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Original Article

First-line antimuscarinic monotherapy is safe and effective in men with predominant storage symptoms of the lower urinary tract

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ABSTRACT

Objective: To investigate the safety and efficacy of first-line antimuscarinic monotherapy for men with predominant storage symptoms in the lower urinary tract based on the International Prostate Symptom Score (IPSS) voiding-to-storage subscore ratio (IPSS-V/S).
Materials and Methods: We conducted a prospective open-label study of first-line tolterodine (4 mg daily) monotherapy in 132 men (age 41–90 years) with a total IPSS (IPSS-T) $\geq$ 8 and IPSS-V/S $\leq$ 1. The IPSS storage subscore (IPSS-S), voiding subscore, IPSS-T, quality of life (QoL), maximal flow rate, voided volume, and post-void residual urine (PVR) were evaluated after treatment for 1 month and 3 months.
Results: The treatment results were satisfactory (global response assessment $\geq$ 1) in 103 men (78.0%). Mean IPSS-T, IPSS-S, nocturnal frequency, and QoL improved significantly. No patient developed acute urinary retention. However, mean PVR increased significantly (from 51.8 to 63.9 mL), especially among patients older than 70 years. The treatment results did not differ significantly between patients with a total prostate volume (TPV) $\geq$ 30 mL and those with TPV $<$ 30 mL.
Conclusion: First-line antimuscarinic monotherapy is safe and effective for men with IPSS $\geq$ 8 and IPSS-V/S $\leq$ 1. The treatment results were similar in men with TPV larger or smaller than 30 mL. However, we recommend that first-line antimuscarinic monotherapy in men older than 70 years should be administered with caution.

1. Introduction

Lower urinary tract symptoms (LUTS) include voiding, storage, and postmicturition symptoms [1]. Although LUTS are not organ-specific, most initial treatments for male LUTS focus on the prostate and are traditionally based on α-blockers [2]. Antimuscarinic therapy is always used as second-line monotherapy or added to α-blockers when LUTS do not improve or there are persistent storage symptoms [3–8]. Physicians are usually concerned that the inhibitory effect of antimuscarinics might aggravate voiding difficulties or cause urinary retention, especially in men with bladder outlet obstruction (BOO) [9,10].

Recently updated guidelines indicate that antimuscarinics, alone or in combination with α-blockers, appear to be an effective and safe treatment for male storage LUTS, and are suggested as an alternative treatment for men without elevated post-void residual urine (PVR) [11–13]. For men with storage LUTS without voiding LUTS or BOO, antimuscarnic monotherapy can be used as a first-line treatment. By contrast, combination therapy or sequential use of α-blockers and antimuscarinics is usually suggested for men with concomitant significant BOO [12–15]. However, in clinical practice, the presence of BOO is not very clear in some men, and the degree of BOO is usually difficult to determine without a pressure–flow study. PVR, total prostate volume (TPV), serum prostate-specific antigen (PSA), and the maximal flow rate (Qmax) are commonly used as parameters to guide the treatment choice for male LUTS [12,13]. However, the parameters that need to be determined before initiating treatment are still controversial and no cutoff values have been determined for the safe use of first-line antimuscarinic monotherapy.

The International Prostate Symptom Score (IPSS) questionnaire has been used for decades to evaluate the severity of LUTS and benign prostatic hypertrophy (BPH) [11]. Although the IPSS total (IPSS-T) score cannot differentiate voiding from storage lower

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urinary tract dysfunction (LUTD), we reported that measurement of IPSS subscores and calculation of the IPSS voiding-to-storage subscore ratio (IPSS-V/S) are simple and useful methods for differentiating voiding and storage LUTD [16]. To further investigate the safety and efficacy of first-line antimuscarinic monotherapy for men with predominant storage LUTS based on the IPSS-V/S, especially for those with a large prostate, we conducted a prospective open-label study of first-line antimuscarinic monotherapy for men with moderate to severe LUTS (IPSS-T $\geq$ 8) and IPSS-V/S $\leq$ 1, regardless of their TPV, serum PSA, PVR, or Qmax.

