Effects of Tadalafil Once Daily on Maximum Urinary Flow Rate in Men with Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia

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Purpose: Tadalafil significantly improves lower urinary tract symptoms suggestive of benign prostatic hyperplasia. We post hoc characterized changes in the maximum urinary flow rate using integrated data from 4 international, placebo controlled studies of tadalafil once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia.

Materials and Methods: After a 4-week placebo lead-in period 1,500 men were randomized to tadalafil 5 mg or placebo for 12 weeks. Data were analyzed using ANCOVA. Maximum urinary flow rate values were rank transformed for analysis.

Results: Baseline maximum urinary flow rate data were available on 1,371 men with a mean age of 63.1 years and end point data were available on 1,197. Tadalafil 5 mg significantly increased maximum urinary flow vs placebo (median 1.1 vs 0.4 ml per second, $p = 0.003$). At a baseline voided volume of 125 to less than 250 ml the median change in the maximum urinary flow rate was 0.9 and 1.2 ml per second ($p = 0.142$) in 731 patients, at a baseline of 250 to 450 ml the change was −0.3 and 0.7 ml per second ($p = 0.011$) in 428, and at a baseline of greater than 450 ml the change was −0.2 and 2.0 ml per second ($p = 0.186$) in 38 for placebo and tadalafil, respectively. The difference was 0.3, 1.0 and 2.2 ml per second, respectively. At a baseline maximum urinary flow rate of greater than 15 ml per second in 128 patients the median flow rate change was −2.1 and −0.8 ml per second ($p = 0.246$), at a maximum of 10 to 15 ml per second in 522 the change was 0.2 and 0.8 ml per second ($p = 0.044$), and at a maximum of less than 10 ml per second in 547 the change was 1.2 and 1.8 ml per second ($p = 0.189$) for placebo and tadalafil, respectively. Tadalafil improved I-PSS (International Prostate Symptom Score) voiding subscores significantly vs placebo across all baseline maximum urinary flow subgroups (each $p < 0.001$).

Conclusions: This integrated analysis revealed a small but statistically significant median maximum urinary flow rate improvement for tadalafil vs placebo. The numerical difference in the maximum urinary flow change from baseline between tadalafil and placebo increased with increased voided volume.

Key Words: prostate, prostatic hyperplasia, lower urinary tract symptoms, tadalafil, drug evaluation

Abbreviations and Acronyms

5ARI = 5α-reductase inhibitor

BOO = bladder outlet obstruction

BOOI = BOO index

BPH = benign prostatic hyperplasia

BPO = benign prostatic obstruction

LUTS = lower urinary tract symptoms

LUTS/BPH = LUTS suggestive of BPH

Q_{max} = maximum urinary flow rate

Vvoid = voided volume

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BENIGN prostatic hyperplasia is a histological diagnosis characterized by smooth muscle and epithelial cell proliferation in the prostate transition zone, leading to nonmalignant prostate enlargement.[1,2] Although prostate enlargement due to BPH has long been associated with LUTS, it is widely recognized that it is not the exclusive cause.[2] Some men with LUTS may not have BPH and some with BPH may not have LUTS. Some LUTS may be attributable to benign prostatic enlargement, a clinical diagnosis made on digital rectal examination and/or transrectal ultrasound. Also, BPO may be diagnosed if evidence of BOO is shown by pressure flow studies or it may be suspected in men with Q_{max} less than 15 ml per second, indicating BOO secondary to benign prostatic enlargement.[3] However, the specificity of free uroflowmetry results for determining BOO is limited because detrusor pressure is also a major contributing factor to Q_{max}.[4,5]

BPO may be reduced surgically or possibly by 5ARI treatment. The latter typically results in a moderate but often statistically significant improvement in Q_{max}. Whether this directly translates into a significant decrease in LUTS is under debate since it is generally recognized that there is poor correlation between symptoms and Q_{max}.[2,6] In addition, the association between changes in symptoms and changes in Q_{max} has not been adequately studied.

