Effect of Testosterone Solution 2% on Testosterone Concentration, Sex Drive and Energy in Hypogonadal Men: Results of a Placebo Controlled Study

Gerald Brock,*,† Darell Heiselman,‡ Mario Maggi,† Sae Woong Kim,† José M. Rodríguez Vallejo,† Hermann M. Behre,† John McGettigan,† Sherie A. Dowsett,‡ Risa P. Hayes,† Jack Knorr,‡ Xiao Ni‡ and Kraig Kinchen‡

From the Department of Surgery, University of Western Ontario (GB), London, Ontario, Canada, Eli Lilly and Co. (DH, SAD, RPH, JK, XN, KK), Indianapolis, Indiana, Department of Clinical Physiopathology, University of Florence (MM), Florence, Italy, Department of Urology, Seoul St. Mary's Hospital, The Catholic University of Korea (SWK), Korea, Urology Service, Hospital Infanta Leonor (JMRV), Madrid, Spain, Center for Reproductive Medicine and Andrology, University Hospital Halle (Saale) (HMB), Halle, Germany, and Quality of Life Medical and Research Center (JM), Tucson, Arizona

Purpose: We determined the effect of testosterone solution 2% on total testosterone level and the 2 symptoms of hypogonadism, sex drive and energy level.

Materials and Methods: This was a randomized, multicenter, double-blind, placebo controlled, 16-week study to compare the effect of testosterone and placebo on the proportion of men with a testosterone level within the normal range (300 to 1,050 ng/dl) upon treatment completion. We also assessed the impact of testosterone on sex drive and energy level measured using SAID (Sexual Arousal, Interest and Drive scale) and HED (Hypogonadism Energy Diary), respectively. A total of 715 males 18 years old or older with total testosterone less than 300 ng/dl and at least 1 symptom of testosterone deficiency (decreased energy and/or decreased sexual drive) were randomized to 60 mg topical testosterone solution 2% or placebo once daily.

Results: Of study completers 73% in the testosterone vs 15% in the placebo group had a testosterone level within the normal range at study end point ($p < 0.001$). Participants assigned to testosterone showed greater baseline to end point improvement in SAID scores (low sex drive subset $p < 0.001$ vs placebo) and HED scores (low energy subset $p = 0.02$ vs placebo, not significant at prespecified $p < 0.01$). No major adverse cardiovascular or venous thrombotic events were reported in the testosterone group. The incidence of increased hematocrit was higher with testosterone vs placebo ($p = 0.04$).

Abbreviations and Acronyms

AE = adverse event

FDA = Food and Drug Administration

HDL = high density lipoprotein

IIEF = International Index of Erectile Function

ITT = intent to treat

MMRM = mixed model repeated measures

PDQ = Psychosexual Daily Questionnaire

PGI-I = Patient Global Impression and Improvement

PSA = prostate specific antigen

TEAE = treatment emergent adverse event

TRT = testosterone replacement therapy

Accepted for publication October 9, 2015.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

ClinicalTrials.gov NCT01816295.

* Correspondence: Department of Surgery, University of Western Ontario, London, Ontario, Canada (telephone: 519-646-6042; e-mail: gebrock@sympatico.ca).

† No direct or indirect commercial incentive associated with publishing this article.

‡ Financial interest and/or other relationship with Eli Lilly.

0022-5347/16/1953-0699/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2015.10.083
Vol. 195, 699-705, March 2016
Printed in U.S.A.

Conclusions: Once daily testosterone solution 2% for 12 weeks was efficacious in restoring normal testosterone levels and improving sexual drive in hypogonadal men. Improvement was also seen in energy levels on HED though not at the prespecified $p < 0.01$. No new safety signals were identified.