2. Materials and methods

Male patients older than 40 years with IPSS-T >8 were recruited from January 2010 to December 2010. The IPSS voiding (IPSS-V) and storage (IPSS-S) subscores were recorded separately according to the validated Chinese version of the IPSS, and IPSS-V/S was calculated. Baseline data for TPV, transition zone index (TZI), Qmax, PVR, voided volume, serum PSA, and quality of life (QoL) index were obtained. Men with documented genitourinary cancer, acute or chronic urinary retention, poorly controlled diabetes mellitus, frank neuropathy, urinary tract infection, or previous urethral surgery were excluded. Patients with abnormal findings on digital rectal examination or elevated serum PSA ($\geq$4 ng/mL) were referred for a prostate biopsy to verify the possibility of prostate cancer. Patients with biopsy-proven prostate cancer were also excluded. The study was reviewed and approved by the Research Ethics Committee of Buddhist Tzu Chi General Hospital, and written informed consent was obtained from each individual.

All men with IPSS-S greater than or equal to their IPSS-V (IPSS-V/S $\leq$1) received first-line tolterodine (4 mg daily) monotherapy, regardless of their TPV, TZI, Qmax, PVR, or PSA. IPSS-S, IPSS-V, IPSS-T, QoL, Qmax, voided volume, and PVR. They were then evaluated at 1 month (Visit 1) and 3 months (Visit 2) after treatment was initiated. The treatment results were compared between patients with TPV $\geq$ 30 mL and those with TPV < 30 mL to investigate if men with IPSS-V/S $\leq$ 1 and a large prostate can benefit from first-line antimuscarinic monotherapy as much as those with a small prostate.

Patients rated their symptoms using a global response assessment (GRA), a 7-point scale ranging from markedly worse (−3) to markedly improved (+3). After treatment for 1 month, addition of a α-blocker or switching to α-blocker monotherapy was done for patients with GRA <1 based on the investigator's choice. Parameters were compared between those with GRA $\geq$ 1 and GRA < 1 after antimuscarinic monotherapy for 1 month. We also investigated possible risk factors for increased PVR ($\geq$50 mL) and aggravated IPSS-V ($\geq$4) after first-line tolterodine monotherapy for 1 month.

2.1. Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) and categorical data as number (percentage). Statistical comparisons between the groups were tested using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Statistical assessments were considered significant for $p < 0.05$. Statistical analyses were performed using SPSS 15.0 statistical software (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 132 consecutive male patients (age 41–90 years) received first-line tolterodine monotherapy. Mean TPV was 41.6 mL and mean PSA was 3.9 ng/mL (Table 1). The patients were further divided into two groups according to their baseline TPV. Patients with TPV $\geq$ 30 mL were older and had higher serum PSA and lower voided volumes than those with TPV < 30 mL. However, IPSS-T, IPSS-V, IPSS-S, QoL, Qmax, and PVR did not significantly differ between the two groups (Table 1).

Table 1
Baseline data.

	Total (n = 132)	TPV $\geq$ 30 mL (n = 80)	TPV < 30 mL (n = 52)	p[a]
Age (y)	68.6 ± 12.1	71.3 ± 10.2	66.1 ± 1.7	0.018
IPSS-T	14.9 ± 5.6	15.2 ± 5.7	14.3 ± 5.8	0.319
IPSS-V	5.4 ± 3.6	5.5 ± 3.6	5.1 ± 3.7	0.329
IPSS-S	9.5 ± 3.1	9.7 ± 3.3	9.2 ± 2.9	0.379
Nocturia	3.8 ± 1.3	3.8 ± 1.3	3.8 ± 1.2	0.772
QoL	3.9 ± 1.0	3.9 ± 1.0	3.8 ± 0.9	0.436
PSA (ng/mL)	3.9 ± 5.1	5.4 ± 5.3	1.8 ± 3.9	<0.001
TPV (mL)	41.9 ± 26.1	53.0 ± 28.0	23.9 ± 2.9	<0.001
TZI	0.34 ± 0.14	0.38 ± 0.14	0.27 ± 0.11	<0.001
Qmax (mL/s)	13.3 ± 8.2	12.5 ± 7.4	14.3 ± 9.0	0.427
Volume (mL)	214.2 ± 169.1	141.0 ± 16.0	197.0 ± 28.7	0.040
PVR (mL)	50.9 ± 63.3	53.0 ± 66.5	48.3 ± 59.5	0.941

