Urodynamic Effects of Once Daily Tadalafil in Men With Lower Urinary Tract Symptoms Secondary to Clinical Benign Prostatic Hyperplasia: A Randomized, Placebo Controlled 12-Week Clinical Trial

Roger Dmochowski,*,† Claus Roehrborn,‡ Suzanne Klise,‡ Lei Xu,‡ Jed Kaminetsky† and Stephen Kraus§

From the Department of Urology, Vanderbilt University, Nashville, Tennessee (RD), the Department of Urology, UT Southwestern Medical School, Dallas (CR), Department of Urology, University of Texas Health Science Center at San Antonio, San Antonio (SK), Texas, Eli Lilly and Company, Lilly Research Laboratories, Indianapolis, Indiana (SK, LX), and New York University, New York, New York (JK)

Purpose: We explored the impact of once daily tadalafil on urodynamic measures in men with lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia via invasive and noninvasive urodynamic studies.

Materials and Methods: We conducted a multicenter, randomized, double blind, placebo controlled clinical trial comparing once daily tadalafil 20 mg vs placebo during 12 weeks in men with lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia with or without bladder outlet obstruction. Invasive and noninvasive urodynamics, International Prostate Symptom Score and general safety were assessed. The primary study end point was change in detrusor pressure at maximum urinary flow rate.

Results: Urodynamic measures remained largely unchanged during the study with no statistically significant or clinically adverse difference between tadalafil and placebo in change in detrusor pressure at maximum urinary flow rate (mean difference between treatments -2.2 cm H_2O, $p = 0.33$) or any other urodynamic parameter assessed including maximum urinary flow rate, maximum detrusor pressure, bladder outlet obstruction index or bladder capacity (all measures $p \geq 0.13$). Treatment with tadalafil resulted in significant improvements in International Prostate Symptom Score (mean difference between treatments -4.2, $p < 0.001$). Tadalafil was generally well tolerated with the majority of adverse events being mild to moderate in severity and few patients discontinuing due to adverse events (tadalafil 2.0%, placebo 1.0%).

Conclusions: Treatment with tadalafil once daily for lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia showed no negative impact on bladder function as measured by detrusor pressure at maximum urinary flow rate or on any other urodynamic parameter assessed. Nonetheless men receiving tadalafil reported significant improvements in International Prostate Symptom Score with an adverse events profile similar to other recent studies of tadalafil for lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia.

Key Words: prostatic hyperplasia, phosphodiesterase inhibitors, urodynamics, urinary bladder neck obstruction

Abbreviations and Acronyms

BOOI = bladder outlet obstruction index

BPH = benign prostatic hyperplasia

BPH-LUTS = LUTS secondary to clinical BPH

ED = erectile dysfunction

I-PSS = International Prostate Symptom Score

LUTS = lower urinary tract symptoms

PDE5 = phosphodiesterase type 5

$p_{detQmax}$ = detrusor pressure at maximum urinary flow rate

PFS = pressure flow studies

PSA = prostate specific antigen

PVR = post-void residual

PVR_{cath} = PVR measured via catheter

Qave = mean urinary flow rate

Qmax = maximum urinary flow rate

UDS = urodynamic studies

V_{comp} = voided volume

Submitted for publication June 10, 2009.

Study received institutional review board approval.

* Correspondence: A1302 Medical Center North, Nashville, Tennessee 37232 (telephone: 615-343-5602; FAX: 615-322-8990; e-mail: roger.dmochowski@Vanderbilt.Edu).

† Financial interest and/or other relationship with Allergan, Astellas, Lilly, Novartis, Pfizer and Watson.

‡ Financial interest and/or other relationship with Eli Lilly.

§ Financial interest and/or other relationship with Pfizer and Laborie Medical Technologies.

0022-5347/13/1891-0135/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2012.11.025
Vol. 189, S135-S140, January 2013
Printed in U.S.A.

Please cite this article as J Urol 2013;189: S135-S140. DOI: http://dx.doi.org/10.1016/j.juro.2012.11.025

Men with BPH may experience LUTS, which include increased urinary frequency, urgency, nocturia, intermittency, straining, incomplete emptying and weak urinary stream, commonly classified as irritative or obstructive symptoms. The incidence of LUTS secondary to clinical BPH increases with aging and is often a comorbid condition in men with ED. Medical therapies currently available for the treatment of BPH-LUTS, such as α1-adrenergic blockers and/or 5α-reductase inhibitors, have proven effective. However, side effects associated with these therapies including dizziness, hypotension and sexual dysfunction may prompt some men to avoid or discontinue treatment.

