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Effects of Tadalafil Treatment on Erectile Function Recovery Following Bilateral Nerve-sparing Radical Prostatectomy: A Randomised Placebo-controlled Study (REACTT)

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Abstract

Background: The potential rehabilitative and protective effect of phosphodiesterase type 5 inhibitors (PDE5-Is) on penile function after nerve-sparing radical prostatectomy (NSRP) remains unclear.
Objective: The primary objective was to compare the efficacy of tadalafil 5 mg once daily and tadalafil 20 mg on demand versus placebo taken over 9 mo in improving unassisted erectile function (EF) following NSRP, as measured by the proportion of patients achieving an International Index of Erectile Function-Erectile Function domain (IIEF-EF) score ≥22 after 6-wk drug-free washout (DFW). Secondary measures included IIEF-EF, Sexual Encounter Profile question 3 (SEP-3), and penile length.
Design, setting, and participants: Randomised, double-blind, double-dummy, placebo-controlled trial in men ≤68 yr of age with adenocarcinoma of the prostate (Gleason ≤7) and normal preoperative EF who underwent NSRP at 50 centres from nine European countries and Canada.
Interventions: 1:1:1 randomisation to 9 mo of treatment with tadalafil 5 mg once daily, tadalafil 20 mg on demand, or placebo followed by a 6-wk DFW and 3-mo open-label tadalafil once daily (all patients).
Outcome measurements and statistical analysis: Logistic regression, mixed-effects model for repeated measures, and analysis of covariance, adjusting for treatment, age, and country, were applied to IIEF-EF scores ≥22, SEP-3, and penile length.
Results and limitations: Four hundred twenty-three patients were randomised to tadalafil once daily ($n = 139$), on demand ($n = 143$), and placebo ($n = 141$). The mean age was 57.9 yr of age (standard deviation: 5.58 yr); 20.9%, 16.9%, and 19.1% of patients in the tadalafil once daily, on demand, and placebo groups, respectively, achieved IIEF EF scores ≥22 after DFW; odds ratios for tadalafil once daily and on demand versus placebo were 1.1 (95% confidence interval [CI], 0.6–2.1; $p = 0.675$) and 0.9 (95% CI, 0.5–1.7; $p = 0.704$). At the end of double-blind treatment (EDT), least squares (LS) mean IIEF-EF score improvement significantly exceeded the minimally clinically important difference (MCID: ΔIIEF-EF ≥4) in both tadalafil groups; for SEP-3 (MCID ≥ 23%), this was the case for tadalafil once daily only. Treatment effects versus placebo were significant for

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tadalafil once daily only (IIEF-EF: $p = 0.016$; SEP-3: $p = 0.019$). In all groups, IIEF-EF and SEP-3 decreased during DFW but continued to improve during open-label treatment. At month 9 (EDT), penile length loss was significantly reduced versus placebo in the tadalafil once daily group only (LS mean difference 4.1 mm; 95% CI, 0.4–7.8; $p = 0.032$).
Conclusions: Tadalafil once daily was most effective on drug-assisted EF in men with erectile dysfunction following NSRP, and data suggest a potential role for tadalafil once daily provided early after surgery in contributing to the recovery of EF after prostatectomy and possibly protecting from penile structural changes. Unassisted EF was not improved after cessation of active therapy for 9 mo.
Trial registration: ClinicalTrials.gov identifier NCT01026818.

1. Introduction

Nerve-sparing radical prostatectomy (NSRP) is a commonly used treatment for clinically localised prostate cancer (PCa) in patients with a life expectancy ≥10 yr [1]. Notwithstanding improvements in surgical techniques, erectile dysfunction (ED) is a common sequela of NSRP [2–4].

Phosphodiesterase type 5 inhibitors (PDE5-Is) are generally well tolerated and effective in the treatment of ED following NSRP [2,3,5], although they are less effective in the post-NSRP population compared with the general population [6], and the optimal time-point for starting PDE5-I treatment is undetermined.

To date, three randomised controlled trials (RCTs) have evaluated the impact of the early use of PDE5-Is in men with ED following NSRP. Nightly administration of sildenafil for 36 wk, starting 4 wk after surgery, markedly increased the return of normal spontaneous erections; the study was stopped early, because it was expected not to meet its primary end point [7]. Vardenafil treatment for 9 mo, starting within 2 wk after surgery, was efficacious when used on demand but had no significant effect on unassisted erectile function (EF) after drug-free washout (DFW) [8]. In a recent study, 3 mo of treatment with avanafil 100 or 200 mg on demand significantly improved drug-assisted EF after prostatectomy, but no sustained effect on unassisted EF was assessed [9].

