Direct Effects of Tadalafil on Lower Urinary Tract Symptoms versus Indirect Effects Mediated through Erectile Dysfunction Symptom Improvement: Integrated Data Analyses from 4 Placebo Controlled Clinical Studies

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Purpose: Tadalafil has regulatory approval for the treatment of men with signs/symptoms of benign prostatic hyperplasia with and without erectile dysfunction. We assessed whether the effects of treatment with tadalafil for lower urinary tract symptoms/benign prostatic hyperplasia are independent of improvements in erectile dysfunction.

Materials and Methods: Four separate analyses used integrated data from 4 randomized, double-blind, placebo controlled studies in men with lower urinary tract symptoms/benign prostatic hyperplasia with and without erectile dysfunction to test whether total I-PSS (International Prostate Symptom Score) improvement was due to improvement in IIEF-EF (International Index of Erectile Function-Erectile Function domain score). Unidirectional and bidirectional path analysis models determined direct and indirect treatment effects mediated by improvements in lower urinary tract symptoms/benign prostatic hyperplasia and erectile dysfunction symptoms.

Results: A total of 1,496 men, of whom 77% had erectile dysfunction, received at least 1 dose of tadalafil 5 mg once daily or placebo. The placebo adjusted treatment effect for men with erectile dysfunction was represented by a mean decrease of −2.3 ($p < 0.0001$) in total I-PSS vs −2.2 ($p = 0.0007$) for men without erectile dysfunction. The correlation between change from baseline in total I-PSS and IIEF-EF was weak ($r^2 = 0.08$, $p < 0.0001$). The unidirectional path analysis model suggested that the total treatment effect on total I-PSS score improvement (2.25) was derived from a direct treatment effect of 1.57 (70%, $p < 0.001$) and an indirect treatment effect of 0.67 (30% via IIEF-EF improvement, $p < 0.001$). Bidirectional path analysis showed that total I-PSS improvement was largely attributed to direct (92.5%, $p < 0.001$) vs indirect (7.5%, $p = 0.32$) treatment effects via IIEF-EF improvement.

Conclusions: Regardless of the analytical approach, self-reported erectile dysfunction status did not appreciably influence tadalafil treatment response in men with lower urinary tract symptoms/benign prostatic hyperplasia, supporting the dual action of tadalafil on lower urinary tract symptoms/benign prostatic hyperplasia and erectile dysfunction.

Key Words: prostatic hyperplasia, erectile dysfunction, phosphodiesterase 5 inhibitors, tadalafil

Abbreviations and Acronyms

BPH = benign prostatic hyperplasia

ED = erectile dysfunction

LUTS = lower urinary tract symptoms

PDE5 = phosphodiesterase type 5

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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 564 and 565.

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BENIGN prostatic hyperplasia suggestive of lower urinary tract symptoms and erectile dysfunction are chronic comorbid conditions that share a common epidemiological association.[1–3] There is a strong interconnection between the conditions in that men with LUTS suggestive of BPH are more likely to experience ED, the severity of LUTS corresponds to the severity of ED and increasing severity of either condition is associated with a decreased quality of life.[3] While it is widely recognized that BPH is not the exclusive cause of LUTS and clinical drug trials often enroll men based in part on a clinical diagnosis of nonneurogenic LUTS suggestive of BPH (LUTS/BPH), the term has been considered meaningful to clinicians.[4]

Tadalafil, a selective cyclic guanosine monophosphate specific PDE5 inhibitor, was approved by the FDA (Food and Drug Administration) in 2003 for on demand use for ED (10 to 20 mg), in 2008 for once daily use for ED (2.5 to 5.0 mg) and in 2011 for once daily use for BPH (5 mg).[5] Improvement in LUTS/BPH with tadalafil was evident from 4 pivotal randomized, double-blind, placebo controlled studies[6–9] reporting a significantly greater mean change from baseline to week 12 in total I-PSS (primary end point) vs placebo, which was maintained during a 1-year period.[10] One study that specifically enrolled men with concomitant ED and LUTS demonstrated that tadalafil was effective for both conditions.[7]