Approved pharmacological treatments for LUTS/BPH have long included α_1-blockers and 5ARIs.[2,6] Improvement in LUTS/BPH using these therapies may be early (α_1-blockers within weeks and Q_{max} improvements within hours[2,7]) or delayed (5ARIs after several months[2]). Improvements in Q_{max} are moderate compared to those after surgical intervention but they are still statistically significant.

Tadalafil, a long-acting phosphodiesterase type 5 inhibitor, is an efficacious treatment of erectile dysfunction that is now widely approved for once daily use in men with signs and symptoms of LUTS/BPH, and in men with coexisting erectile dysfunction and LUTS/BPH. Clinical trials have consistently demonstrated that tadalafil provides a statistically and clinically meaningful improvement in LUTS/BPH, including in storage (irritative) and voiding (obstructive) symptoms. However, mean Q_{max} changes have typically been small and improvements with tadalafil 5 mg vs placebo were statistically significant in only 1 of 4 registered studies.[8–12]

In this post hoc integrated analysis of data from 4 international pivotal studies we assessed the effect of tadalafil 5 mg once daily compared to placebo on Q_{max} in a larger sample of men with LUTS/BPH. We also performed subgroup analysis.

MATERIALS AND METHODS

Study Design and Participants

Analysis was based on integrated data from the 4 tadalafil registered clinical studies, which had similar designs.[9–12] After a 4-week placebo lead-in period men 45 years old or younger were randomized to tadalafil 5 mg or placebo once daily for 12 weeks. In some studies additional treatment arms included tadalafil 2.5, 10 or 20 mg, or tamsulosin 0.4 mg. We did not include those arms in analysis since tamsulosin was included in only 1 study and tadalafil 5 mg once daily is the recommended dose for LUTS/BPH. All studies used multinational, randomized, double-blind, placebo controlled, parallel group designs and were reported previously.[9–12]

In each study screening was followed by a 4-week LUTS/BPH treatment washout period, which ended at visit 2. At that visit patient demographics were assessed. To continue in the study participants were required to have an I-PSS of 13 or greater and an investigator read Q_{max} of 4 ml per second or greater to 15 or less with a Vvoid of 125 ml or greater. After visit 2 there were the placebo lead-in period, baseline/randomization visit (visit 3) and 12-week treatment period. Baseline values of Q_{max} and efficacy measures were established at visit 3. At that time the men were not required to again meet the visit 2 I-PSS or Q_{max} requirements.

In the current analysis we examined changes from baseline (visit 3) to end point (12 weeks or the last measurement on treatment). Q_{max} was assessed as a safety parameter in 3 studies and as an efficacy parameter in 1.[9–12] All studies were done in compliance with the Helsinki Declaration.

Measures

Uroflowmetry was performed using standard calibrated uroflowmetry devices. Valid Q_{max} measurements required a prevoid total bladder volume on ultrasound of 150 ml or greater to 550 or less and a Vvoid of 125 ml or greater. For analysis we used uroflowmetry values from the baseline and end point visits. In 3 studies these values were interpreted by a blinded central reader who used the 2-second rule, ie to be valid Q_{max} had to be maintained for 2 seconds or longer.[9,11,12] Central reading was not done in 1 study.[10] The change in Q_{max} from baseline to end point was a secondary objective in all studies.

Total I-PSS and the I-PSS voiding subscore (questions 1, 3, 5 and 6) were assessed.[13] In each study the change in total I-PSS from baseline to end point was a primary objective and the change in the I-PSS voiding subscore was a secondary objective.[9–12] Other symptom scores and adverse events were reported previously.

Statistical Analysis

Baseline characteristics were summarized by treatment group for the analysis population of all patients who had valid baseline Q_{max} data available. Post hoc comparisons were made via the t-test for continuous variables and the chi-square test for categorical variables. Before analysis the distributional properties of the change in Q_{max} were examined and discovered to be significantly nonnormal and skewed. As such, Q_{max} changes were assessed based on rank transformed values and data were characterized