Given the multiple pathways by which nitric oxide influences and mediates male prostatic and urinary function, and the frequent comorbid presentation of BPH and ED, there has been substantial interest in the potential of PDE5 inhibitors as treatments for LUTS. Prior studies of daily treatment with tadalafil and other PDE5 inhibitors for BPH-LUTS have demonstrated significant improvements in LUTS as assessed by I-PSS compared to placebo.[1–4] However, in contrast to currently approved therapies for BPH-LUTS, those improvements were not associated with statistically significant increases in Qmax. While the mechanisms by which PDE5 inhibitors act to reduce LUTS in men with clinical BPH are still not well understood, PDE5 inhibition has been shown to cause the relaxation of human prostatic and bladder smooth muscle in vitro,[5] as well as relaxation of the bladder neck and decreased detrusor muscle overactivity in animal[6] and human studies.[7] Taken with the improvements seen in I-PSS without corresponding increases in flow rates, this potential impact on detrusor activity raises the theoretical possibility that improvements in LUTS with daily PDE5 inhibitor treatment could be associated with impaired bladder function, which might result in adverse long-term consequences.

Limited invasive urodynamic data exist for current and investigational BPH therapies, with most studies conducted in a relatively small number of men. We assessed the impact of tadalafil treatment (20 mg once daily) compared to placebo on $p_{detQmax}$, as well as on several other invasive and noninvasive urodynamic parameters in a large number of men with BPH-LUTS with or without bladder outlet obstruction at baseline. In particular this study was designed to provide evidence to contradict the notion that improvements in I-PSS following tadalafil treatment for BPH-LUTS might be related to impaired bladder function.

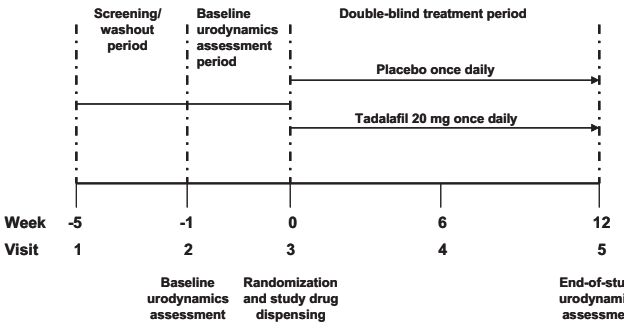
MATERIALS AND METHODS

Study Design and Participants

This study was a randomized, double blind, placebo controlled clinical trial performed at 20 centers in the United States and Canada. Men at least 40 years old with a greater than 6-month history of BPH-LUTS (with or without bladder outlet obstruction) and an I-PSS of 13 or more at the screening visit were eligible for enrollment unless PSA was greater than 10 ng/ml (men with PSA 4 to 10 ng/ml were eligible only with evidence of a prostate biopsy negative for malignancy within 12 months or stable PSA since the prior biopsy), or PVR was 350 ml or greater at the screening visit. A 4-week washout period was required for men reporting the use of other BPH or ED therapies.

Men were excluded from the study if they met any of the criteria such as 5α-reductase inhibitor use within the previous 4 months; a history of penile or pelvic surgery or radiotherapy; lower urinary tract malignancy, trauma or recent instrumentation; urinary retention or bladder stones; urethral obstruction due to stricture, valves, sclerosis or tumor; bladder calculi; atonic, decompensated or hypocontractile bladder; detrusor-sphincter dyssynergia; intravesical obstruction; 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 inducer; or uncontrolled diabetes (glycosylated hemoglobin greater than 9%).

All patients underwent baseline UDS approximately 1 week before randomization to placebo or 20 mg tadalafil once daily for 12 weeks. End of study UDS were performed on completion of the treatment period or early study discontinuation (fig. 1). The clinical trial was performed in accordance with the Declaration of Helsinki and all applicable local regulations. The institutional review boards for each site approved the study and all men provided written informed consent before undergoing any trial procedure or intervention.



Note: The duration of study periods may have varied depending on whether or not a subject required a wash out period or a repeat urodynamics assessment.

Figure 1. Study design