Although studies with tadalafil have shown significant improvement in LUTS/BPH,[6–9] it is prudent to assess the potential mediating role that an erectogenic effect may have given that patients with coexisting ED also derive improvement in erectile function from tadalafil. This study focuses on the perception that improvement in the signs and symptoms of LUTS/BPH is due to indirect effects (eg psychological benefits of improved erectile function in men with both conditions). In this study we tested the hypothesis that the impact of tadalafil on LUTS/BPH improvement is mediated through ED changes in men with both conditions.

PATIENTS AND METHODS

Four analyses were performed using integrated data from 4 randomized, double-blind, placebo controlled studies in men with LUTS/BPH with or without concomitant ED. Each analysis tested whether total I-PSS improvement with tadalafil was due to improvement in IIEF-EF. Path analysis modeling, a set of mathematical equations that assess whether one event influences another,[11] has been used to explore associations in other disease states.[12,13]

Two path analysis models explored the relationship between LUTS/BPH and ED (ie is improvement of one condition a mediator for treatment effect on the other?). 1) Treatment has a direct effect on LUTS/BPH improvement and an indirect effect through improvement of ED (unidirectional model). 2) Treatment has a direct effect on LUTS/BPH improvement after accounting for an indirect effect through improvement of ED, and a direct effect on ED improvement after accounting for an indirect effect through improvement of BPH (bidirectional model).

Patient Population and Treatment

Each of 4 studies conducted between August 2006 and December 2011 investigated the efficacy and safety of once daily tadalafil for up to 12 weeks.[6–9] All studies were registered at clinicaltrials.gov as NCT00384930, NCT00827242, NCT00855582 and NCT00970632.

A total of 1,496 men were enrolled and received at least 1 dose of tadalafil 5 mg once daily or placebo. In 3 of 4 LUTS/BPH studies ED was not an inclusion criterion.[6,8,9] For these 3 studies the mean change from baseline in total I-PSS was the primary efficacy measure and the mean change from baseline in IIEF-EF domain score was a secondary efficacy measure. A fourth study required that all men have LUTS/BPH and ED (history and clinical diagnosis), and were sexually active.[7] Total I-PSS and IIEF-EF domain scores were co-primary end points. Complete descriptions of entry criteria were previously published.[6–9]

These studies were conducted in accordance with ethical principles originating in the Declaration of Helsinki. The institutional review board at each site approved the study and all men provided written informed consent.

Hypotheses

If BPH symptom response is not direct and largely dependent on the tadalafil treatment effect on ED, several observations would be expected. 1) Men without ED would have little to no improvement in LUTS/BPH and would demonstrate a strong subgroup effect of ED comorbidity. 2) A dominant (eg greater than 50%) indirect treatment effect on LUTS/BPH (mediated through improvement in erectile function as measured by IIEF-EF) would be observed. 3) A strong correlation between changes in IIEF-EF and total I-PSS would be observed (ie changes in IIEF-EF would increase as I-PSS decreases). This integrated analysis plan was predicated on rejecting a hypothesis that the tadalafil treatment effect on LUTS/BPH is mediated primarily through improvement in IIEF-EF.

Analyses

Efficacy analyses were performed on an intent to treat basis. Baseline was defined as the start of the double-blind treatment period. Efficacy end points were defined as data collected at week 12 of the double-blind period or the last nonmissing post-baseline data. Analyses that involved IIEF-EF were performed in a subset of sexually active men (with a female partner).

Subgroup efficacy analyses were conducted using ANCOVA models to compare treatment effects with once daily tadalafil or placebo in men with only LUTS/BPH and in men with LUTS/BPH with ED.

Pearson's correlation coefficient was calculated to examine relationships between changes in total I-PSS and IIEF-EF domain score. Correlations of medium or strong