Key Words: testes, hypogonadism, testosterone, treatment outcome, questionnaires

SYMPTOM assessment has a major role in understanding the burden of hypogonadism and the effectiveness of TRT. Yet there is a paucity of data from well designed, placebo controlled, multicenter trials to determine whether TRT results in symptomatic improvement in hypogonadal men.[1,2] In a previous phase 3 study of testosterone solution 2% (Axiron®) testosterone was within the normal range (300 to 1,050 ng/dl) in 84% of subjects following 3 months of treatment.[3] While study participants recorded symptomatic improvements from baseline as measured by PDQ,[4] the study, like many TRT studies,[5,6] did not include a placebo arm. Additionally PDQ was not developed in accordance with FDA guidelines on patient reported outcome instruments.[7]

We performed this placebo controlled, multicenter trial to determine whether TRT is associated with improvements in sexual drive and energy, which are key symptoms that drive patients to seek treatment.[8,9] The study used 2 new patient reported outcome instruments, SAID and HED,[10] which were developed according to FDA guidelines.[7]

MATERIALS AND METHODS

Study Design

This was a randomized, multicenter, double-blind, placebo controlled, parallel group, 16-week (4-week screening and 12-week treatment) study. After completion eligible men had the option to enroll in a 6-month open label extension.

The primary objective was to compare the effect of testosterone solution and placebo on the proportion of hypogonadal men with serum total testosterone within the normal range of 300 to 1,050 ng/dl (10.4 to 36.4 nmol/l) upon completion of 12 weeks of treatment.

Secondary objectives were 1) in participants with low sex drive to assess the impact of testosterone on levels of sexual arousal, interest and drive as measured using SAID and 2) in participants with low energy to assess the impact of testosterone on levels of energy as measured using HED. Exploratory measures (self-administered) included energy and sexual drive scores on PGI-I, as adapted from the version used in trials of other conditions,[11,12] IIEF[13] administered to participants who were or desired to be sexually active with the same female partner and PDQ.[4]

Males 18 years old or older with 2 total testosterone levels less than 300 ng/dl measured 1 week or more apart and at least 1 symptom of testosterone deficiency (decreased energy or decreased sexual drive as determined by the investigator using nonstandardized methodology) were eligible for study. Key exclusion criteria included hemoglobin A1c greater than 11%, body mass index greater than 37 kg/m^2, hematocrit 50% or greater, breast cancer (or history of breast cancer) or other active cancer (except nonmelanoma skin cancer), a history of prostate cancer or clinical suspicion of prostate cancer during rectal examination or PSA 4 ng/ml or greater at screening.

Participants were randomized 1:1 to 60 mg topical testosterone solution 2% or placebo solution once daily. Treatment group assignment was determined by a computer generated random sequence using an interactive voice response system. Participants were randomized at the study level and stratified by the average of the 2 screening testosterone levels (less than 200, or 200 ng/dl or greater), presence of low sexual drive and presence of low energy. To maintain blinding participants were required to apply a dose of study drug from each of 4 bottles to the axillae each day. A dose 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 system to maintain blinding. If required, the dose was decreased to 30 mg or increased in 30 mg increments up to a maximum of 120 mg daily.

The study was performed in agreement with applicable laws and regulations, good clinical practices and ethical principles in line with the Declaration of Helsinki. The study protocol was approved by the institutional review board at each study site participating in that trial. Written informed consent for study participation was provided by each participant. Participants did not receive a stipend for study participation.

Primary and Secondary End Points

Total serum testosterone was determined at weeks 2, 6 and 12 in a single blood sample collected between 7:00 and 11:00 a.m. Analysis was performed at a central laboratory using the liquid chromatography-mass spectrometry/mass spectrometry method.

SAID and HED, which are self-administered on hand held devices, were developed in accordance with FDA guidance with content validity established prior to study initiation.[10] SAID is intended to rate the level of thinking about sex (2 items), arousal (1 item), and interest in sex and sex drive (2 items) as recalled in the last 7 days in men with decreased sex drive. Men responded to all 5 items on Likert-type scales scored from 1 to 5 with 5 corresponding to greater levels of sexual arousal, interest or drive. HED comprises 2 questions administered 3 times per day. It is intended to assess real-time energy levels (the extent to which a respondent feels energetic or has feelings of tiredness/exhaustion). Men responded to both questions using an 11-point numerical rating scale with 10 corresponding to full of energy or extreme tiredness. The tiredness question score was subsequently reverse scored so that a higher total score corresponded to greater