Change in Sexual Function in Men with Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia Associated with Long-Term Treatment with Doxazosin, Finasteride and Combined Therapy

Chyng-Wen Fwu,*,† Paul W. Eggers,‡ Ziya Kirkali,‡ Kevin T. McVary,§ Pamela K. Burrows and John W. Kusek‡

From Social & Scientific Systems, Inc. (CWF), Silver Spring and Division of Kidney, Urologic and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (PWE, ZK, JWK), Bethesda and George Washington University Biostatistics Center (PKB), Rockville, Maryland, and Division of Urology, Southern Illinois University School of Medicine (KTM), Springfield, Illinois

Abbreviations and Acronyms

5ARI = 5α-reductase inhibitor

AB = α-adrenergic receptor blocker

BMSFI = Brief Male Sexual Function Inventory

BPH = benign prostatic hyperplasia

LUTS = lower urinary tract symptoms

MTOPS = Medical Therapy of Prostatic Symptoms

RCT = randomized clinical trial

Accepted for publication December 6, 2013.

Study received institutional review board approval.

Supported by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Contract HHSN 276201200161U (CWF) and NIDDK (MTOPS).

This manuscript was not prepared in collaboration with MTOPS study investigators and does not necessarily reflect the opinions or views of the MTOPS study, NIDDK Central Repositories or NIDDK.

* Correspondence: Social & Scientific Systems, Inc., 8757 Georgia Ave., 12th floor, Silver Spring, Maryland 20910 (telephone: 301-628-0342; FAX: 301-628-0301; e-mail: cfwu@s-3.com).

† Financial interest and/or other relationship with Social & Scientific Systems.

‡ Financial interest and/or other relationship with National Institute of Diabetes and Digestive and Kidney Diseases.

§ Financial interest and/or other relationship with Allergan, Lilly/ICOS, Nxthera, Watson Pharmaceuticals, Neotract, NIDDK and GlaxoSmithKline.

Purpose: We examined the effects of doxazosin, finasteride and combined therapy in men with lower urinary tract symptoms associated with benign prostatic hyperplasia on sexual function, as assessed by the Brief Male Sexual Function Inventory during 4 years.

Materials and Methods: The MTOPS (Medical Therapy of Prostatic Symptoms) study was a multicenter, randomized, double-blind, placebo controlled clinical trial with a primary outcome of time to benign prostatic hyperplasia progression. Change in sexual function was a secondary outcome. We analyzed the records of 2,783 men enrolled in the study who completed the inventory at baseline and at least once during followup.

Results: In men enrolled in MTOPS sexual function decreased with time. Men assigned to finasteride and combined therapy experienced overall statistically significant but slight worsening of ejaculatory function compared with men on placebo. Men assigned to combined therapy also experienced significant worsening in erectile function and sexual problem assessment. There was no significant difference in changes in any inventory domain in men assigned to doxazosin alone compared to placebo.

Conclusions: This study significantly extends understanding of the effects of long-term treatment with these drugs on sexual function in men with lower urinary tract symptoms associated with benign prostatic hyperplasia. Treatment with finasteride or combined therapy was associated with worsening sexual function while treatment with doxazosin alone was associated with minimal negative impact, if any. Physicians should discuss with their patients the possible long-term effects of these drugs for lower urinary tract symptoms associated with benign prostatic hyperplasia on sexual function.

Key Words: prostate; lower urinary tract symptoms; sexual dysfunction, physiological; doxazosin; finasteride

LOWER urinary tract symptoms associated with BPH are common and adversely affect quality of life.[1] Men with LUTS/BPH also frequently experience sexual dysfunction,[2–5] suggesting that 1 complaint should prompt screening for the other. Since these men are often treated for an

0022-5347/14/1916-1828/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2013.12.014
Vol. 191, 1828-1834, June 2014
Printed in U.S.A.

extended period with 5ARIs and/or ABs, it is important to consider long-term effects on sexual function. Of particular concern are side effects from 5ARIs since prior studies suggest a negative impact on sexual function using this drug class.[6,7] However, current understanding of the impact of 5ARIs and ABs on sexual function in men with LUTS/BPH comes from adverse event reporting in short-term RCTs,[8,9] registries[10] or real life practice.[11,12] More comprehensive assessment is lacking of sexual function in men associated with long-term treatment with these drugs using validated instruments.

