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Platinum Priority – Benign Prostatic Hyperplasia

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Silodosin Therapy for Lower Urinary Tract Symptoms in Men with Suspected Benign Prostatic Hyperplasia: Results of an International, Randomized, Double-Blind, Placebo- and Active-Controlled Clinical Trial Performed in Europe

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Abstract

Background: Silodosin is a new selective therapy with a high pharmacologic selectivity for the α_{1A}-adrenoreceptor.
Objective: Our aim was to test silodosin's superiority to placebo and noninferiority to tamsulosin and discuss the findings in the context of a comprehensive literature review of the new compound silodosin.
Design, setting, and participants: We conducted a multicenter double-blind, placebo- and active-controlled parallel group study. A total of 1228 men ≥50 yr of age with an International Prostate Symptom Score (IPSS) ≥13 and a urine maximum flow rate (Q_{max}) >4 and ≤15 ml/s were selected at 72 sites in 11 European countries. The patients were entered into a 2-wk wash-out and a 4-wk placebo run-in period. A total of 955 patients were randomized (2:2:1) to silodosin 8 mg (n = 381), tamsulosin 0.4 mg (n = 384), or placebo (n = 190) once daily for 12 wk.
Measurements: We calculated the change from baseline in IPSS total score (primary), storage and voiding subscores, quality of life (QoL) due to urinary symptoms, and Q_{max}. Responders were defined on the basis of IPSS and Q_{max} by a decrease of ≥25% and an increase of ≥30% from baseline, respectively.
Results and limitations: The change from baseline in the IPSS total score with silodosin and tamsulosin was significantly superior to that with placebo ($p < 0.001$): difference active placebo of −2.3 (95% confidence interval [CI], −3.2, −1.4) with

[1] A complete list of study participants is provided in the appendix.

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silodosin and −2.0 (95% CI, −2.9, −1.1) with tamsulosin. Responder rates according to total IPSS were significantly higher ($p < 0.001$) with silodosin (66.8%) and tamsulosin (65.4%) than with placebo (50.8%). Active treatments were also superior to placebo in the IPSS storage and voiding subscore analyses, as well as in QoL due to urinary symptoms. Of note, only silodosin significantly reduced nocturia versus placebo (the change from baseline was −0.9, −0.8, and −0.7 for silodosin, tamsulosin, and placebo, respectively; $p = 0.013$ for silodosin vs placebo). An increase in Q_{max} was observed in all groups. The adjusted mean change from baseline to end point was 3.77 ml/s for silodosin, 3.53 ml/s for tamsulosin, and 2.93 ml/s for placebo, but the change for silodosin and tamsulosin was not statistically significant versus placebo because of a particularly high placebo response (silodosin vs placebo: $p = 0.089$; tamsulosin vs placebo: $p = 0.221$). At end point, the percentage of responders by Q_{max} was 46.6%, 46.5%, and 40.5% in the silodosin, tamsulosin, and placebo treatment groups, respectively. This difference was not statistically significantly ($p = 0.155$ silodosin vs placebo and $p = 0.141$ tamsulosin vs placebo).

Active treatments were well tolerated, and discontinuation rates due to adverse events were low in all groups (2.1%, 1.0%, and 1.6% with silodosin, tamsulosin, and placebo, respectively). The most frequent adverse event with silodosin was a reduced or absent ejaculation during orgasm (14%), a reversible effect as a consequence of the potent and selective α_{1A}-adrenoreceptor antagonism of the drug. The incidence was higher than that observed with tamsulosin (2%); however, only 1.3% of silodosin-treated patients discontinued treatment due to this adverse event.

Conclusions: Silodosin is an effective and well-tolerated treatment for the relief of both voiding and storage symptoms in patients with lower urinary tract symptoms suggestive of bladder outlet obstruction thought to be associated with benign prostatic hyperplasia. Its overall efficacy is not inferior to tamsulosin. Only silodosin showed a significant effect on nocturia over placebo.

Trial registration: ClinicalTrials.gov Identifier NCT00359905.

1. Introduction

Benign prostatic hyperplasia (BPH) is a nonmalignant enlargement of the prostate caused by cellular hyperplasia of both glandular and stromal elements [1]. As the prostate increases in size, it may occlude the lumen of the prostatic urethra, obstructing urine flow [2]. However, studies have shown that prostate size and urinary flow rate usually do not correlate with the severity of lower urinary tract symptoms (LUTS), which may vary from subject to subject [3]. In clinical practice, patients are treated for LUTS suggestive of bladder outlet obstruction (BOO) due to BPH, often called "LUTS/BPH."

Even if voiding symptoms are the most prevalent in cases of LUTS/BPH, patients usually perceive the storage symptoms as the most bothersome group of symptoms [4]. The objective of therapy for such patients is to improve LUTS/BPH and hence quality of life (QoL). In addition, treatment is aimed at preventing complications such as acute urinary retention or upper urinary tract dilation consequent to BOO. Existing medical therapy includes α-blockers, which are currently the preferred first-line therapy for all men with moderate or severe LUTS/BPH [5], and 5α-reductase inhibitors (5-ARIs), which are a recommended treatment option for men with moderate or severe LUTS/BPH and an enlarged prostate. α-Blockers can be used regardless of prostate size because they act on the dynamic/neurally mediated contraction of the muscular stroma that is increased in BPH; 5-ARIs act by shrinking the stromal component of the gland. Both components are thought to contribute to the symptoms and impairment of outflow in patients with LUTS/BPH [6].

Nonselective α_1-adrenoceptor blockers increase urinary flow rate and improve symptoms in men with symptomatic BPH; however, they may be associated with side effects related to peripheral vasodilation, such as postural hypotension, dizziness, and headache [7–9]. Conversely, drugs with a high affinity for α_{1A}-adrenoceptors may be more prostate specific and may maintain the therapeutic response in the treatment of symptomatic BPH with less effect on blood pressure and fewer cardiovascular side effects [10,11].

Silodosin is a new agent with high selectivity for α_{1A}-receptors, which predominate in the male bladder outflow tract relative to α_{1B}-receptors. It has been demonstrated in vitro that silodosin's α_{1A}-to-α_{1B} binding ratio is extremely high (162:1), suggesting the potential to markedly reduce dynamic neurally mediated smooth muscle relaxation in the lower urinary tract while minimizing undesirable effects on blood pressure regulation [12]. In this context, the evaluation of the uroselectivity of silodosin versus that of tamsulosin and prazosin in vivo has shown good uroselectivity (determined from the ratio of the dose-reducing intraurethral pressure as contrasted to blood pressure) in rats and dogs [13,14].