Hypogonadal Men Nonresponders to the PDE5 Inhibitor Tadalafil Benefit from Normalization of Testosterone Levels with a 1% Hydroalcoholic Testosterone Gel in the Treatment of Erectile Dysfunction (TADTEST Study)

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ABSTRACT

Introduction. Addition of testosterone (T) may improve the action of phosphodiesterase type 5 inhibitors (PDE5-Is) in patients with erectile dysfunction not responding to PDE5-Is with low or low-normal T levels.

Aims. To confirm this add-on effect of T in men optimally treated with PDE5-Is and to specify the baseline T levels at which such an effect becomes significant.

Methods. A multicenter, multinational, double-blind, placebo-controlled study of 173 men, 45–80 years, nonresponders to treatment with different PDE5-Is, with baseline total T levels ≤4 ng/mL or bioavailable T ≤ 1 ng/mL. Men were first treated with tadalafil 10 mg once a day (OAD) for 4 weeks; if not successful, they were randomized in a double-blind, placebo-controlled design to receive placebo or a 1% hydroalcoholic T gel (50 mg/5 g gel), to be increased to 10 mg T if results were clinically unsatisfactory.

Main Outcomes Measures. Mean change from baseline in the Erectile Function Domain Score of the International Index of Erectile Function and rate of successful intercourses (Sexual Encounter Profile 3 question).

Results. Erectile function progressively improved over a period of at least 12 weeks in both the placebo and T treatment groups. In the overall population with a mean baseline T level of 3.37 ± 1.48 ng/mL, no additional effect of T administration to men optimally treated with PDE5-Is was encountered. The differences between the T and placebo groups were significant for both criteria only in the men with baseline T ≤3 ng/mL.

Conclusions. The maximal beneficial effects of OAD dosing with 10 mg tadalafil may occur only after as many as 12 weeks. Furthermore, addition of T to this PDE5-I regimen is beneficial, but only in hypogonadal men with baseline T levels ≤3 ng/mL. **Buvat J, Montorsi F, Maggi M, Porst H, Kaipia A, Colson MH, Cuzin B, Moncada I, Martin-Morales A, Yassin A, Meuleman E, Eardley I, Dean JD, and Shabsigh R. Hypogonadal men nonresponders to the PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1% hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST study). J Sex Med 2011;8:284–293.**

Key Words. Combined Therapy; Erectile Dysfunction; Nonresponders; Phosphodiesterase Type 5 Inhibitors; Tadalafil Once A Day; Testosterone Therapy

Introduction

About 30–35% of patients fail to respond to treatment of erectile dysfunction (ED) with phosphodiesterase type 5 inhibitors (PDE5-Is). This is sometimes explained by associated testosterone (T) deficiency [1]. In animal experiments, the pharmacological activity of PDE5-Is appears androgen dependent [2–5]. Also in humans, the expression of PDE5 appears androgen dependent [3]; T deficiency seems to predict a poor response to sildenafil [6–14] or tadalafil [15] and addition of T seemed helpful in five uncontrolled studies [7,9,13–15].

Two previous randomized placebo-controlled trials support this notion but had some methodological shortcomings. The small number of patients, the short study duration, and inclusion of men who did not have true hypogonadal values limit the significance of the first one [16]. More convincingly, Shabsigh et al. combined sildenafil with T or placebo in patients with low T (≤4 ng/mL) nonresponders to sildenafil 100 mg alone [17]. The initially positive effects of sildenafil no longer manifested after 4 weeks. Conversely, Rochira et al. demonstrated that sildenafil restores nocturnal erections of men with almost undetectable levels of T similarly to T replacement [18]. A recent meta-analysis of three controlled trials found insufficient evidence to determine the superiority of PDE5-Is + T therapy vs. PDE5-Is + placebo in improving the erections, or the frequency or percentage of successful intercourse attempts, in hypogonadal men with ED refractory to previous PDE5-I therapy [19].

The present study aimed to test whether the action of PDE5-I in men is androgen dependent: does a combination of T add to the efficacy of PDE5-Is therapy in patients with low or low-normal levels of T not responding to PDE5-Is, even after daily dosing with tadalafil, which may salvage a part of the failures of on-demand dosing [20]? Our study intended also to investigate whether there are threshold values of T for the additive effect on PDE5-I to become manifest.

Patients and Methods

Objectives

This multicenter study assessed the efficacy of combined treatment of tadalafil and T to improve erectile function in ED patients with low or low-normal levels of T previously not responding to treatment with tadalafil alone. Administration of T was randomized, double blind, and placebo controlled, while administration of tadalafil, given to all participants, was open. The trial was registered at http://www.clinicaltrials.gov (identifier NCT 00244023)

Study Design and Patients

TADTEST study followed the declaration of Helsinski and was approved by the ethical review boards of the 17 European participating centers. Each subject gave written informed consent. The study began in October 2005 and was completed in July 2007.

Eligible men were 45 to 80 years old who had ED >3 months, involved in a stable heterosexual relationship >3 months, had a serum total T ≤4 ng/mL and/or bioavailable T ≤1 ng/mL (upper limits of the lower quartile of the normal range for men ≤45 years old in the central study laboratory), to be confirmed in blood sampled before 10 AM at V1, and had not responded adequately to the highest available dosage of sildenafil, tadalafil, or vardenafil therapy on at least four separate occasions (i.e., score of 2 to 4 at Q3 and 2 or 3 at Q4 of the International Index of Erectile Function [IIEF]) [21,22].

This randomized, parallel group study involved five visits (Figure 1). V1: screening visit and start of a 4-week run-in period with 10 mg tadalafil (Cialis®) once-a-day (OAD) monotherapy; V2: baseline and start of a double-blind adjunctive therapy; V3, V4, and V5: weeks 4, 8, and 12 of combined therapy. At V2, randomization of hypogonadal men with an inadequate response to 10 mg tadalafil OAD (same criteria as at V1 + at least 50% of unsuccessful attempts at intercourse according to a "No" answer at Q1, Q2, or Q3 of the Sexual Encounter Profile diary [SEP]) in a 1:1 ratio to receive 1% T-gel or placebo-gel (5 g) adjunctive therapy to tadalafil 10 mg OAD for 12 weeks; T-gel (Testogel®, Androgel®) and placebo gel also administered OAD per the manufacturer labeling; randomization prepared and kept confidential by the manufacturer, Besins International; sachets of T and placebo gels, identical in appearance, provided to the investigators in numbered packs allocated to the patients in consecutive order; if insufficient subjective clinical response after 4 or 8 weeks of combined therapy, increase in T-gel or placebo-gel dose (T gel from 50 mg T/5 g gel up to 100 mg/10 g daily).

Efficacy Criteria

The main assessment tools were the IIEF and questions 2 to 5 of the SEP. The primary efficacy variable was the mean change from baseline in the