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Demographic and Clinical Correlates of Patient-Reported Improvement in Sex Drive, Erectile Function, and Energy With Testosterone Solution 2%

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ABSTRACT

Introduction: Evidence from well-designed studies documenting the benefit of testosterone replacement therapy as a function of patient demographic and clinical characteristics is lacking.

Aim: To determine demographic and clinical predictors of treatment outcomes in hypogonadal men with low sex drive, low energy, and/or erectile dysfunction.

Methods: Post hoc analysis of a randomized, multicenter, double-blinded, placebo-controlled, 16-week study of 715 hypogonadal men (mean age = 55.3 years, age range = 19–92 years) presenting with low sex drive and/or low energy who received placebo or testosterone solution 2% for 12 weeks.

Main Outcomes and Measures: Two levels defined patient-reported improvement (PRI) in sex drive or energy: level 1 was at least "a little better" and level 2 was at least "much better" in energy or sex drive on the Patient Global Impression of Improvement at study end point. PRI in erectile function was stratified by erectile dysfunction severity at baseline as measured by the erectile function domain of the International Index for Erectile Function: mild at baseline (change of 2), moderate at baseline (change of 5), and severe at baseline (change of 7). Associations of demographic and clinical characteristics with PRI were calculated with stepwise forward multiple logistic regression analysis. Odds ratios represented the likelihood of PRI in symptoms among variable categories.

Results: Higher levels of end-point testosterone were associated with higher rates of PRI (at levels 1 and 2) in sex drive and energy ($P < .001$ for the two comparisons). Lower baseline testosterone levels were associated with higher rates of level 1 PRI in sex drive ($P = .028$); and classic hypogonadism (vs non-classic hypogonadism) was associated with higher rates of level 2 PRI in sex drive ($P = .005$) and energy ($P = .006$).

Conclusion: When assessing the potential for improvements in men with testosterone deficiency using patient-reported outcome questionnaires, possible predictors of treatment outcomes to consider include the etiology of hypogonadism and testosterone levels (baseline and end point).

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Key Words: Hypogonadism; Sexual Desire; Energy; Testosterone Replacement Therapy; Androgen Deficiency

INTRODUCTION

Recently, in one of the largest placebo-controlled, prospective, randomized testosterone trials, testosterone replacement therapy (TRT) with testosterone solution 2% showed clinical improvement of the most common patient-reported symptoms of hypogonadism (low sex drive, low energy, and erectile dysfunction [ED]) in a broad population of hypogonadal men over 12 weeks. Clinical improvement was documented in part using the Patient Global Impression of Improvement (PGI-I) and the International Index for Erectile Function (IIEF) questionnaires.[1] For clinicians treating hypogonadal patients, it is important to understand whether observed and reported improvements in outcomes are clinically meaningful and whether the outcomes vary by patient demographic and clinical characteristics. Treatment-induced improvement of specific demographic and clinical characteristics remains of particular interest given the recent controversy surrounding the increased

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use and potential risks of TRT in middle-age and older men with non-classic hypogonadism,[2–4] defined in the present study as men with low testosterone levels but no identified testicular, hypothalamic, or pituitary etiology.

AIM

The objective of this post hoc analysis of the aforementioned clinical trial was to examine the clinical and demographic attributes in hypogonadal men that are associated with improvements in symptoms of low sex drive, low energy, and ED in response to treatment with testosterone solution 2%.

METHODS

Data Source

This analysis used data from a previous 3-month, randomized, double-blinded, placebo-controlled phase 3 study assessing the efficacy of testosterone therapy for low sex drive and energy in hypogonadal men.[1] The design and methods of the double-blinded study have been previously described.[1] Briefly, men at least 18 years old with two total testosterone level measurements lower than 10 nmol/L (measured at least 1 week apart) and at least one symptom of testosterone deficiency (decreased sexual drive or decreased energy as determined by the investigator, using non-standardized methodology) were eligible to enter the trial. Key exclusion criteria included hemoglobin A_{1c} level higher than 11%; body mass index (BMI) greater than 37 kg/m^2; hematocrit level of at least 50%; breast cancer (or history of thereof) or other active cancer (with the exception of non-melanoma skin cancer); a history of prostate cancer; or a clinical suspicion of prostate cancer during rectal examination or a prostate-specific antigen level of at least 4 ng/mL at screening. A dosage adjustment algorithm was used at weeks 4 and 8 based on a single total testosterone level measurement at the preceding visit (using an interactive voice response to maintain blinding). If required, dosage was decreased to 30 mg or increased by 30-mg increments to a maximum of 120 mg daily.

