

# ADJUNCTIVE USE OF AndroGel (TESTOSTERONE GEL) WITH SILDENAFIL TO TREAT ERECTILE DYSFUNCTION IN MEN WITH ACQUIRED ANDROGEN DEFICIENCY SYNDROME AFTER FAILURE USING SILDENAFIL ALONE

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## ABSTRACT

**Objectives.** To evaluate whether combination therapy with testosterone gel (T-gel) and sildenafil citrate is effective in achieving adequate potency in subjects with low-normal serum testosterone levels in whom sildenafil alone has failed.

**Methods.** From July 2000 to June 2001, we evaluated 90 men (aged 32 to 72 years) in whom 3 months of sildenafil therapy at the maximal recommended dose (100 mg) with at least three attempts at intercourse during the 3-month period had failed. Of these, 24 men had testosterone levels less than 400 ng/dL (range 92 to 365, mean 231.4) and were subsequently started on 1% T-gel monotherapy (AndroGel, 5 g daily). After 4 weeks of T-gel alone (week 4), sildenafil citrate (Viagra, 100 mg) was added to the treatment regimen for an additional 12 weeks (through week 16). Potency was defined as the ability to have at least one episode of satisfactory intercourse during the treatment period.

**Results.** All the men had normalized serum testosterone levels after 4 weeks of T-gel monotherapy (range 424 to 596 ng/dL, mean 525). However, none of the men regained potency. At week 16, almost all (22 of 24, 92%) of the men reported improved potency with combination therapy. Improvement in erection quality was also observed.

**Conclusions.** The results of this study support the use of T-gel with sildenafil citrate in men with low-normal serum testosterone levels in whom sildenafil alone fails. It also underscores the numbers of men with low to low-normal testosterone levels who would benefit from testosterone screening when evaluated for erectile dysfunction. UROLOGY 67: 571–574, 2006. © 2006 Elsevier Inc.

Erectile dysfunction (ED) is a common complaint reported by men in the primary care setting. Until recently, however, this condition commanded little clinical attention and had relatively poor treatment options. The advent of orally administered phosphodiesterase-type 5 (PDE-5) inhibitors has had a revolutionary effect on the treatment of ED. Such compounds are highly effective in helping men achieve and maintain a satisfactory

erection and have become the mainstay of ED therapy. Despite their popularity, however, oral PDE-5 inhibitors are only effective in the appropriate clinical situation and do not have 100% efficacy. In the case of sildenafil citrate, the first orally administered PDE-5 inhibitor to be marketed in the United States and abroad, up to 50% of subjects who receive the drug do not respond adequately to therapy.<sup>1</sup>

Many patients who find oral PDE-5 inhibitors to be ineffective are referred to a urologist for evaluation. On further endocrinologic workup, we found that many of these patients had low testosterone levels. Therefore, we investigated whether adjunctive use of transdermal testosterone gel (T-gel) with an oral PDE-5 inhibitor (ie, sildenafil citrate) would be effective in improving erectile function in men with low or low-normal serum testosterone levels in whom sildenafil alone has failed.

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## MATERIAL AND METHODS

This was an open-label, prospective, observational study conducted in a clinic setting in Philadelphia, Pennsylvania from July 2000 to June 2001. All patients provided appropriate informed consent. Men with ED in whom 3 months of sildenafil citrate therapy at the maximal recommended dose (100 mg) had failed were referred to the urology clinic for follow-up and consultation. Subjects were considered to have treatment failure if they had an erection inadequate for penetration and had failed at least three attempts at intercourse while taking sildenafil citrate during a 3-month period. On referral to the urology clinic, the men underwent a complete history and physical examination, with focus placed on the vascular, neurologic, endocrine, and genitourinary systems, as well as sexual history. The total serum testosterone and prostate-specific antigen (PSA) levels were measured in each subject, and those with low to low-normal serum testosterone levels (less than 400 ng/dL), normal digital rectal examination findings, and normal PSA levels (2.0 ng/mL or less) were eligible for study participation. Luteinizing hormone, follicle-stimulating hormone, and prolactin levels were not evaluated in this study, because the etiology of the subjects' low testosterone level was not the focus of this work. The arbitrary PSA cutoff for eligibility of 2.0 ng/mL was chosen to exclude subjects with equivocal PSA values. Subjects also had to answer "yes" to at least question 1 ("Do you have a decrease in libido?") or 7 ("Are your erections less strong?") of the Androgen Deficiency in Aging Males questionnaire<sup>2,3</sup> to participate in the study. The men were also asked to quantify the quality of their erections on a scale of 1 (minimal or no erections) to 5 (rigid erections).

