State-of-the-Art Lecture

Tadalafil Administered Once Daily for Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: A Dose Finding Study

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Purpose: Phosphodiesterase type 5 inhibitors are widely used to treat erectile dysfunction. Preliminary data have suggested phosphodiesterase type 5 inhibitor efficacy in men with lower urinary tract symptoms associated with clinical benign prostatic hyperplasia.

Materials and Methods: After a 4-week placebo run-in period 1,058 men with benign prostatic hyperplasia lower urinary tract symptoms were randomly allocated to receive 12-week, once daily treatment with placebo or tadalafil (2.5, 5, 10 or 20 mg).

Results: The International Prostate Symptom Score least squares mean change from baseline to end point was significantly improved for 2.5 (−3.9, $p = 0.015$), 5 (−4.9, $p < 0.001$), 10 (−5.2, $p < 0.001$) and 20 mg (−5.2, $p < 0.001$) tadalafil compared to placebo (−2.3). International Prostate Symptom Score improvements at 4, 8 and 12 weeks were significant for all tadalafil doses and they demonstrated a dose-response relationship. Tadalafil (2.5 mg) significantly improved the International Prostate Symptom Score obstructive subscore and the International Index of Erectile Function-Erectile Function domain, the latter in sexually active men with a history of erectile dysfunction. Statistically significant improvements were noted for 5, 10 and 20 mg tadalafil compared to placebo, as assessed by the International Prostate Symptom Score irritative and obstructive subscores, International Prostate Symptom Score Quality of Life, Benign Prostatic Hyperplasia Impact Index (nonsignificant for 10 mg), Global Assessment Question and International Index of Erectile Function-Erectile Function domain. No statistically significant effect of treatment compared to placebo was noted for peak flow at any tadalafil dose. Treatment emergent adverse events were infrequent in all tadalafil groups.

Conclusions: Once daily tadalafil demonstrated clinically meaningful and statistically significant efficacy and it was well tolerated in men with benign prostatic hyperplasia lower urinary tract symptoms. Of the doses studied 5 mg tadalafil appeared to provide a positive risk-benefit profile.

Key Words: prostate; tadalafil; dose-response relationship, drug; prostatic hyperplasia; questionnaires

Men with signs of BPH may experience LUTS, such as urinary frequency, urgency, intermittence, nocturia, straining, incomplete emptying or a weak urinary stream.[1] LUTS increase with age with an overall prevalence of greater than 50% in men 50 years or older.[2–4] The current standard of care in men with bothersome moderate to severe BPH LUTS is treatment with an α1-adrenergic blocker (α-blocker) or in men with an enlarged prostate a 5α-reductase inhibitor.[5] Although they are effective, each of these drug classes can produce unwanted side effects, including dizziness, hypotension and sexual dysfunction. These side effects may be exacerbated by combination therapy.[6]

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Since reports of ED incidence, pathophysiology and treatment have shown a possible link between BPH LUTS and ED,[7] PDE5 inhibitors have received increased attention for treating BPH LUTS. Tadalafil (Cialis®) is a PDE5 inhibitor that is currently only approved for ED. The half-life of tadalafil is 17.5 hours,[8] making it suitable as once daily therapy.

Although the precise mechanism of action by which PDE5 inhibitors may alleviate LUTS is not completely understood, several putative mechanisms are currently under investigation. One mechanism focuses on the accumulation of intracellular prostatic and bladder smooth muscle cyclic guanosine monophosphate following PDE5 inhibition, which may decrease tension in the smooth muscle of the prostatic stroma and capsule. This muscle relaxation results in bladder neck opening and improved voiding function,[9] and it decreases detrusor muscle overactivity in the bladder body and neck.[10,11] Another possible mechanism involves pelvic arterial insufficiency and ischemia, which may compromise normal bladder detrusor function and cause a change in the prostatic structure.[12,13] Increased vascular perfusion of the lower urinary tract, especially the prostatic or bladder neck,

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could result in a beneficial therapeutic effect and decrease LUTS.[12–14] Additional theories of PDE5 inhibition on the lower urinary tract suggest a LUTS decrease via modifications of afferent nerve signaling from the bladder, urethra and prostate.[15–18]

In a recent proof of concept, 12-week dose titration study enrolling 281 men with BPH signs and symptoms tadalafil once daily (5 mg for 6 weeks, followed by dose escalation to 20 mg for 6 weeks) was well tolerated.[19] It demonstrated statistically significant and clinically meaningful improvement of LUTS compared to that of placebo. In the current dose finding study we further examined the efficacy, dose response and safety of tadalafil in men with LUTS secondary to BPH.