IPSS-S = IPSS storage subscore; IPSS-T = IPSS total score; IPSS-V = IPSS voiding subscore; PSA = prostate specific antigen; PVR = post-void residual urine; Qmax = maximum flow rate; QoL = quality of life index; TPV = total prostate volume; TZI = transition zone index.
[a] Comparisons between patients with TPV $\geq$ 30 mL and <30 mL were performed using the Wilcoxon rank-sum test.

After first-line antimuscarinic monotherapy for 1 month, 103 men (78.0%) demonstrated satisfactory results (GRA $\geq$ 1). For those with GRA < 1, 22 of 27 men (81.5%) improved to GRA $\geq$ 1 after combining or switching to α-blocker therapy at the second visit. No patient developed acute urinary retention. The adverse effects reported included 13 cases of dry mouth (9.8%), 10 of blurred vision (7.6%), seven of dry eyes (5.3%), six of dysuria (4.5%), three of constipation (2.3%), two of dizziness (1.5%), one of general weakness (0.8%), and one of palpitations (0.8%).

The parameters at baseline and 1 and 3 months were evaluated (Fig. 1). Mean IPSS-T, IPSS-S, nocturnal frequency, and QoL decreased significantly. The voided volume increased, but a significant increased in PVR (from 51.8 mL to 63.9 mL) was noted. After antimuscarinic monotherapy for 1 month, PVR decreased in all five patients with baseline PVR $\geq$ 200 mL, and four of these patients (80%) reported GRA $\geq$ 1. Patients with TPV $\geq$ 30 mL had treatment results similar to those with TPV < 30 mL (Table 2).

Patients with GRA $\geq$ 1 after tolterodine monotherapy for 1 month had less nocturnal frequency and higher serum PSA at baseline than those with GRA < 1, whereas the other baseline parameters were similar (Table 3). When the parameters after treatment for 1 month were compared, patients with GRA $\geq$ 1 also had lower IPSS-T, IPSS-V, IPSS-S, nocturnal frequency, and QoL, while Qmax, voided volume, and PVR were similar (Table 3).

After tolterodine monotherapy for 1 month, aggravated IPSS-V ($\geq$4) was observed in 22 (16.7%) of 132 patients and increased PVR ($\geq$50 mL) in 25 (20%) of 125 patients. Most baseline parameters were similar in patients with and without an increase in PVR or IPSS-V after treatment. Only age greater than 70 years was significantly associated with an increase in PVR ($\geq$50 mL) after tolterodine monotherapy (Table 4).

4. Discussion

Our preliminary results demonstrate the safety and efficacy of first-line tolterodine monotherapy in men with IPSS-T $\geq$ 8 and IPSS-V/S $\leq$ 1. Some 78% of 132 patients reported GRA $\geq$ 1 after tolterodine monotherapy for 1 month. Mean IPSS-T and IPSS-S decreased, and quality of life improved significantly. No patient developed urinary retention, but mean PVR increased from 51.8 mL to 63.9 mL.

