Combined Testosterone and Vardenafil Treatment for Restoring Erectile Function in Hypogonadal Patients who Failed to Respond to Testosterone Therapy Alone

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ABSTRACT

Introduction. The role of testosterone in erectile dysfunction (ED) is increasingly recognized. It is suggested that assessment of testosterone deficiency in men with ED and symptoms of hypogonadism, prior to first-line treatment, may be a useful tool for improving therapy.

Aim. In this prospective, observational, and longitudinal study, we investigated the effects of vardenafil treatment as adjunctive therapy to testosterone undecanoate in hypogonadal ED patients who failed to respond to testosterone treatment alone.

Methods. One hundred twenty-nine testosterone deficient (serum total testosterone ≤3.4 ng/mL) patients aged 56 ± 3.9 years received intramuscular injections of long-acting parenteral testosterone undecanoate at 3-month intervals for 8 months mean follow-up.

Main Outcome Measures. Scores on the International Index of Erectile Function Questionnaire-five items (IIEF-5) and partner survey scores were compared at baseline and posttreatment with testosterone therapy alone or in combination with vardenafil. Patient baseline demographics and concomitant disease were correlated with patients' IIEF-5 scores.

Results. Seventy one (58.2%) responded well to monotherapy within 3 months. Nonresponders had lower testosterone levels and higher rates of concomitant diseases and smoking. Thirty-four of the 51 nonresponders accepted the addition of 20 mg vardenafil on demand. Efficacy assessments were measured by the IIEF–erectile function domain (IIEF-EF, questions 1–5 plus 15, 30 points) and partner self-designed survey at baseline after 4–6 weeks and at study end point. Thirty out of 34 patients responded well to this combination. IIEF-EF Sexual Health Inventory for Men score improved from 12 to 24 ($P < 0.0001$), and partner survey showed significantly higher satisfaction ($P < 0.001$). These patients reported spontaneous or nocturnal and morning erections or tumescence. No changes in adverse effects were recorded.

Conclusions. These data suggest that combination therapy of testosterone and vardenafil is safe and effective in treating hypogonadal ED patients who failed to respond to testosterone monotherapy. **Yassin D-J, Yassin AA, and Hammerer PG. Combined testosterone and vardenafil treatment for restoring erectile function in hypogonadal patients who failed to respond to testosterone therapy alone. J Sex Med 2014;11:543–552.**

Key Words. Erectile Dysfunction; Hypogonadism; Testosterone; PDE5 Inhibitor

Introduction

The incidence and severity of erectile dysfunction (ED) in men increase with age [1]. In parallel, both cross-sectional and longitudinal studies demonstrate that testosterone levels decline with increasing age in males [2]. Androgens are known to have a profound role in male sexual function with potent effects on the physiological mechanisms of penile erection [3,4]. By coordinating and facilitating the delicate balance between the effect of endogenous vasoconstrictors and vasorelaxing agents of vascular tone, and through the maintenance of erectile tissue

anatomy, testosterone regulates normal erectile function (EF) [5–8]. Accordingly, hypogonadism is associated with a reduced number and quality of erections [9] with approximately one-third of men with ED displaying overt hypogonadism regardless of age [10]. As such, a testosterone deficiency is considered a predisposing factor for ED [11–13].

Therapeutically restoring testosterone to physiological levels in men with proven subphysiological concentrations has been demonstrated to improve libido in the majority of subjects and improve EF in more than 50% of these men [14–17]. In a series of case reports, Yassin et al. [18] suggest that a subset of patients with venous leakage benefit greatly from testosterone therapy for ED. Likewise, testosterone therapy in hypogonadal men with ED improves EF by diminishing venous leakage and improving penile arterial blood flow and venous occlusion assessed by magnetic resonance imaging and duplex Doppler ultrasonography, respectively [19].

Testosterone deficiency is rarely the only explanation for ED, and even with castration levels of circulating testosterone, men may still have functional erections [20,21]. Therefore, not all ED patients are hypogonadal, and differences in response to testosterone replacement are observed with the greatest improvements associated with the lowest baseline levels. Bhasin et al. [22] demonstrated that androgen supplementation produced only arguable improvements in patients with low-normal testosterone levels; however, overtly hypogonadal men had much more pronounced beneficial effects. Although beneficial effects are reported, testosterone replacement is not currently a proven panacea in the management of ED or other sexual problems in men.

Phosphodiesterase-5 (PDE5) inhibitors are considered as the treatment of choice for advanced medical management of ED and are currently the first line treatment option for ED independent of the etiology of the disorder [23]. PDE5 catalyzes the breakdown of cyclic guanosine monophosphate, a key signaling molecule in the smooth muscle and vascular relaxing effects of nitric oxide (NO), and thus increases penile blood flow. The clinical efficacy and tolerability of PDE5 inhibitors in patients with a range of ED severity have been demonstrated [24]. Despite their effectiveness, approximately 30% to 50% of patients fail to respond [25]. The mechanisms that cause PDE5 inhibitor therapy to fail are not fully understood; however, knowledge that testosterone may directly control penile PDE5 expression and activity implicates a potential androgen action [26]. Indeed, the efficacy of ED therapy with PDE5 inhibitors was blunted in patients with subclinical hypogonadism [27], and PDE5 inhibitors have been demonstrated to be ineffective in improving EF in androgen-deficient animals [28]. Consequently, it is suggested that men presenting with ED be assessed for hypogonadism before initiating first-line therapy [29,30].

Many studies now indicate that testosterone replacement can rescue the erectile response to PDE5 inhibitors in men with ED who failed to respond to PDE5 inhibitor treatment alone [29,31–36]. Buvat and colleagues [37] confirmed that the addition of transdermal testosterone to daily PDE5 inhibitor treatment was beneficial but only in hypogonadal men. Greenstein et al. [38] demonstrated that EF could be restored through the application of the PDE5 inhibitor sildenafil combined with transdermal testosterone supplementation in hypogonadal men not responding to testosterone alone. These data suggest that combination therapy may be a more suitable treatment regimen for the subset of patients not responding to monotherapy. Conversely, Spitzer et al. [39] recently reported that combination of sildenafil with a daily application of transdermal testosterone for 14 weeks did not improve ED above that of PDE5 and placebo treatment in men with low testosterone. The criterion for low testosterone in this group, however, was in the low–normal range.

Aims

The aim of this study was to investigate the efficacy and safety of combination therapy of long-acting intramuscular testosterone undecanoate and vardenafil for the treatment of ED in hypogonadal patients who had previously failed to respond to testosterone therapy alone.

Methods

Subjects

A total of 129 hypogonadal men (total serum testosterone concentration ≤3.4 ng/mL on two blood samples) presenting with ED (established using the international definition for ED, the International Index of Erectile Function (IIEF), and analysis of patient history) for at least 6 months were recruited onto the study (mean age 65 ± 6.7 years, range 47–80 years). Severity of ED was defined as IIEF–EF domain (questions 1–5 + 15)