THE JOURNAL OF
SEXUAL MEDICINE

Efficacy and Safety of Sildenafil by Age in Men With Erectile Dysfunction

Irwin Goldstein, MD,[1] Li-Jung Tseng, PhD,[2] Dana Creanga, PhD,[2] Vera Stecher, PhD,[2] and Jed C. Kaminetsky, MD[3]

ABSTRACT

Introduction: Sildenafil, an oral phosphodiesterase type 5 inhibitor, has been extensively investigated for the treatment of erectile dysfunction in randomized controlled trials.

Aim: To assess the efficacy and safety of sildenafil vs placebo according to age subgroups (<65, 65−74, and ≥75 years) in 11,364 men with erectile dysfunction using pooled data from 48 randomized, double-blinded, placebo-controlled, parallel-group, flexible-dose trials.

Methods: Most trials had a 12-week treatment duration. The starting sildenafil dose was 50 mg, taken 1 hour before sexual activity, with subsequent adjustment to 100 or 25 mg based on efficacy and safety. Men taking nitrate therapy or nitric oxide donors and men with severe cardiac failure, unstable angina, or recent stroke or myocardial infarction were excluded. Efficacy analyses included all subjects with baseline and at least one postrandomization evaluation. Safety analyses included subjects who received study medication.

Main Outcome Measures: The International Index of Erectile Function and a global assessment question ("Did the treatment improve your erections?").

Results: Mean International Index of Erectile Function scores for question 3 (frequency of penetration), question 4 (maintenance of erections after penetration), and the erectile function domain were statistically significantly improved with sildenafil vs placebo for each age subgroup; orgasmic function, intercourse satisfaction, sexual desire, and overall satisfaction domain scores also were statistically significantly improved with sildenafil vs placebo. The percentage of men reporting improved erections on the global assessment question was statistically significantly higher with sildenafil vs placebo for all age subgroups; the percentage with sildenafil tended to decrease with increasing age (<65 years, 80%; 65−74 years, 69%; ≥75 years, 59%). The most common adverse events with sildenafil were headache and flushing in each age subgroup.

Conclusion: Sildenafil is an effective and well-tolerated treatment for erectile dysfunction regardless of patient age, including men at least 75 years old.

Key Words: Erectile Dysfunction; Sildenafil; Phosphodieterase Type 5 Inhibitors; Age Groups; Elderly; Middle Age

INTRODUCTION

Erectile dysfunction (ED), defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance,[1] is a common and age-associated condition. Based on studies published in the past decade,[2−10] the overall prevalence of ED has been estimated at 18%[2] to 47%[3] in the United States and 6%[10] to 49%[9] in international studies, with prevalence rates dependent on the age of men in the sample assessed and the method used to identify ED. Based on data from the U.S. National Health and Nutrition Examination Survey, the prevalence of ED increases from 8.2% in men 40 to 49 years old to 77.5% in those at least 75 years old.[2] In addition to age, factors identified as significantly associated with ED include diabetes, obesity, smoking, cardiovascular disease, stroke, hypertension, and lower urinary tract symptoms.[2,4,8,11−14] In men 40 to 70 years old with ED, the risk of cardiovascular disease mortality is increased 43% vs men without ED.[15]

Sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, was the first in-class oral medication approved by the U.S. Food and Drug Administration in 1998 for the treatment of ED based on its efficacy and safety profiles in randomized clinical trials.[16] Other oral PDE5 inhibitors, including tadalafil, vardenafil, and avanafil, also have been approved for the treatment of ED.

The 15-item International Index of Erectile Function (IIEF) was developed and validated as a patient-reported outcome

Received October 8, 2015. Accepted February 10, 2016.

[1]San Diego Sexual Medicine, Alvarado Hospital, San Diego, CA, USA;
[2]Pfizer Inc., New York, NY, USA;
[3]University Urology Associates, New York, NY, USA

http://dx.doi.org/10.1016/j.jsxm.2016.02.166

measurement for assessing ED in clinical trials and treatment response in men with ED.[17] The six-item IIEF erectile function domain is widely accepted by regulatory agencies as a primary end point in clinical trials of ED therapies worldwide. The IIEF erectile function domain is a validated diagnostic tool that is useful for classifying ED severity and for assessing treatment response.[18] More recently, estimates of minimal clinically important differences (MCIDs) in the treatment-related change in the IIEF erectile function domain score have provided additional information on treatment response for clinicians managing men with ED.[19]

Sildenafil has been extensively evaluated in 74 double-blinded, placebo-controlled, clinical trials, with a database of efficacy and safety data from more than 16,000 men with ED. However, published data on the treatment response to sildenafil in men with ED according to patient age are limited,[20–23] especially in men at least 75 years old.

