dose increase therapy. Int J Urol 2013;20:513–519.

27. Chung JW, Choi SH, Kim BS, Kim TH, Yoo ES, Kim CI, Lee KS, Kwon TG: Efficacy and tolerability of tamsulosin 0.4 mg in patients with symptomatic benign prostatic hyperplasia. Korean J Urol 2011;52:479–484.

28. Kim JW, Oh MM, Yeo JK, Bae JH, Joo KJ, Choi JB, Park HS, Kim HJ, Moon du G, Lee JG: Efficacy of dose escalation of tamsulosin for the treatment of lower urinary tract symptoms. Low Urin Tract Symptoms 2012;4:96–102.

29. Park JS, Lee SW, Choi HY, Moon HS: The effects of tamsulosin dose escalation in benign prostate hyperplasia patients with lower urinary tract symptoms. Med Surg Urol 2012; S1:001.

30. Lepor H: Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia. Tamsulosin Investigator Group. Urology 1998;51:892–900.

31. Malde S, Namibar AK, Umbach R, Lam TB, Bach T, Bachmann A, Drake MJ, Gacci M, Gratzke C, Madersbacher S, Mamoulikis C, Tikkinen KA, Gravas S: Systematic review of the performance of noninvasive tests in diagnosing bladder outlet obstruction in men with lower urinary tract symptoms. Eur Urol 2017;71:391–402.
Kawabe K, Yoshida M, Homma Y: Silodosin, a new alpha1A-adrenoceptor-selective antagonist for treating benign prostatic hyperplasia: results of a phase III randomized, placebo-controlled, double-blind study in Japanese men. BJU Int 2006;98:1019–1024.

Lee E: Comparison of tamsulosin and finasteride for lower urinary tract symptoms associated with benign prostatic hyperplasia in Korean patients. J Int Med Res 2002;30:584–590.

Chapple CR, Al-Shukri SH, Gattegno B, Holmes S, Martinez-Sagarra JM, Scarpa RM, van Vierssen Trip OB, Vik V, Van Der Putten-Slob I: Tamsulosin oral controlled absorption system (OCAS) in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH): efficacy and tolerability in a placebo and active comparator controlled Phase 3a study. Eur Urol Suppl 2005;4:33–44.

Athanasopoulos A, Chapple C, Fowler C, Gratzke C, Kaplan S, Stief C, Tubaro A: The role of antimuscarinics in the management of men with symptoms of overactive bladder associated with concomitant bladder outlet obstruction: an update. Eur Urol 2011;60:94–105.

Zhang S, Meng L, Qiu F, Yang JD, Sun S: Medication-related risk factors associated with health-related quality of life among community-dwelling elderly in China. Patient Prefer Adherence 2018;12:529–537.