Main Outcome Measures

The instruments for this analysis were PGI-I energy and sex drive and the IIEF erectile function domain (IIEF-EF). The PGI-I is a one-item questionnaire that asks a patient to rate the perceived symptom change in response to therapy. The global instrument from which these questions were adapted has been used and/or validated in clinical studies assessing urogenital prolapse,[5] stress incontinence,[6] lower urinary tract symptoms associated with benign prostatic hyperplasia,[7] and other non-urologic conditions.[8] Patients reported on two PGI-I questionnaires at study end point (week 12): PGI-I energy and PGI-I sex drive. In the PGI-I sex drive questionnaire, patients were asked to "Mark the box that best describes your sexual drive since you started taking the medication in this study." In the PGI-I energy questionnaire, patients were asked to "Mark the box that best describes your energy since you started taking the medication in this study." For the two questionnaires, patients could select from one of seven responses (1 = "very much better"; 2 = "much better"; 3 = "a little better"; 4 = "no change"; 5 = "a little worse"; 6 = "much worse"; 7 = "very much worse"). For sex drive or energy, patient-reported improvement (PRI), as measured by the PGI-I questionnaires, was categorized as follows: (i) less robust PGI-I responses of at least "a little better" were referred to as level 1 PRI and (ii) more robust PGI-I responses of at least "much better" were referred to as level 2 PRI. PRI in erectile function was measured using the IIEF-EF (Q1−Q5, A15) after applying the minimum clinically important difference-by-severity criteria established by Rosen et al[9] in determining patients with meaningful improvement in erectile function. To determine sex drive and energy levels at randomization, patient-reported Sexual Arousal, Interest, and Drive Scale (SAID) and Hypogonadism Energy Diary (HED) scores were evaluated. The SAID and HED are content-validated patient-reported outcome instruments developed in accordance with U.S. Food and Drug Administration guidance to assess sex drive and energy in hypogonadal men.[1,10]

Statistical Analysis

Testosterone solution 2% vs placebo comparisons were assessed using the Fisher exact test. Of the men treated with placebo or testosterone solution 2%, variables of age (<45 vs 45−65 and >65 years), etiology (classic vs non-classic hypogonadism), obesity (BMI <30 vs ≥30 kg/m^2), geographic location (North America vs rest of the world), baseline total testosterone levels (<300 ng/dL [<10.4 nmol/L] vs ≥300 ng/dL [≥10.4 nmol/L]), end-point total testosterone levels (<300 ng/dL [<10.4 nmol/L] vs 300−500 ng/dL [10.4−17.4 nmol/L] and >500 ng/dL [>17.4 nmol/L]), history of testosterone use (yes vs no), and ED (yes vs no) were included in a stepwise forward logistic regression model to determine which variables most closely associated with the rate of PRI in sex drive, energy, or erectile function. For the sensitivity analysis, a second stepwise logistic regression model was run with the aforementioned variables only for men treated with testosterone solution 2%. A variable had to meet statistical significance at the 0.05 level for entry and for remaining in the models. All analyses were carried out using SAS 9.1 (SAS Institute, Inc, Cary, NC, USA).

RESULTS

Demographic and Clinical Characteristics

Baseline characteristics of the patients have been previously described[1] and are presented in Table 1. Overall, 715 men, randomized to placebo or testosterone solution 2% at 98 sites in Argentina, Canada, Germany, Spain, Great Britain, Italy, South Korea, Puerto Rico, and the United States, were pooled for this analysis. Mean age was 55.3 years (range = 19−92 years), with 80% of the study population younger than 65 years. Approximately half the study population had received at