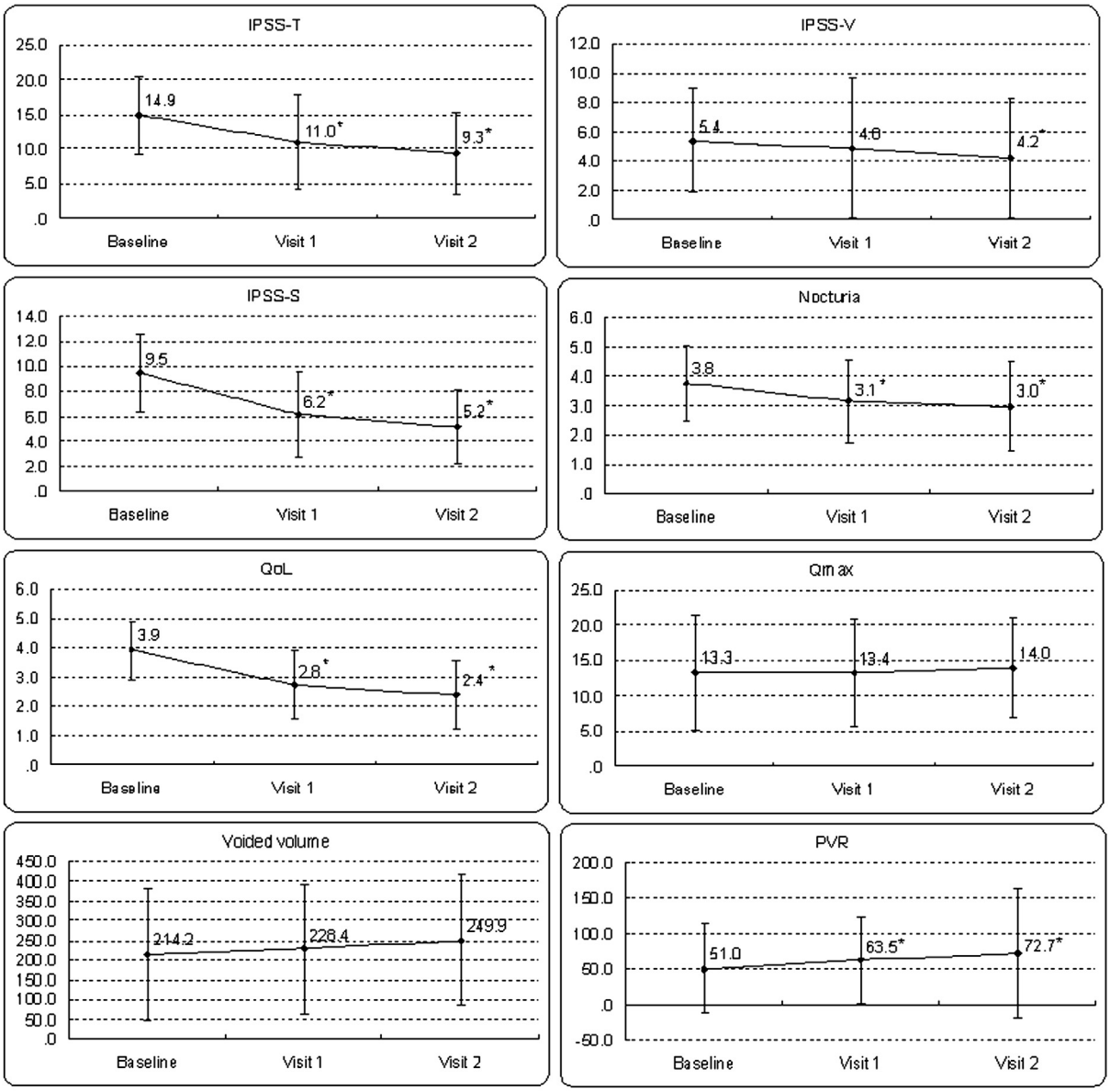

Fig. 1. All parameters improved after tolterodine (4 mg daily) monotherapy for 1 month and 3 months. IPSS-T = total IPSS; IPSS-V = IPSS voiding subscore; IPSS-S = IPSS storage subscore; QoL = quality of life index; Qmax = maximal flow rate; PVR = post-void residual urine. $^{*}p < 0.05$ compared with baseline.