We report the effects of treatment with finasteride, doxazosin and the 2 drugs combined on sexual function assessed by the BMSFI in men enrolled in the MTOPS study, a long-term RCT of BPH progression.

MATERIALS AND METHODS

Study Design

The design and primary results of the MTOPS study were published previously.[13–15] Men at least 50 years old with an AUA symptom index score of between 8 and 30, a maximal urinary flow rate of between 4 and 15 ml per second and a voided volume of at least 125 ml were eligible for study. Men were equally randomized to placebo, 8 mg doxazosin (4 mg if not tolerated), 5 mg finasteride or the 2 drugs combined. The study was double-blind. Sexual function, a secondary outcome of the study, was assessed by the BMSFI at baseline and annually thereafter for at least 4 years. Men who completed the BMSFI at baseline and at least once during followup were included in this report. The proportion of men in each active drug group who had discontinued the assigned drug at year 4 was similar (data not shown).

Sexual Function Measures

The BMSFI is an 11-item, validated, self-administered questionnaire to assess functional aspects of male sexuality (10 questions) and overall sexual satisfaction (1 question) within the last 30 days.[16] The range of possible scores on each item is 0 to 4 with higher score indicating better sexual function. The score on each domain is the total of scores on the individual items in the domains of sexual drive (2 items, score range 0 to 8), erectile function (3 items, 0 to 12), ejaculatory function (2 items, 0 to 8), sexual problem assessment related to sexual drive, erection and ejaculation (3 items, 0 to 12) and overall sexual satisfaction (1 item, 0 to 4).

Statistical Analysis

Statistical analysis was done according to randomized treatment group (intent to treat). Characteristics at baseline were categorized by group assignment. Means of continuous variables and percent distributions of categorical variables were calculated.

We analyzed change in BMSFI as a continuous and a categorical variable. Primarily changes from baseline during 4 years in each BMSFI domain were assessed between the active groups and the placebo group using linear regression models with generalized estimating equations.[17] To account for correlation among repeated measures in a participant we specified the unstructured covariance structure (most general form) as the within subject correlations. Separate models were fit for each BMSFI domain for each comparison (doxazosin vs placebo, finasteride vs placebo and combined therapy vs placebo). Indicators for drug group, visit year (year 0 to 4 as a categorical variable) and interaction terms between the drug group and each followup year were included in these models. Followup years (visit years 1 to 4) were compared with baseline (visit year 0). The interaction terms tested differences between the drug groups and the placebo group in the change from baseline. An overall test of interactions was performed.

Differences in mean changes from baseline to each followup year between the groups were assessed using the nonparametric Wilcoxon rank sum test. The magnitude of the difference in change was assessed by the Cohen d,[18] which is the difference between the mean change in each group and the mean change in the placebo group divided by the pooled SD of the 2 groups at baseline. A zero value of Cohen d indicates no effect and values between 0.2 and 0.5 represent small effects.[18]

For categorical analysis we used previously described BMSFI cutoff points as sexual dysfunction.[19,20] Men were considered to have low libido if the sexual drive domain was 2 or less, erectile dysfunction if the erectile function domain was 3 or less, ejaculatory dysfunction if the ejaculatory function domain was 2 or less, perceived sexual problems if the problem assessment domain was 3 or less and low sexual satisfaction if the sexual satisfaction domain was 1 or less. Men were considered to have worse sexual function if baseline values decreased below the cutoff points noted during followup years 1 and 4, that is worse sexual drive with the sexual drive domain score greater than 2 at baseline but 2 or less at followup, worse erectile function with the erectile domain score greater than 3 at baseline but 3 or less at followup, worse ejaculatory function with the ejaculatory domain score greater than 2 at baseline but 2 or less at followup, worse sexual problems with the problem assessment domain score greater than 3 at baseline but 3 or less at followup and worse sexual satisfaction with the sexual satisfaction domain score greater than 1 at baseline but 1 or less at followup. The drug groups and the placebo group were compared using the chi-square test.

To assess the impact of missing data during followup we performed sensitivity analysis by simple imputation methods, including the last observation carried forward and assigning 0 for each missing value. Tests of statistical significance were 2-sided with the Bonferroni adjusted criterion of $p < 0.0167$ to account for 3 comparisons. All analysis was done with SAS® for Windows®, version 9.2.

RESULTS

A total of 3,047 men were randomized, of whom 2,783 (91%) completed the BMSFI at baseline and at least once during followup. The BMSFI completion