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Role of silodosin in patients with LUTS/BPE non responding to medical treatment with tamsulosin: a prospective, open-label, pilot study

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Abstract. – OBJECTIVE: Lower urinary tract symptoms (LUTS) are frequently experienced in association with benign prostatic enlargement (BPE). Current guidelines state that alpha-blockers should be considered the first-line therapy of LUTS associated with BPE in most patients. However, in clinical practice treatment efficacy differs among individuals and, therefore, intra-class switch from one alpha-blocker to another, is frequently applied. In particular, switching to silodosin in clinical practice appears an intriguing therapeutic strategy due to the peculiar pharmacological properties of this molecule. This study evaluates the efficacy of silodosin in patients with LUTS associated with BPE who were not-responders to tamsulosin.

PATIENTS AND METHODS: This was a prospective, open-label, single-center study. Patients treated with tamsulosin 0.4 mg once daily for BPE/LUTS for at least 12 months and not responding to therapy were switched to silodosin 8 mg once daily. The co-primary endpoints for evaluation of efficacy were the change in IPSS and quality of life (QoL) from the beginning of silodosin therapy to week 8.

RESULTS: In total, 96 patients were enrolled. Mean International Prostatic Symptoms Score (IPSS) score at baseline was 20.0 ± 4.4, and it significantly decreased to 18.6 ± 4.5 at week 8 (mean change: -1.3 ± 1.4; 95% CI -1.6 – -1.0; $p < 0.03$). A decrease was also observed for the two IPSS subscores; in particular, the IPSS subscore for storage symptoms was significantly reduced at week 8, compared with baseline. A significant improvement in QoL was observed after switching to silodosin, as compared with baseline (-0.8 ± 1.0; 95% CI -1.0 – -0.6; $p < 0.001$).

CONCLUSIONS: Silodosin improves IPSS symptoms score and QoL in patients with LUTS associated with BPE who were not-responders to tamsulosin therapy.

Key Words:
BPE, LUTS, Silodosin, Tamsulosin, Switching.

Introduction

Lower urinary tract symptoms (LUTS) include urinary frequency, urgency, weak/intermittent stream, incomplete voiding and nocturia, and they can ultimately lead to complications such as acute urinary retention[1]. These symptoms are frequently experienced in association with benign prostatic enlargement (BPE), and are quite common in patients aged > 50 years[2]. In more details, the prevalence of moderate-to-severe LUTS increases from 22% among 50-59 year-old patients to 45% in subjects > 70 years[3]. Importantly, LUTS are associated with a major impact on quality of life (QoL) and they greatly contribute to the healthcare burden[4]. However, only one out of five men with BPE-associated LUTS seek for medical treatment[3]. Treatment options for LUTS include alpha1-blockers, 5-alpha-reductase inhibitors, transurethral resection of the prostate, other surgical techniques, and herbal treatments (e.g. saw palmetto extract). The guidelines issued by the European Association of Urology (EAU) state that alpha-blockers should be considered the first-line therapy in most patients[5]. However, in clinical practice treatment efficacy differs among individuals and, therefore, intra-class switch from one alpha-blocker to another is frequently applied[6,7]. Currently-available alpha blockers include terazosin, doxazosin, tamsulosin, naftopidil, alfuzosin and silodosin, which overall show a similar efficacy in the treatment of LUTS. However, in a recent meta-analysis of 17 studies, among all alpha-blockers silodosin showed the more pronounced effect on bladder outlet obstruction index (BOOI), which is considered the most important pathophysiological link between BPE and LUTS[8,9]. Noteworthy, an improvement in BOOI can also lead to slower

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progression of BPE[9]. In this line, it has been suggested that the higher efficacy of silodosin in terms of urodynamic measures as compared with the other drugs may be due to its high selectivity for alpha-1A-adrenoreceptors[9]. Indeed, silodosin showed the highest selectivity for the -1A subtype compared with other alpha-blockers[9-12]. Moreover, high selectivity for the -1A receptor subtype induces a more prostate-specific effect and allows maintain a therapeutic response in the treatment of symptomatic BPE with negligible systemic adverse effects associated with the interaction with the -1B receptor[7-9]. On these bases, switching to silodosin in clinical practice appears an intriguing therapeutic strategy. However, although silodosin has shown efficacy was effective in cross-over studies[6,7,13,14], evidence on its efficacy in patients not-responders to prior alpha-blocker treatment remains scant. This study evaluates the efficacy of silodosin in patients with LUTS associated with BPE who were not-responders to tamsulosin.