MATERIALS AND METHODS

Study Design and Participants

This study was a randomized, double-blind, placebo controlled, parallel design, dose finding, 12-week study performed at 92 centers in a total of 10 countries. Men at least 45 years old with a history of LUTS secondary to BPH of 6 months or longer were eligible for this study unless 1) PSA was more than 10 ng/ml (in men with PSA 4 to 10 ng/ml prostate biopsy negative for malignancy within 12 months was required) or 2) PVR volume was 300 ml or greater at screening visit 1 (fig. 1). Patients reporting the use of other BPH or ED treatments upon study entry underwent a 4-week treatment-free screening/washout period. Otherwise patients began the placebo run-in period after screening results were reviewed. Other key inclusion criteria were a total I-PSS of 13 or greater, a Qmax of 4 to 15 ml per second from pre-void bladder volume, as assessed by ultrasound, and between 150 and 550 ml with a voided volume of 125 ml or greater at visit 2. Men were not required to have a history of ED and the frequency of sexual intercourse was not discussed at study entry.

Excluded from enrollment were men who received recent finasteride or dutasteride treatment within 3 and 12 months, respectively, before visit 2 (the start of the placebo run-in period) and those with penile or pelvic surgery, radiotherapy, lower urinary tract malignancy, trauma or recent instrumentation, urinary retention or bladder stones, a history of urethral obstruction due to stricture, valves, sclerosis or tumor, a neurological condition affecting bladder function, detrusor-sphincter dyssynergia, intravesical obstruction secondary to the prostate median lobe, urinary tract inflammation or infection, or prostate cancer. Other exclusionary medical conditions were clinically significant renal or hepatic insufficiency, cardiovascular conditions such as significant angina, recent myocardial infarction or poorly controlled blood pressure, a recent history of stroke or spinal cord injury, current treatment with nitrates, cancer chemotherapy, antiandrogens or a potent cytochrome P450 3A4 inhibitor, or uncontrolled diabetes (glycosylated HbA1c greater than 9%).

The clinical study was performed in accordance with the Declaration of Helsinki and all applicable regulations. The institutional review board at each site approved the study and all men provided written informed consent before undergoing any study procedure or receiving any study therapy.

Outcomes

The primary study end point was the I-PSS change after 12 weeks of treatment with 5 mg tadalafil compared with pla-

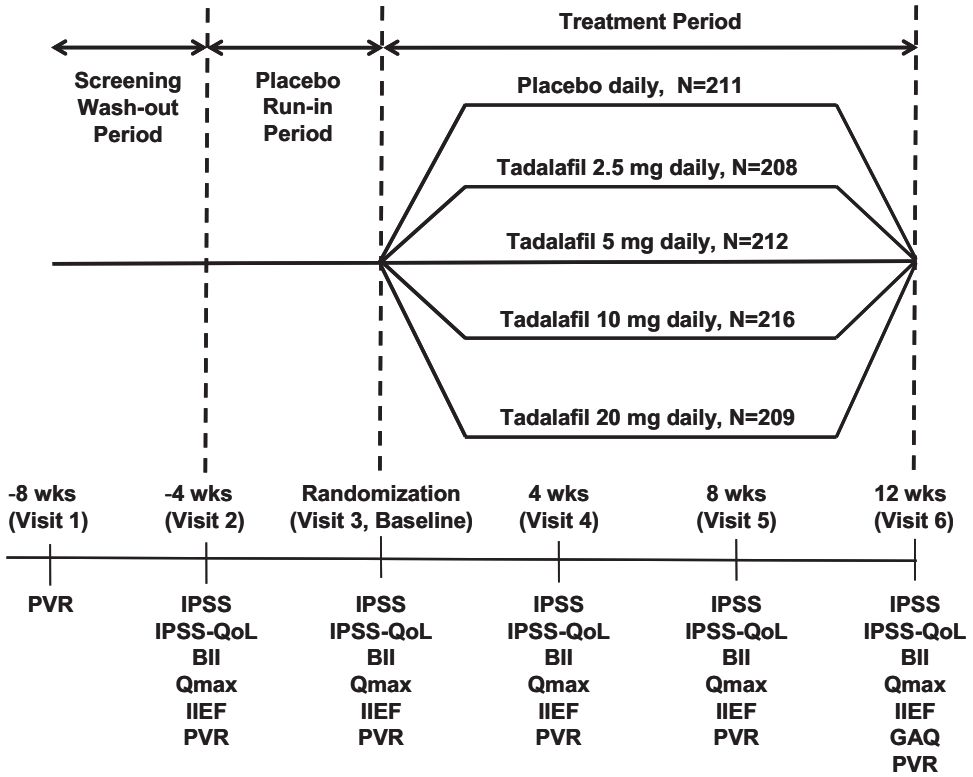

FIG. 1. Study design with schedule of events