Factors Influencing Prostate-Specific Antigen Response among Men Treated with Testosterone Therapy for 6 Months

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ABSTRACT

Introduction. Factors influencing prostate-specific antigen (PSA) changes in men undergoing testosterone (T) therapy have not been well studied.

Aim. The aim of this study was to assess the influence of selected variables on PSA changes in hypogonadal men administered with 1.62% testosterone gel (T-gel) for 6 months.

Methods. A double-blind, placebo-controlled study of 274 (234 T-gel, 40 placebo) hypogonadal men >18 years of age, with baseline T concentrations <300 ng/dL, PSA ≤2.5 ng/mL, and negative digital rectal examination. Subjects received once-daily T-gel for T therapy.

Main Outcome Measures. Changes in mean serum PSA, percentage of free PSA (%fPSA), and T from baseline to 6 months (182 days).

Results. Mean age was 53.5 years and baseline mean values were total T 247 ng/dL, PSA 0.9 ng/mL, and %fPSA 24.6%. Among men treated with T-gel, T increased to 499 ng/dL and PSA increased by 0.1 ng/mL ($P = 0.0012$). PSA increased ≥0.3 ng/mL in 26.3%, <0.3 ng/mL in 73.7%, including a decline from baseline in 33.0%. In the placebo group, T increased 29 ng/dL to 274 ng/dL, and PSA decreased 0.1 ng/mL, compared with baseline. A greater increase in PSA was noted in men ≥60 years old than in men <60 years old (0.4 vs. 0.05 ng/mL, respectively; $P = 0.0006$). Mean PSA did not change in men with baseline serum T >250 ng/dL, whereas it increased by 0.2 ng/mL in men with T ≤250 ng/dL ($P = 0.0031$). PSA increased 0.3 ng/mL in men with baseline %fPSA <20% and 0.1 ng/mL in men with %fPSA ≥20%.

Conclusions. Overall, T-gel treatment was associated with a minor increase in PSA, of questionable clinical significance. Factors predicting greater PSA increases included age ≥60 years, baseline T ≤250 ng/dL, and %fPSA <20%. Men with T >250 ng/dL and age <60 years demonstrated minimal or no PSA change. **Morgentaler A, Benesh JA, Denes BS, Kan-Dobrosky N, Harb D, and Miller MG. Factors influencing prostate-specific antigen response among men treated with testosterone therapy for 6 months. J Sex Med 2014;11:2818–2825.**

Key Words. Hormone Replacement Therapy; Prostate-Specific Antigen; Testosterone; Androgens

Introduction

Potential benefits of testosterone (T) therapy in men with T deficiency include improvements in body composition, bone mineral density, mood, and sexual function [1]. However, because the prostate is androgen dependent, there is concern that T therapy may cause growth of benign prostate tissue or progression of occult cancer (reflected by changes in prostate-specific antigen [PSA]) and lead to unwarranted prostatic investigations [2]. However, there are limited data regarding what degree of change is anticipated in

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serum PSA with T therapy. We are aware of no prior prospective intervention studies that investigated the impact of factors such as baseline serum T concentrations or percentage of free prostate-specific antigen (%fPSA) on PSA change with T therapy in a placebo-controlled setting.

Serum PSA levels are widely used for prostate-cancer screening. Although historically the primary indication for PSA-triggered prostate biopsy was an absolute value greater than 4.0 ng/mL, a significant PSA increase within the normal range is now also considered an indication for biopsy [3–5]. It is therefore important to investigate what degree of PSA changes can be expected with T therapy in hypogonadal men.

Among currently approved T therapy products, transdermal gel formulations are the most frequently used treatment. A 1.62% testosterone gel (T-gel) formulation has been developed, with increased viscosity, enhanced skin permeation, and a reduced volume of daily application compared with 1% formulations [6,7]. In a double-blind, placebo-controlled, 6-month study, this formulation demonstrated efficacy and safety with titration-based doses of 1.25, 2.5, 3.75, or 5.0 g/day (20.25, 40.5, 60.75, and 81 mg T/day) [7].

Aims

The purpose of this study was to investigate the influence of baseline age, serum T concentrations, and %fPSA on PSA response to treatment with T 1.62% gel.

Methods

Readers are referred to the original study results for a more detailed description of patients and methods (NCT00433199, http://clinicaltrials.gov/) [7].

Study Subjects

Subjects were hypogonadal, but otherwise healthy men 18–80 years old with a serum total T level <300 ng/dL (average of two screening blood samples collected 30 minutes apart and before 10:00 AM). Hypogonadal symptoms were not assessed. Potential subjects were excluded for impaired liver function; body mass index <18 or >40 kg/m^2, moderate to severe lower urinary tract symptoms, serum PSA >2.5 ng/mL, or any abnormal digital rectal examination finding other than prostate enlargement; a history of prostate or breast cancer; or hematocrit >48%. Subjects not naïve to androgen replacement therapy were required to undergo washout (12 weeks for intramuscular injections, 4 weeks for topical or buccal, and 3 weeks for oral therapy).

Study Design

Enrolled subjects were randomized to 1.62% T-gel or matching placebo in a 6:1 ratio, beginning at 2.5 g (40.5 mg T) applied once daily to intact, clean, dry skin of either the upper arm/shoulder or abdomen [8]. On days 14, 28, and 42, subjects underwent predose assessments of serum T, enabling their dose to be titrated up or down by 1.25 g (not below 1.25 or above 5.0 g) if the T level was not within the range 350–750 ng/dL. After the last such adjustment, each subject's dosage was maintained until day 182 [7]. On days 84 and 182, PSA and %fPSA were assayed using chemiluminescent immunometric assays (DPC Immulite Chemistry Analyzer, Siemens, Washington, DC, USA). Subjects were discontinued if the mean of a follow-up PSA value and a repeat test was >4.0 ng/mL or PSA showed a mean increase >0.75 ng/mL from baseline. Serum T concentrations were assayed using validated liquid chromatography–mass spectrometry methodology by Pharmaceutical Product Development (PPD, Inc., Richmond, VA, USA). Serum total T concentrations used for screening and titration were measured by immunoassay by a central laboratory (Quintiles Laboratories, Smyrna, GA, USA). PSA levels and safety assessments were also measured by Quintiles. No ultrasonography to determine prostate volume was performed as part of this study.

Main Outcome Measures

Primary pharmacokinetic outcome measures of the study have been reported elsewhere [6,7]. Baseline values and changes in PSA and %fPSA during the study were components of the safety evaluation. In the present report, PSA changes from baseline to last available observation have been analyzed in active-treatment subjects. The last observation carried forward method was used for 43 subjects missing day 182 PSA data. Subgroup analysis was performed for men ≥60 and <60 years old, for baseline serum T groups of ≤200 ng/dL, 201–250 ng/dL, and >250 ng/dL, and for %fPSA <20% and ≥20%.

Statistical Analysis

The analysis was performed on the safety sample consisting of all consented subjects who had at least one dose of study medication administered.

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