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Efficacy and Safety of a Fixed-Dose Combination Therapy of Tamsulosin and Tadalafil for Patients With Lower Urinary Tract Symptoms and Erectile Dysfunction: Results of a Randomized, Double-Blinded, Active-Controlled Trial

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ABSTRACT

Background: Phosphodiesterase type 5 inhibitors and α-adrenergic blocking agents (α-blockers) are widely used for the treatment of erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH).

Aims: To assess the efficacy and safety of fixed-dose combinations (FDCs) of tamsulosin and tadalafil compared with tadalafil monotherapy in patients with comorbid BPH-associated LUTS and ED.

Methods: A randomized, double-blinded, active-controlled trial was conducted of 510 men with BPH-associated LUTS and ED. Patients were treated with FDCs of tamsulosin 0.4 mg plus tadalafil 5 mg (FDC 0.4/5 mg), tamsulosin 0.2 mg plus tadalafil 5 mg (FDC 0.2/5 mg), or tadalafil 5 mg for a 12-week treatment period. For a subsequent 12-week extension period, the patients were administered FDC 0.4/5 mg.

Outcomes: The primary outcomes were changes from baseline in total International Prostate Symptom Score (IPSS) and International Index of Erectile Function erectile function domain (IIEF-EF) score at week 12 to prove superiority and non-inferiority of FDCs compared with tadalafil 5 mg. The safety assessments were adverse reactions, laboratory test results, and vital signs at week 24.

Results: The mean changes in total IPSS and IIEF-EF scores were −9.46 and 9.17 for FDC 0.4/5 mg and −8.14 and 9.49 for tadalafil 5 mg, respectively, which indicated superiority in LUTS improvement ($P = .0320$) and non-inferiority in ED treatment with FDC 0.4/5 mg compared with tadalafil 5 mg. However, the results from FDC 0.2/5 mg failed to demonstrate superiority in LUTS improvement. No clinically significant adverse events regarding the investigational products were observed during the 24-week period.

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Clinical Implications: The FDC 0.4/5 mg is the first combined formulation of an α-blocker and a phosphodiesterase type 5 inhibitor that offers benefits in patient compliance and as add-on therapy in patients with comorbid BPH-associated LUTS and ED.

Strengths and Limitations: The study clearly demonstrated the advantage of FDC 0.4/5 mg. The main advantage of FDC 0.4/5 mg was the enhanced efficacy on BPH-associated LUTS comorbidity with ED, the lower incidence of side effects, and the simplification and convenience of therapy, which led to better overall patient compliance. However, the lack of a tamsulosin monotherapy control group was a limitation of this study.

Conclusion: The FDC 0.4/5 mg therapy was safe, well tolerated, and efficacious, indicating that combination therapy could provide clinical benefits for patients with BPH-associated LUTS complaints and ameliorate the comorbidity of ED. **Kim SW, Park NC, Lee SW, et al. Efficacy and Safety of a Fixed-Dose Combination Therapy of Tamsulosin and Tadalafil for Patients With Lower Urinary Tract Symptoms and Erectile Dysfunction: Results of a Randomized, Double-Blinded, Active-Controlled Trial. J Sex Med 2017;14:1018−1027.**

Key Words: Benign Prostatic Hyperplasia; Lower Urinary Tract Symptoms; Erectile Dysfunction; Fixed-Dose Combination; Tadalafil; Tamsulosin

INTRODUCTION

The current global aging phenomenon is not unexpected, and one main reason would be increasing life expectancy. The impact of aging involves various physical changes of the body including signs and symptoms of lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) and erectile dysfunction (ED) in middle-age men.[1]

One study found that men with LUTS have a higher incidence of ED by 2.7 to 3.1 times than those without LUTS.[2] In a German study, 72.2% of men had LUTS with ED and only 37.7% had LUTS without ED, indicating that LUTS is an independent risk factor for ED.[3] There was a relatively high prevalence of LUTS in patients with ED, which indicates a prevalent ED comorbidity with LUTS in Asian men.[4] The presence and severity of LUTS are known risk factors for sexual dysfunction, including ED, in older men.[5] In addition to the comorbidity of LUTS and ED, metabolic syndrome, hypertension, diabetes, and hyperlipidemia are increased in the elderly population. Multidrug therapy is an option that can be used for the treatment of metabolic syndrome but also can increase the incidence of adverse drug reactions (ADRs). When at least six drugs are administered in elderly patients for the treatment of multiple diseases, such as hypertension, diabetes, hyperlipidemia, and BPH, the multiple drug intakes can exacerbate the symptoms and severity of LUTS, presumably caused by high water intake, which can result in frequent urination.[6,7]

The possibility of ADRs and serious drug-drug interactions are major concerns for all cases of polypharmacy.[8] Many ADRs are preventable in elderly people.[9] One solution to these problems is to simplify the complexity by combining the necessary drugs into one compound as a fixed-dose combination (FDC). The most common classes for treating LUTS and ED are α-blockers and phosphodiesterase type 5 (PDE5) inhibitors: the five most widely available α-blockers are doxazosin, terazosin, tamsulosin, alfuzosin, and silodosin; and the available PDE5 inhibitors include sildenafil, vardenafil, udenafil, mirodenafil, and tadalafil. The combination of these two classes of drugs has been shown to be safe and more effective in alleviating LUTS with ED than using each separately.[10−12] The 2015 European Association of Urology (EAU) guidelines on the management of LUTS state that PDE5 inhibitors with α-blockers improve the International Prostate Symptom Score (IPSS; −1.8), the International Index of Erectile Function (IIEF) score (+3.6), and maximum urinary flow rate (Q_{max}; +1.5 mL/s) compared with α-blockers alone. Tadalafil 5 mg has been shown to decrease the IPSS by 22% to 37% and, to date, tadalafil 5 mg/d is the only approved drug for patients with comorbid LUTS and ED.[13,14] Furthermore, tadalafil is suitable for daily use because it has the longest half-life among the PDE5 inhibitors, making it an ideal candidate to be used with an α-blocker in an FDC. A recent increase in the number of prescriptions of tamsulosin and tadalafil has confirmed its validity.[15] The combination of tamsulosin and tadalafil was favored because some reports found that the combination of tamsulosin 0.4 mg plus tadalafil 10 or 20 mg did not result in significant hemodynamic changes.[16] In addition, tamsulosin was the only α-blocker approved by the Food and Drug Administration (FDA) for use in combination with tadalafil at its approval. Because patients with these diseases tend to be elderly and multidrug users, the development of FDCs can improve drug compliance. Based on the safety aspects of combination treatment with tadalafil that were reported by the FDA, tamsulosin and tadalafil do not exert clinically relevant blood pressure changes.[17] Therefore, we expected a low likelihood of ADRs and an additive effect of tadalafil and tamsulosin on LUTS and ED comorbidity.

AIM

The objective of this study was to validate the safety and superior efficacy of a newly developed FDC of tamsulosin and