Efficacy and Safety of the Coadministration of Tadalafil Once Daily with Finasteride for 6 Months in Men with Lower Urinary Tract Symptoms and Prostatic Enlargement Secondary to Benign Prostatic Hyperplasia

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Purpose: Medical treatment for men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia is 5α-reductase inhibitor monotherapy or coadministration with an α-blocker. We assessed the effects of tadalafil 5 mg coadministered with finasteride 5 mg during 26 weeks on lower urinary tract symptoms and sexual symptoms.

Materials and Methods: In an international, randomized, double-blind, parallel study of men 45 years old or older who were 5α-reductase inhibitor naïve and had an I-PSS (International Prostate Symptom Score) of 13 or greater and prostate volume 30 ml or greater, 350 were treated with placebo/finasteride and 345 received tadalafil/finasteride for 26 weeks. Changes in lower urinary tract symptoms secondary to benign prostatic hyperplasia were assessed with the I-PSS, erectile dysfunction improvements were assessed with the IIEF-EF (International Index of Erectile Function-Erectile Function) in sexually active men and safety was assessed by evaluating adverse events.

Results: Least squares mean changes from baseline in I-PSS after 4, 12 and 26 weeks of tadalafil/finasteride coadministration were −4.0, −5.2 and −5.5, respectively. Corresponding values for placebo/finasteride coadministration were −2.3, −3.8 and −4.5 ($p \leq 0.022$ at all visits favoring tadalafil/finasteride coadministration). I-PSS subscores (storage and voiding) and quality of life index were also numerically improved with tadalafil/finasteride coadministration. Least squares mean changes from baseline in IIEF-EF with tadalafil/finasteride coadministration were 3.7 after 4 weeks, and 4.7 after 12 and 26 weeks. Corresponding values for placebo/finasteride coadministration were −1.1, 0.6 and −0.0 ($p < 0.001$ at all visits favoring tadalafil/finasteride coadministration). Tadalafil/finasteride coadministration was well tolerated and most adverse events were mild/moderate.

Abbreviations and Acronyms

5-ARI = 5α-reductase inhibitor
AE = adverse event
BPH = benign prostatic hyperplasia
BPH-LUTS = lower urinary tract symptoms secondary to benign prostatic hyperplasia
ED = erectile dysfunction
LS = least squares
LSTD = least squares treatment difference
LUTS = lower urinary tract symptoms
PBO/FIN = placebo/finasteride coadministration
PDE5I = phosphodiesterase type 5 inhibitor
PE = prostate enlargement
Q_{max} = peak urinary flow rate
QoL = quality of life
SAE = serious adverse event
TAD/FIN = tadalafil/finasteride coadministration
TEAE = treatment emergent adverse event

Accepted for publication September 4, 2013.
Study received institutional review board approval.
* Financial interest and/or other relationship with Eli Lilly.
† Nothing to disclose.
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Editor's Note: This article is the fourth of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 878 and 879.

0022-5347/14/1913-0727/0
THE JOURNAL OF UROLOGY®
© 2014 by American Urological Association Education and Research, Inc.
http://dx.doi.org/10.1016/j.juro.2013.09.059
Vol. 191, 727-733, March 2014
Printed in U.S.A.

Conclusions: The coadministration of tadalafil/finasteride provides early improvement in lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement. Tadalafil/finasteride coadministration also improves erectile function in men who have comorbid erectile dysfunction.

Key Words: prostatic hyperplasia, erectile dysfunction, finasteride, lower urinary tract symptoms, tadalafil

PROSTATE gland enlargement secondary to benign prostatic hyperplasia may result in LUTS, including storage symptoms (increased frequency/urgency, incontinence) and voiding symptoms (slow/intermittent urine stream, straining).[1–3] Moderate to severe LUTS secondary to BPH is estimated to affect 10% to 25% of the current worldwide male population (approximately 900 million men)[4–6] and it is estimated that approximately 1.1 billion men will have BPH-LUTS by the year 2018.[7]