Table 2
Results for antimuscarinic monotherapy for 1 month.

	Total ($n = 132$)	TPV $\geq$ 30 mL ($n = 80$)	TPV $<$ 30 mL ($n = 52$)	p [a]
ΔIPSS-T	−3.9 ± 0.5	−4.1 ± 0.6	−3.2 ± 1.0	0.383
ΔIPSS-V	−0.5 ± 0.4	−0.5 ± 0.5	−0.4 ± 0.8	0.876
ΔIPSS-S	−3.3 ± 0.3	−3.6 ± 0.4	−2.8 ± 0.4	0.155
ΔNocturia	−0.6 ± 0.1	−0.6 ± 0.1	−0.6 ± 0.1	0.928
ΔQoL	−1.1 ± 0.1	−1.2 ± 0.1	−1.0 ± 0.1	0.592
ΔQmax (mL/s)	+0.19 ± 0.51	+0.15 ± 0.62	+0.28 ± 0.94	0.867
ΔVolume (mL)	+12.5 ± 10.0	+23.0 ± 12.4	−5.4 ± 16.9	0.161
ΔPVR (mL)	+12.1 ± 5.9	+13.9 ± 8.3	+9.0 ± 7.7	0.274

Data expressed as mean ± standard error.
IPSS-S = IPSS storage subscore; IPSS-T = IPSS total score; IPSS-V = IPSS voiding subscore; PVR = post-void residual urine; Qmax = maximum flow rate; QoL = quality of life index.
[a] Comparisons between patients with TPV $\geq$ 30 mL and <30 mL were performed using the Wilcoxon rank-sum test.

We found that 75.7% of patients with IPSS-V/S $\leq$ 1 had storage LUTD [16]. Antimuscarinics are the mainstay of pharmacotherapy for storage LUTD, such as overactive bladder (OAB). A systematic review revealed that antimuscarinics reduce the severity of urgency, decrease micturition frequency, and improve the quality of life in patients with OAB [17]. The decreases in mean IPSS-T, IPSS-S, nocturnal frequency and QoL in our study reflect the treatment results of antimuscarinics in OAB.

Although there is still no consensus on which patients are suitable for first-line antimuscarinic monotherapy, TPV, serum PSA, PVR, and Qmax are the parameters most commonly used to guide initial treatment for male LUTS [12,13]. Djavan et al suggested that antimuscarinic monotherapy is only suitable for men with predominant storage symptoms, Qmax $\geq$ 10 mL/s, and TPV $<$ 30 mL [12]. Kaplan et al recommended that antimuscarinic therapy should be avoided for men with an enlarged prostate, high serum PSA, and high PVR or a low flow rate. These suggestions regarding TPV came in part from a *post hoc* analysis of the TIMES study (Tolterodine and

Table 3
Results for patients with GRA ≥ 1 and GRA < 1 after antimuscarinic monotherapy for 1 month.