Patients and Methods

Patients

Patients treated with tamsulosin 0.4 mg once daily for BPE/LUTS for at least 12 months and non-responders to treatment were eligible. Other inclusion criteria were as follows: International Prostate Symptoms Score (IPSS) $\geq$ 8 points[15], QoL $\geq$ 3 points[16] (QoL measured by question #8 of the standard IPSS questionnaire, assigning a score of 1 to 6), prostate volume by ultrasonography $\leq$ 40 mL; maximal urinary flow rate (Qmax) < 15 mL/s and post-voiding residual (PVR) $\leq$ 150 ml; prostate specific antigen (PSA) < 4 ng/ml. Diabetic patients were not eligible. The presence of stones was excluded by ultrasonography and all patients had to be negative at urine culture.

Study Setting and Design

This was a prospective, open-label, single-center study conducted at a specialized Urology Center in L'Aquila (Italy). The study was started in May 2015 and lasted up to July 2016. The local Ethical Committee approved the study design; all patients signed an informed consent before inclusion.

Study Procedures

All patients who met the above-mentioned criteria interrupted tamsulosin and were switched to silodosin 8 mg once daily. The symptom scores and uroflowmetry with PVR evaluation were measured 8 weeks after silodosin administration. Safety evaluations were also performed, and adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (NIH, Bethesda, MD, USA).

Statistical Analysis

The co-primary endpoints for evaluation of efficacy were the change in IPSS and QoL from the beginning of silodosin therapy to week 8. Secondary end-points were the changes in the storage IPSS subscore (i.e. the sum of scores of questions #2, #4 and #7) and the voiding subscore (i.e. the sum of scores of questions #1, #3, #5 and #6), as well as changes in objective parameters (Qmax, PVR) from treatment initiation to week 8.

Data were analyzed by descriptive statistics. Changes from baseline after the initiation of silodosin were evaluated by the Student *t*-test for paired values, with a p-value < 0.05 considered as significant. All analyses were performed using Microsoft Excel (Redmond, WA, USA).

Results

Patient Population

In total, 96 patients (mean age 67 ± 8 years; range 43-87) were enrolled, and all of them completed the study.

IPSS Score

Table I reports information on IPSS score. Mean IPSS score at baseline was 20.0 ± 4.4, and it significantly decreased to 18.6 ± 4.5 at week 8 (mean change: -1.3 ± 1.4; 95% CI -1.6 – -1.0; $p < 0.03$). A decrease was also observed for the two IPSS items; in particular, the IPSS subscore for storage symptoms was significantly reduced at week 8, compared with baseline (baseline: 10.8±2.2; week 8: 9.9 ± 2.4; $p = 0.03$). In total, 18 patients (18.5%) achieved a clinically-meaningful reduction in IPSS score ($\geq$ 3).

Quality of Life

Figure 1 reports the results of the QoL assessment. Overall, a significant improvement in this parameter was observed after switching to silodosin, as compared with baseline (-0.8 ± 1.0; 95% CI -1.0 – -0.6; $p < 0.001$).

Table I. Results of the IPSS evaluation (N = 96). *$p < 0.03$ *vs.* baseline.

	Baseline		Week 8		Change	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
IPSS total score	20.0 (4.4)	13-34	18.6 (4.5)*	11-32	-1.3 (1.4)	-5 - +2
IPSS – storage symptoms	10.8 (2.2)	5-15	9.9 (2.4)*	5-19	-1.0 (1.4)	-4 - +6
IPSS – voiding symptoms	9.1 (1.9)	5-14	8.9 (2.0)	5-14	-0.2 (1.2)	-3 - +4

IPSS: International Prostate Symptoms Score.

Objective Parameters

Both Qmax (11.9 ± 1.5 *vs.* 12.0 ± 1 .7) and PVR (82.3 ± 28.3 *vs.* 77.2 ± 27.1) did not change during silodosin treatment, with respect to baseline.

Safety

Adverse events were observed in 19 out of 109 patients (19.7%). The most frequently observed adverse event was ejaculatory disorder in fifteen patients (15.9%).

Discussion

In clinical practice, alpha1-blockers represent one of the most frequently prescribed first-line therapies for LUTS-associated BPE. Overall, the efficacy of different alpha-blockers appears similar. However, a number of patients do not respond to first-line therapy and in this case a switch to another alpha-blocker is often decided. However, further information on clinical outcomes after this intra-class switch appears necessary. In our work we evaluated the clinical outcomes associated with switching to silodosin in patients who did not respond to tamsulosin therapy. We must, however, acknowledge that the results of the present study should be overall considered as preliminary, due to the small sample size, the short duration of observation, and the lack of a control.

