ORIGINAL RESEARCH—ED PHARMACOTHERAPY

The ENDOTRIAL Study: A Spontaneous, Open-Label, Randomized, Multicenter, Crossover Study on the Efficacy of Sildenafil, Tadalafil, and Vardenafil in the Treatment of Erectile Dysfunction

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ABSTRACT

Introduction. The three effective, commercially available drugs for the treatment of erectile dysfunction—sildenafil, vardenafil, and tadalafil—inhibit the same substrate, the erectolytic enzyme phosphodiesterase type 5 (PDE5). Although there are pharmacological differences between these three compounds, few comparative studies have been conducted to date.

Aim. The aim of this study was to determine the efficacy of sildenafil, tadalafil, and vardenafil in a randomly assigned 8-week fixed regimen.

Methods. This was a spontaneous, open-label, randomized, multicenter, crossover study where the patients were randomized to receive sildenafil 50 mg, sildenafil 100 mg, tadalafil 20 mg, or vardenafil 20 mg.

Main Outcome Measures. The primary outcome included the posttreatment analysis of erectile function domains of the abridged International Index of Erectile Function (IIEF5+1). The secondary objectives included the analysis of peak-systolic velocities (PSVs), end-diastolic velocities (EDVs), and resistive index (RI), and the estimate of the percentage of men with normal penile hemodynamic parameters after each treatment.

Results. In all groups of patients taking sildenafil 50 mg, sildenafil 100 mg, tadalafil 20 mg, and vardenafil 20 mg at a frequency reflecting the common treatment regimens in real life, there was a statistically significant baseline-to-end point improvement in subjective perception of erectile function measured by IIEF5+1. When the four groups were compared, the treatments were not different in modifying IIEF5+1 and penile flow parameters. However, the within-group analysis showed that PSV improved in the sildenafil 50 mg group and that PSV together with RI

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significantly ameliorated in patients receiving 100 mg of sildenafil. Regression analysis confirmed an independent effect of sildenafil on hemodynamic efficacy parameters.

Conclusions. An overall equivalence was demonstrated in the subjective perception of treatment benefits for all the PDE5i tested. However, sildenafil, in a dose-dependent manner, was the unique PDE5i able to ameliorate some of the penile flow parameters within the 8-week treatment period. These findings should be interpreted conservatively because of the observational nature of the study. **Jannini EA, Isidori AM, Gravina GL, Aversa A, Balercia G, Bocchio M, Boscaro M, Carani C, Corona G, Fabbri A, Foresta C, Forti G, Francavilla S, Granata ARM, Maggi M, Mansani R, Palego P, Spera G, Vetri M, and Lenzi A on behalf of the Endotrial Study Group. The ENDOTRIAL study: A spontaneous, open-label, randomized, multicenter, crossover study on the efficacy of sildenafil, tadalafil, and vardenafil in the treatment of erectile dysfunction. J Sex Med 2009;6:2547–2560.**

Key Words. Sildenafil; Tadalafil; Vardenafil; Doppler; Erectile Dysfunction; PDE5

Introduction

The introduction, 10 years ago, of the first safe, effective medication (sildenafil, Viagra®, Pfizer Inc., New York, NY, USA) [1] for erectile dysfunction (ED) both increased the patient base and revolutionized health-care delivery, with sexual dysfunctions now entering the realm of not only the specialist, but also the general practitioner [2]. These advances have favored the expansion of the field through innovative basic and clinical research, and the search for new compounds.

Sildenafil, a potent inhibitor of the erectolytic enzyme phosphodiesterase type 5 inhibitor (PDE5i), whose efficacy in treating ED was serendipitously discovered in phase II angina trials, was the first compound fulfilling the major criteria for an ideal drug for ED, being reliable, with minimal side effects, and simple to use. Other PDE5i, vardenafil (Levitra®, Bayer Healthcare, Wuppertal, Germany) and tadalafil (Cialis®, Eli Lilly and Company, Indianapolis, IN, USA), have been discovered more recently. The former has a pharmacokinetic profile similar to sildenafil, with a higher affinity for PDE5, while the latter is characterized by a much longer $T^1/_2$ (17.5 hours vs. 4–5 hours) and a greater T_{max} (twice the others, at 120 minutes) [2]. For this reason, the three drugs can be classified as "short acting—short lasting" (sildenafil and vardenafil) and "late onset—long lasting" (tadalafil). These differences have an obvious clinical impact and may suggest their diversified use in selected subsets of patients (psychogenic ED, singles, couples, etc.). Pharmacodynamic differences may also suggest a varying efficacy on different sexual parameters (number of sexual acts per pill [3], hardness [4,5], hormonal effects [3], satisfaction [6,7], switching from one medication to another [8], patient's preference [5], couple's quality of life [9], etc.). However, the literature in this area is flawed: almost all studies comparing the three drugs are seriously biased by manufacturer sponsorship, and unsurprisingly, in all sponsored studies, the best drug is invariably produced by the sponsoring company.

This study compared the efficacy of randomly allocated PDE5i and the effectiveness of subsequent treatment personalization in a group of patients with ED receiving sildenafil, tadalafil, or vardenafil. The aim was to conduct a survey on drug efficacy and treatment adherence that was completely free of any industry interference. The study was also designed to exclude any conditioning by the central organization on local recruiting centers.

Materials and Methods

Methods

Study Design and Patient Recruitment

This was a spontaneous, open-label, randomized, multicenter, crossover study. The study was conducted from June 2005 to June 2007 at eight public andrology and sexual medicine centers in Italy in compliance with the Declaration of Helsinki, Guidelines for Good Clinical Practice, and applicable laws and regulations. The centers did not receive any benefit or reimbursement for enrolled patients.

Each patient gave his informed written consent, and the Institutional Review Board approved the study. The protocol consisted of a 4-week washout period, followed by three consecutive treatment phases: (i) an 8-week treatment period with a randomly assigned PDE5i, (ii) a subsequent