	GRA ≥ 1 (n = 103)	GRA < 1 (n = 29)	p
Baseline			
Age (y)	69.0 ± 12.5	67.2 ± 10.7	0.255
IPSS-T	14.9 ± 5.7	14.7 ± 5.6	0.813
IPSS-V	5.4 ± 3.6	5.2 ± 3.5	0.886
IPSS-S	9.5 ± 3.2	9.5 ± 3.0	0.881
Nocturia	3.6 ± 1.3	4.2 ± 1.1	0.023
IPSS-V/S	0.60 ± 0.32	0.56 ± 0.33	0.561
QoL	3.9 ± 1.0	3.8 ± 1.0	0.578
TPV (mL)	42.1 ± 27.6	41.4 ± 21.2	0.666
TZI	0.35 ± 0.13	0.32 ± 0.15	0.107
PSA (ng/mL)	4.4 ± 5.4	2.5 ± 3.5	0.030
Qmax (mL/s)	13.7 ± 8.6	11.9 ± 6.4	0.447
Volume (mL)	213.8 ± 166.8	215.4 ± 180.1	0.924
PVR (mL)	52.5 ± 62.6	45.1 ± 66.3	0.241
Post-treatment (Visit 1)			
IPSS-T	9.8 ± 6.4	15.2 ± 6.7	<0.001
IPSS-V	4.2 ± 4.5	7.0 ± 5.0	0.003
IPSS-S	5.6 ± 3.3	8.2 ± 3.2	<0.001
Nocturia	2.9 ± 1.4	3.9 ± 1.1	0.001
QoL	2.5 ± 1.1	3.6 ± 1.0	<0.001
Qmax (mL/s)	13.5 ± 8.2	12.8 ± 5.7	0.879
Volume (mL)	223.6 ± 155.5	245.0 ± 196.3	0.835
PVR (mL)	62.6 ± 56.1	66.8 ± 80.8	0.692

IPSS-S = IPSS storage subscore; IPSS-T = IPSS total score; IPSS-V = IPSS voiding subscore; PSA = prostate specific antigen; PVR = post-void residual urine; Qmax = maximum flow rate; QoL = quality of life index; TPV = total prostate volume; TZI = transition zone index.

Tamsulosin In Men with LUTS Including OAB: Evaluation of Efficacy and Safety) [18,19]. The analysis revealed that tolterodine monotherapy was effective only in patients with TPV < 29 mL, while combination therapy was effective regardless of prostate size.

Table 4
Comparison of baseline parameters between increased IPSS-V of ≥ 4 and <4, and between increased PVR of ≥50 mL and <50 mL.

Baseline data	Increased IPSS-V			Increased PVR		
	≥4 (n = 22)	<4 (n = 110)	p	≥50 mL (n = 25)	<50 mL (n = 100)	p
Age						
≥70	12 (18.5)	53 (81.5)	0.645	19 (30.2)	44 (69.8)	0.007
<70	10 (14.9)	57 (85.1)		6 (9.7)	56 (90.3)	
TPV (mL)						
≥30	12 (15.0)	68 (85.0)	0.474	16 (20.5)	62 (79.5)	1.000
<30	10 (20.4)	39 (79.6)		9 (20.0)	37 (80.0)	
TPV (mL)						
≥40	8 (16.7)	40 (83.3)	1.000	11 (23.9)	35 (76.1)	0.489
<40	14 (17.3)	67 (82.7)		14 (18.0)	64 (82.1)	
IPSS-T						
≥20	7 (23.3)	23 (76.7)	0.274	4 (13.3)	26 (86.7)	0.433
<20	15 (14.7)	87 (85.3)		21 (22.1)	74 (77.9)	
IPSS-V						
≥10	3 (16.7)	19 (83.3)	1.000	1 (5.6)	17 (94.4)	0.120
<10	15 (16.7)	95 (83.3)		24 (22.4)	83 (77.6)	
PVR (mL)						
≥50	9 (20.9)	34 (79.1)	0.458	7 (16.3)	36 (83.7)	0.491
<50	13 (14.9)	74 (85.1)		18 (22.0)	64 (78.1)	
PVR						
≥100	3 (17.6)	14 (82.4)	1.000	1 (5.9)	16 (94.1)	0.191
<100	19 (16.8)	94 (83.2)		24 (22.2)	84 (77.8)	
Qmax (mL/s)						
≥10	11 (14.5)	65 (85.5)	0.349	10 (14.1)	61 (85.9)	0.106
<10	11 (21.2)	41 (78.8)		14 (26.9)	38 (73.1)	
PSA (ng/mL)						
≥1.6	10 (13.9)	62 (86.1)	0.346	16 (22.5)	55 (77.5)	0.489
<1.6	12 (21.4)	44 (78.6)		8 (15.7)	43 (84.3)	

Data are presented as n (%)., IPSS-T = IPSS total score; IPSS-V = IPSS voiding subscore; PSA = prostate-specific antigen; PVR = post-void residual urine; Qmax = maximum flow rate; TPV = total prostate volume.