Eligible subjects received 1% (5 g) T-gel (AndroGel [testosterone gel 1% CIII], Unimed/Solvay Pharmaceuticals, Marietta, Ga) once daily per the AndroGel labeling. Before the initiation of T-gel, the men were fully informed of the potential risks and benefits of testosterone replacement therapy. After 4 weeks of T-gel monotherapy (week 4), the total serum testosterone and PSA levels were re-assessed. The interval between the last AndroGel application and phlebotomy was not standardized, because of the relatively stable serum testosterone concentrations resulting from transdermal application. Subjects were asked to complete another Androgen Deficiency in Aging Males questionnaire and to assess the quality of their erections as previously described. Potency was defined as the ability to have at least one erection satisfactory for intercourse during the treatment period.

After the week 4 assessments were completed, sildenafil citrate (Viagra, Pfizer, New York, NY) was added to the treatment regimen at the maximal recommended dose (100 mg), except for 1 patient for whom the dose was reduced to 50 mg because of headache, flushing, and visual disturbance. For the next 12 weeks, the men continued daily use of T-gel and took sildenafil once daily for each day of sexual activity per the Viagra labeling. Each of the evaluations performed at week 4 was repeated at week 16.

Summary statistics were used to compare the total serum testosterone levels before the start of T-gel (week 0) and before the addition of sildenafil (week 4) to show that the testosterone levels normalized before the initiation of combination therapy. The proportion of subjects who were able to achieve potency was compared before (week 4) and after (week 16) the addition of sildenafil citrate to the treatment regimen, as were the mean erection quality scores. No formal statistical analyses were used in this study.

## RESULTS

A total of 90 men with ED (aged 32 to 72 years) in whom 3 months of sildenafil citrate therapy at

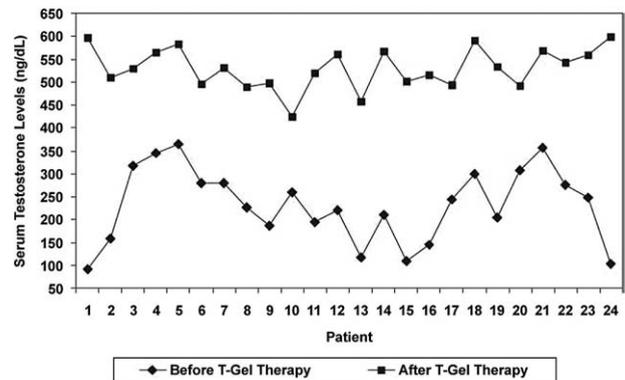


FIGURE 1. Serum testosterone levels before and after initiation of T-gel monotherapy. Serum testosterone levels presented by subject. Measurements taken at week 0 (before initiation of T-gel) and again 4 weeks later before sildenafil citrate was added to treatment regimen.

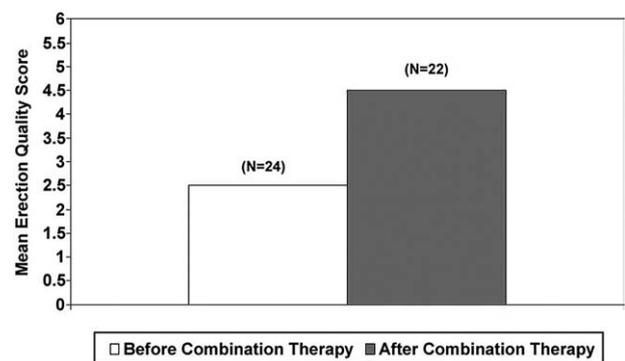


FIGURE 2. Erection quality before and after combination therapy with sildenafil citrate. Mean erectile quality scores (overall range 1 to 5) presented at week 4 (before addition of sildenafil citrate) and again after 12 weeks of combination therapy (week 16). Higher scores indicate better status.

the maximal recommended dose (100 mg) had failed were referred to the urology clinic. Of these 90 men, 25 had low to low-normal serum testosterone levels (range 92 to 365 ng/dL, mean 231.4; Fig. 1). Of these, 24 men had a PSA level of 2.0 ng/mL or less. None of the subjects had abnormal digital rectal examination findings consistent with carcinoma of the prostate. Overall, 24 subjects received therapy (T-gel monotherapy followed by T-gel plus sildenafil) and were eligible for evaluation.