Currently several drug modalities are recommended to treat BPH-LUTS, including α_1-adrenoceptor antagonists (α-blockers), 5-ARIs and the PDE5I tadalafil.[2,3] In men with moderate to severe LUTS and confirmed PE, 5-ARI therapy is indicated to prevent BPH progression, reduce prostate size, and reduce the risk of urinary retention and future surgery.[2] Finasteride, a 5-ARI originally approved in 1992, is effective in treating men with BPH-LUTS and PE, but significant improvement in LUTS is typically not observed before 6 to 12 months of therapy, and sexual AEs are frequently reported.[8–12] The American Urological Association and the European Association of Urology recommend coadministering an α-blocker with a 5-ARI to achieve earlier LUTS improvement.[2,3]

In recent clinical studies 5-ARI/α-blocker coadministration frequently resulted in significantly greater LUTS improvement compared to monotherapy or placebo.[9,12–15] However, most of these studies evaluated BPH and PE during several years, and only 2 (the CombAT [Combination of Avodart® and Tamsulosin] and VA-COOP [Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia] studies) examined LUTS changes during the first 6 months of coadministration.[9,14] In addition, AEs related to sexual/ejaculatory dysfunction appear to increase with 5-ARI/α-blocker coadministration.[11,15]

Alternatively, a long-acting PDE5I could be coadministered with a 5-ARI to treat BPH-LUTS and PE. Tadalafil, with its half-life of 17.5 hours, is currently the only PDE5I for daily use that is indicated to treat men with ED, the signs and symptoms of BPH, and men with both disorders.[16] Clinical studies of men with BPH-LUTS have demonstrated that tadalafil 5 mg once daily leads to statistically significant improvements in I-PSS total scores as early as 1 to 2 weeks after beginning therapy.[16–18] However, until now, to our knowledge no placebo controlled studies have been performed on the coadministration of tadalafil with finasteride in men with BPH-LUTS and PE. Therefore, we evaluated the efficacy and safety of tadalafil 5 mg once daily coadministered with finasteride 5 mg for 26 weeks compared to placebo coadministered with finasteride 5 mg in men with BPH-LUTS and PE.

MATERIALS AND METHODS

This study was an international, randomized, double-blind, parallel design trial of men with BPH-LUTS and PE that was conducted from November 2010 to September 2012 (fig. 1). The study was performed in accordance with the Declaration of Helsinki and all applicable regulations. Institutional review boards at each site approved the study and all participants provided written informed consent before undergoing any study procedure. Eligible patients included men 45 years old or older with BPH-LUTS for more than 6 months. Patients also had a prostate volume of 30 ml or greater (confirmed via transrectal ultrasound), I-PSS total score 13 or greater and Q_{max} 4 to 15 ml per second, and were naïve to 5-ARI therapy. An interactive voice response system was used to allocate patients to treatment groups. Randomization was stratified by baseline LUTS severity (I-PSS less than 20 vs 20 or greater), ED history and region (United States/Canada vs Latin America/Europe). Patients were randomized in a 1:1 ratio to receive TAD/FIN or PBO/FIN for 26 weeks. Post-baseline study visits/assessments were conducted at weeks 4, 12 and 26 (or end point).

In this study the primary objective was to assess whether TAD/FIN once daily for 12 weeks was superior

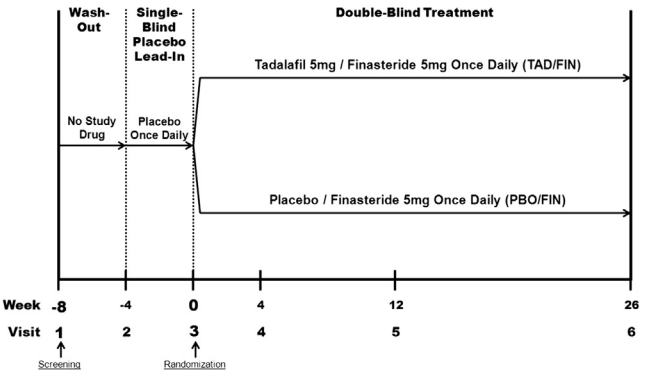

Figure 1. Study design

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