The treatment efficacy was similar between men with TPV ≥ 30 mL and those with TPV < 30 mL in our study. The discrepancy may be due to different inclusion criteria. The TIMES study was a randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of extended-release tolterodine and/or tamsulosin in men who met research criteria for both overactive bladder and BPH. The criteria were IPSS ≥ 12, frequency and urgency, with or without urgency urinary incontinence, PVR < 200 mL, and Qmax > 5 mL/s, and the study included patients with both BOO and OAB [5]. We enrolled patients with IPSS-V/S ≤ 1 in this study, whereas men with significant BOO were excluded. We suggest that IPSS-V/S may be better than TPV in identifying significant BOO and determining if first-line antimuscarinic monotherapy can be initiated. This concept is supported by our previous retrospective study, which showed the IPSS-V/S is a better predictor than TPV for urodynamically proved voiding LUTD [16].

We compared baseline parameters between men with GRA ≥ 1 and GRA < 1 after treatment for 1 month to identify predictors of good and poor responders. Men with GRA < 1 had more nocturnal frequency and lower serum PSA than patients with GRA ≥ 1, which may imply that the prostate or bladder outlet plays less of a role in LUTS in these patients, and nocturia caused by systemic disease may partly explain the poor response to antimuscarinic therapy. In addition, predictors commonly used for poor response to antimuscarinic therapy, such as symptom severity, TPV, PVR, and Qmax, were similar between these groups in our study.

The safety of antimuscarinic monotherapy in men with BOO/BPH and OAB/detrusor overactivity has been reported in several studies [5,20–23]. Assessment of baseline PVR prior to initiation of antimuscarinic therapy is usually suggested [11–15], and antimuscarinics should be used with caution in patients with PVR of 250–300 mL [11]. Our study supports this notion, although most of our patient had baseline PVR of < 200 mL. However, five of our patients had baseline PVR ≥ 200 mL. After antimuscarinic monotherapy for 1 month, PVR decreased in all five patients, four of whom (80%) reported GRA ≥ 1. More data are still needed to determine if antimuscarinics can be used safely in men with IPSS-V/S ≤ 1 and a large baseline PVR.

We also investigated possible risk factors for increases in PVR and IPSS-V after antimuscarinics monotherapy. Elderly (≥70 years) patients are more likely to have an increase in PVR (≥50 mL). Other baseline parameters, such as TPV, IPSS-T, and Qmax, are difficult to correlate with IPSS-V aggravation or an increase in PVR. Age has also been reported as a risk factor for BPH progression [24]. Although we reported the safety of add-on antimuscarinics for men older than 70 years with BPH/BOO [8], we suggest that first-line antimuscarinic monotherapy be used with caution in such men.

One limitation of our study is the lack of a placebo group. We cannot exclude a possible placebo effect after treatment. In addition, some patients dropped out. Some patients might have discontinued their medication because they felt their symptoms had improved a lot. The strengths of our study include its prospective nature and the evaluation of treatment results using both subjective and objective methods.

5. Conclusions

First-line antimuscarinic monotherapy is safe and effective for men with IPSS ≥ 8 and IPSS-V/S ≤ 1. In this patient group, men with a large prostate (≥30 mL) had treatment results similar to those with TPV < 30 mL. IPSS-V/S ≤ 1 may be worth considering as an indicator for initiation of antimuscarinic monotherapy. Elderly (≥70 years) patients are more likely to have an increased PVR (≥50 mL), so first-line antimuscarinic monotherapy should be used with caution in men older than 70 years.

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