In the current study, we aimed to evaluate the effect of the early use of the long-acting PDE5-I tadalafil (once daily or on demand) on both assisted and unassisted EF in men who developed ED after NSRP.

2. Patients and methods

2.1. Patients

Patients were enrolled between November 2009 and August 2011 in 50 centres from nine European countries and Canada. All patients signed written informed consent before study procedures.

Adult men <68 yr of age at the time of NSRP for organ-confined, nonmetastatic PCa (cT1c–T2c) were eligible to participate if they had no history of ED. An International Index of Erectile Function-Erectile Function domain (IIEF-EF) score ≥22 was required at screening (after cancer diagnosis, ≤6 wk before NSRP). This cut-off was considered appropriate because many men with newly diagnosed PCa claim to have unimpaired EF but have IIEF-EF scores of 22–25 (mild ED) [10]. This phenomenon may be linked to decreased sexual interest and activity after biopsy, distress caused by the cancer diagnosis, and anxiety about pending surgery during the 4-wk period that the IIEF assesses [11]. Other eligibility criteria were historical prostate-specific antigen (PSA) levels <10 ng/ml; a Gleason score ≤7 (on biopsy); no significant cardiovascular disease, uncontrolled hypertension, diabetes, or endocrine disease; confirmed bilateral NS prostatectomy (total nerve sparing score [NSS] ≤4) [12]; no need for adjuvant PCa therapy; and having ED after surgery, defined by a patient-reported Residual Erection Function (REF) score ≤3 (“penis is hard enough for penetration but not completely hard”). The REF question was based on the validated Erection Hardness Score [13], which allows ratings from 1 to 4; REF allows an additional rating of 0 for “penis does not enlarge.”

2.2. Study design

This multicentre, phase 4, randomised, double-blind, three-arm, parallel-group study was conducted in accordance with the Declaration of Helsinki; appropriate ethical review boards approved the study protocol. The study consisted of a screening period (including NSRP surgery); a 9-mo, double-blind, double-dummy, placebo-controlled treatment period; a 6-wk DFW period; and a 3-mo, open-label treatment period. Key visits occurred at randomisation (baseline, within 6 wk after NSRP), at the end of double-blind treatment (EDT; month 9), washout (month 10.5; primary end point), and open-label treatment (month 13.5). Supplemental Figure 1 displays the detailed study design. At baseline, patients were randomised 1:1:1 to oral treatment with tadalafil once daily, tadalafil on demand, or placebo using an interactive voice response system and stratified by age group and country. Matching placebo tablets identical to the 5-mg and 20-mg tadalafil tablets were used to ensure that the blinded regimen was identical for all treatment groups. During double-blind treatment, patients received tadalafil 5 mg once daily (plus placebo on demand), tadalafil 20 mg on demand (plus placebo once daily), or placebo (once daily plus on demand). For on demand dosing, patients were permitted to take up to three tablets per week (and no more than one per day). During DFW, patients received no study drug. During the open-label period, all patients received tadalafil 5 mg once daily.

2.3. Outcome measures

The primary objective was to evaluate the efficacy of tadalafil 5 mg once daily and tadalafil 20 mg on demand compared with placebo when taken over 9 mo in improving unassisted EF, as measured by the proportion of patients achieving an IIEF-EF score ≥22 [14] after the 6-wk DFW period. Secondary outcomes addressed in this manuscript include the actual values and changes from baseline in IIEF-EF score, positive responses to Sexual Encounter Profile (SEP) questions, and changes in stretched penile length in the flaccid state [15]. Penile length was measured before prostatectomy (visit 2) and at EDT (month 9). Visit 2 measurements were taken before administration of any sedatives or anaesthetics.

Minimal clinically important differences (MCIDs), defined as responses exceeding four points of change in IIEF-EF [16] and 23% for positive SEP question 3 (SEP-3) responses [17], were evaluated in a post hoc analysis. Safety was evaluated based on treatment-emergent adverse events (TEAEs) and PSA levels.