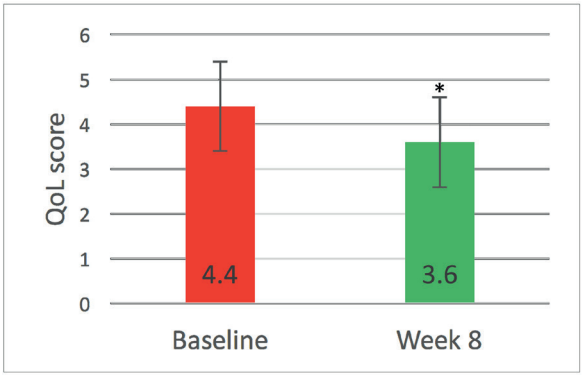

Figure 1. Quality of life (QoL) score (N = 96). *$p < 0.001$ *vs.* baseline.

Overall, switching to silodosin determined, after a 8-week treatment, a significant improvement in IPSS total score, and QoL was observed – also with a narrow confidence interval - thus suggesting an amelioration of subjective symptoms experienced by patients and hence an improved QoL, without any new safety signal. Noteworthy, all patients had been previously treated with a recommended first-line treatment for BPE-associated LUTS, without showing response; therefore, an improvement in IPSS after switching to silodosin appears clinically relevant. As a further confirmation of this finding, about one out of five patients reported a reduction in the IPSS score ≥ 3 points, which is considered a threshold for clinical relevance. When analyzing the specific subscores of the IPSS questionnaire, a significant improvement was observed in storage symptoms, but not in voiding symptoms. Similarly, a trend to improved objective parameters, namely Qmax and PVR, was observed, but statistical significance was not reached. This finding was, however, not unexpected, since alpha-blockers exerts only a minimal effect on Qmax[8,9]. On the other hand, they reduce detrusor pressure (PdetQmax), thus improving prostate obstruction[8,9]. Overall, our findings are in line with some studies analyzing patients who crossed-over to silodosin from other alpha-blockers. In a randomized cross-over study on BPH patients, silodosin was superior over tamsulosin in improving IPSS score and QoL both in the initial period of observation and, importantly, also after the cross-over[7]. More specifically, only silodosin improved IPSS and QoL after crossing-over, whereas tamsulosin did not. Tanaka et al[13] reported the results of a study on 81 patients who switched from other alpha-blockers to silodosin, mostly for

poor efficacy in improving nocturia or weak stream. A significant improvement in the IPSS score was reported after switching (from 12.7 ± 5.9 to 10.6 ± 5.4 at 4 weeks; and 10.9 ± 5.8 at 12 weeks; $p < 0$ .01 for both comparisons). This improvement was particularly evident in voiding and storage symproms. The quality of life index also improved with switching, and silodosin therapy was judged effective by the wide majority of patients (76%). Overall similar findings were reported in a more recent study by Yoshida et al[14], although BPE patients switched from tadalafil – a 5-PDE inhibitor – to silodosin. Remarkably, they suggested that silodosin should be considered one of the first-line therapies in patients with LUTS/BPH due to its rapid and efficient relief of symptoms. It is possible to speculate that these effects of silodosin may be due, at least in part, to its high selectivity for the alpha-1A-adrenoreceptor[7,12]. Indeed, silodosin is characterized by the highest selectivity for the alpha1A-adrenoreceptor, with respect to -1B and -1D isoforms[12]. Noteworthy, prostate function is mainly regulated by the -1A isoform, whereas the -1B isoform is mainly located in the vascular smooth muscle and contributes to regulate cardiac compensatory mechanisms and blood pressure[7]. Overall, these pharmacological properties suggest that silodosin determines a more pronounced effect on prostatic tissue that other alpha-blockers and presents a distinct overall tolerability profile. In this line, in a study on prescription change from alpha1-blocker therapy to another alpha1-blocker, the overall proportion of prescription change (16.3%) and prescription change due to hemodynamic adverse events (2.4%) in the silodosin group were lower than with doxazosin, alfuzosin, and tamsulosin[17].

Conclusions

We showed that silodosin significantly improves symptoms score and QoL in patients with LUTS associated with BPE who were not-responders to tamsulosin therapy. These data can be useful to guide future prospective studies with greater number of patients.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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