After 4 weeks of T-gel monotherapy, a substantial increase was observed in the serum testosterone level of each subject (Fig. 1), with a mean level of 525 ng/dL (range 424 to 596). Very little change was observed in the PSA levels (average increase of 0.1 ng/mL). At week 4, none of the subjects rated the quality of their erection greater than 3 (range 1 to 5, mean 2.5, Fig. 2). None of the men regained potency using T-gel alone. At week 16, after 3 months of combination therapy with T-gel and sildenafil citrate, most (22 of 24, 92%) of the men

reported improved erections capable of penetration during intercourse. All but 1 subject who regained potency had an erection quality score of 4 or greater (mean 4.5, Fig. 2), and none answered yes to questions 1 or 7 of the Androgen Deficiency in Aging Males questionnaire. The remaining subject, who received only 50 mg sildenafil because of adverse side effects at the higher dose, had an erection score of 3 after combination therapy (relative to an initial score of 1).

## COMMENT

Adequate testicular function has been recognized for centuries as an important factor in satisfactory sexual performance.<sup>4</sup> However, because the prevalence of hypogonadism in men with ED is relatively low,<sup>5,6</sup> many men are not evaluated for androgen deficiency before initiation of ED therapy. Hypogonadism is more prevalent than previously suspected in middle-age men (older than 40 years old), with many men having testosterone levels well below normal.<sup>7</sup> This population also has the greatest incidence of ED and an increased prevalence of deterioration in the function of the hypothalamic-pituitary axis.<sup>4</sup> The average rate of decline of testosterone is 110 ng/dL per decade according to one study.<sup>8</sup> Diminished levels of serum testosterone may indicate androgen deficiency as a primary or significant secondary cause of ED and hinder any attempts at correcting or improving ED.

Treatment of hypogonadal men with testosterone ameliorates the effects of testosterone deficiency on bone, muscle, and erythropoiesis.<sup>9</sup> Although some have reported that testosterone therapy provides marked improvement in the libido of hypogonadal men,<sup>10–14</sup> the effect of testosterone on actual potency is less clear,<sup>2,15,16</sup> especially in older men.<sup>17</sup> Thus, the use of testosterone therapy in hypogonadal men solely for the purpose of improving sexual function is not routinely done, especially in the primary care setting. However, given the recent correlation between low serum free testosterone levels and impaired cavernous vasodilation in men with ED,<sup>18,19</sup> interest has increased in evaluating androgen replacement as concomitant therapy to PDE-5 inhibitors in hypogonadal men who do not respond to PDE-5 inhibitors alone. Kalinchenko *et al.*<sup>20</sup> have shown that combining oral testosterone undecanoate and sildenafil in patients with ED related to diabetes mellitus who failed to respond to sildenafil alone resulted in an increase in satisfactory erections.

Although our data set was small, our findings suggest that adjunctive use of T-gel with sildenafil in men with documented low to low-normal levels of total serum testosterone and a previous history of a nonresponse to sildenafil can improve potency once

normal serum testosterone levels are achieved. None of our subjects showed improved potency solely with the use of T-gel, and only after the addition of sildenafil did our subjects have sustainable and satisfactory erections.

We recognize that this study lacked an adequate control group of men with prolonged use of testosterone alone. It also used a relatively loose definition of potency rather than an evaluation based on the well-recognized International Index of Erectile Function questionnaire.<sup>21</sup> Despite these shortcomings, however, our findings are in agreement with those of a recently published randomized, double-blind, placebo-controlled study in which adjunctive use of T-gel with sildenafil significantly improved sexual activity in hypogonadal men with ED who did not respond to sildenafil alone.<sup>22</sup> In that study, treatment outcome was assessed using the International Index of Erectile Function, and testosterone-treated subjects showed greater improvement throughout the 12-week treatment period for each domain of the International Index of Erectile Function and the total score. Most recently, Greenstein *et al.*<sup>23</sup> published a study in which hypogonadal men with ED who failed to improve with T-gel alone experienced improved erectile function after the addition of sildenafil. The current study reports favorable results with the combined use of T-gel and sildenafil from a clinical practice setting in sildenafil nonresponders using referrals from primary care physicians.

## CONCLUSIONS

The findings of this study support the use of T-gel with sildenafil citrate in men with low-normal serum testosterone levels in whom sildenafil alone has failed. It also underscores the numbers of undiagnosed men with low to low-normal testosterone levels who would benefit from testosterone screening when being evaluated for ED.

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