AIMS

To assess the efficacy and safety of sildenafil according to age subgroups (<65, 65–74, and ≥75 years) in men with ED using pooled data from 48 randomized, double-blinded, placebo-controlled, parallel-group, flexible-dose sildenafil trials.

METHODS

Data for 74 double-blinded, placebo-controlled sildenafil clinical trials were entered in a Pfizer clinical data repository. The main determinant of study inclusion in the present analysis was study design. Overall, 48 of the 74 trials had a similar study design (ie, double-blinded, placebo-controlled, parallel-group, flexible-dose design) and were considered for the present analysis. Forty-two of these 48 studies collected IIEF data and were used for efficacy outcomes reported in this analysis; data from all 48 studies were used for safety assessments (ie, adverse events). The age-group distribution for the two treatment groups in the six trials that did not include IIEF end points were the same as the age-group distribution for the two treatment groups in the 42 trials that included IIEF end points (ie, <65 years, 78%–80%; 65–74 years, 19%–22%; ≥75 years, 1%).

In this post hoc analysis of pooled data from 48 randomized, double-blinded, placebo-controlled, parallel-group, flexible-dose sildenafil trials, men with ED were randomized to receive sildenafil or placebo. The starting sildenafil dose was 50 mg, to be taken approximately 1 hour before sexual activity but not more than once daily, with subsequent dose adjustment to 100 or 25 mg based on efficacy and safety. Most trials included a 12-week double-blinded treatment period. Most trials enrolled men with ED of 3 to 6 months' duration and in a stable heterosexual relationship; exclusion criteria included men taking nitrate therapy or nitric oxide donors and men with severe cardiac failure, unstable angina, or recent stroke or myocardial infarction. All studies included in the analyses were conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All trial protocols were approved by appropriate local ethics committees or institutional review boards. All subjects provided written informed consent before enrollment.

For these analyses, data were pooled for the overall population (N = 11,364) and patients were stratified into three age subgroups (<65, 65–74, and ≥75 years) based on their age at study enrollment. Efficacy analyses included all men with ED who were randomized to treatment and had baseline and at least one postbaseline evaluation of the efficacy variable. Safety analyses (all-cause and treatment-related treatment-emergent adverse events) included all randomized men who received at least one dose of study medication. Efficacy variables assessed were IIEF question 3 (Q3; frequency of penetration), question 4 (Q4; maintenance of erections after penetration); the erectile function, intercourse satisfaction, orgasmic function, sexual desire, and overall satisfaction domains at baseline and end point[17]; and a global assessment question (GAQ; "Did the treatment improve your erections?"), with a patient response of yes or no at end point. Treatment-emergent adverse events and serious adverse events were monitored throughout each trial, with investigators assessing the severity and relation to study drug of each event.

For each efficacy variable, comparisons were made between the sildenafil and placebo groups for the overall population and within each age subgroup. Quantitative IIEF pooled data were analyzed using the patient-level change from baseline to end point (or termination with last-observation-carried-forward method) for sildenafil vs placebo using an analysis of covariance model, with terms for treatment, study, and baseline value (42 trials with data available for analysis). For all IIEF end points, the analysis testing for a treatment-by-age interaction demonstrated no statistically significant interaction, except for the overall satisfaction domain ($P = .025$). For the qualitative GAQ, pooled data for the percentage of men reporting improved erections at end point (or termination) for sildenafil vs placebo were analyzed using a Cochran-Mantel-Haenszel general association statistic testing for the association between treatment and GAQ response after adjusting for study (41 trials with data available for analysis). All statistical tests were two-sided with an α level of 5% and with no adjustments for multiple comparisons. Given the small number of men at least 75 years old, nonstatistical comparisons between age groups were performed in this post hoc analysis.

MAIN OUTCOME MEASURES

The main outcome measurements for treatment efficacy were patient-reported quantitative scores for IIEF Q3, Q4, erectile function domain, orgasmic function domain, sexual desire domain, intercourse satisfaction domain, and overall satisfaction domain, and the qualitative yes-or-no response to the GAQ.