The Efficacy of Combination Treatment with Injectable Testosterone Undecanoate and Daily Tadalafil for Erectile Dysfunction with Testosterone Deficiency Syndrome

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ABSTRACT

Introduction. Both testosterone therapy and chronic treatment with phosphodiesterase type 5 inhibitors (PDE5Is) have positive effects on the histology of penile corpora and erectile function. However, few clinical studies have evaluated the efficacy of combination therapy with both testosterone replacement and chronic PDE5Is.

Aim. This study was designed to evaluate the efficacy and safety of combination treatment with long-acting injectable testosterone undecanoate (TU) and a once-daily tadalafil 5 mg for erectile dysfunction with testosterone deficiency syndrome.

Methods. Sixty patients were consecutively enrolled and followed for 36 weeks. Thirty patients were randomly assigned to group I and received 1,000 mg of parenteral TU on day 1, followed by additional injections at weeks 6 and 18 with on-demand tadalafil 10–20 mg during the 30 weeks of treatment. The remaining 30 patients received the same dose and schedule of TU as group I, and were prescribed once-daily tadalafil 5 mg during 30 weeks.

Main Outcome Measures. Serological tests were performed, and the International Index of Erectile Function (IIEF), Aging Males’ Symptoms (AMS) questionnaires, and Global Assessment Question (GAQ) were administered to the patients.

Results. Total IIEF and AMS scores were significantly improved during the 30 weeks of treatment in both groups. When IIEF scores were compared between the two groups, group II showed better symptom scores than group I at weeks 6 and 30. A similar pattern was observed when comparing AMS scores between the groups. At week 36, changes in IIEF and AMS scores that indicated worsened symptoms compared with week 30 were observed in both groups; group II showed better symptom scores than group I. On the GAQ, the ratio of patients reporting improvement in erectile function was significantly higher in group II than group I.

Conclusions. The combination of long-acting injectable TU and once-daily tadalafil 5 mg produced a significant improvement in erectile function. Moreover, the improvement in erectile function was well maintained, even after the cessation of treatment. Park MG, Yeo JK, Cho D-Y, Kim JW, Kim JW, Oh MM, Kim JJ, and Moon DG.


Key Words. Hypogonadism; Tadalafil; Injectable Testosterone Undecanoate; Erectile Dysfunction
Introduction

Animal and clinical studies have indicated that testosterone replacement therapy improves erectile function and response to phosphodiesterase type 5 inhibitors (PDE5Is) in patients with erectile dysfunction (ED) and testosterone deficiency syndrome (TDS) [1]. Testosterone replacement therapy also recovers and preserves the structural and functional integrity of the corpora cavernosa [2]. Therefore, testosterone replacement can be considered first-line therapy for patients with both TDS and ED. However, testosterone replacement monotherapy may not be adequate owing to the multifactorial nature of the pathophysiology of ED [1]. According to Yassin and Saad [3], the combination of a PDE5I with testosterone replacement might be helpful in cases in which treatment with testosterone alone was not successful. Of all PDE5Is used worldwide, tadalafil has the longest half-life; it has a duration of action of 36 hours [4]. Therefore, once-daily dosing regimen was developed for the treatment of ED, which provides a therapeutic option for continuous efficacy compared with on-demand dosing [5,6]. Several clinical studies have evaluated the safety and efficacy of once-daily tadalafil in ED patients, and the results have shown comparable or superior efficacy compared with on-demand dosing of tadalafil [6,7]. In several clinical and experimental studies, chronic treatment with PDE5Is has been shown to improve endothelial function by up-regulating either muscarinic receptors or the transduction mechanisms leading to the activation of endothelial nitric oxide synthase [6]. PDE5I treatment is also effective in preserving the integrity of the corporal structure and compliance, which is most likely due to cyclic guanosine monophosphate-stimulating smooth muscle cell replacement and reduction of collagen synthesis via phosphokinase G activation [8–10]. These characteristics of chronic PDE5Is contribute to erectile rehabilitation [11].

Despite the positive effects of both testosterone and chronic PDE5Is on the histology of penile corpora and erectile function, there are few clinical studies evaluating the efficacy of combination therapy with both testosterone replacement and chronic PDE5Is and the synergistic effects of these two treatments. Therefore, we hypothesized that testosterone replacement and chronic PDE5I treatment exhibit synergistic effects that benefit penile rehabilitation.

Aim

This study was designed to evaluate the efficacy and safety of the combination of testosterone replacement therapy and chronic PDE5I treatment in patients with ED and TDS.

Methods

Beginning in 2010, 60 consecutive patients who complained of ED as a primary symptom and had a serum testosterone level lower than 350 ng/dL were enrolled in present study. We followed each patient for 36 weeks. All of the men included in this study were over the age of 40; each had a normal digital rectal examination (DRE) and a prostate-specific antigen (PSA) level lower than 3.0 ng/mL. For inclusion in this study, each patient was required to have a female sexual partner. The following patients were excluded from this study: patients who were receiving nitrate preparations; patients who had previously been treated for hypogonadism; patients with a history of hypersensitivity reactions to PDE5Is, congestive heart failure, unstable angina, myocardial infarction, cerebrovascular attack, prostate cancer, human immunodeficiency virus, psychosis, or sleep apnea; and patients with active systemic disease.

The patients were randomly divided into two groups using the blocked randomization method. Thirty patients were placed in group I and designated as controls. They received 1,000 mg of parenteral testosterone undecanoate (TU; 4 mL/amp) on day 1, followed by additional injections at weeks 6 and 18. For patients who requested on-demand PDE5Is due to unsatisfactory erectile function, tadalafil 10–20 mg was prescribed in addition to testosterone replacement therapy from day 1 through the end of week 30. The remaining 30 patients were placed in group II. They received the same dose and schedule of parenteral TU as group I, but they were also prescribed a once-daily dose of tadalafil 5 mg from day 1 through the end of week 30. The baseline characteristics of all patients are presented in Table 1.

Main Outcome Measures

Serum testosterone levels were measured by radioimmunoassay during the first visit, at weeks 12 and 24 during the study, and 6 weeks after the treatment cessation (week 36). Blood samples were obtained between 8 and 11 AM. For serum
biochemistry for safety profiles, serum hemoglobin (Hb), hematocrit (Hct), and PSA were checked during the first visit, at weeks 12 and 24, and 6 weeks after treatment cessation; glucose and lipid profiles were also checked during the first visit and at week 30. The height and weight of each patient were measured, and the body mass index (BMI) was calculated at the first visit and at week 30. To determine the clinical efficacy of the treatments, the International Index of Erectile Function (IIEF) questionnaire and the Aging Males’ Symptoms (AMS) questionnaire, which were translated into Korean and validated for use in our population [12,13], were administered to the patients at baseline and at weeks 6, 18, 30, and 36. The following Global Assessment Question (GAQ) was asked at weeks 6, 18, 30, and 36: “Has there been any improvement in your erectile function since the start of therapy?” Possible answers included “improved” and “not improved” (Figure 1).

Primary efficacy was evaluated according to the IIEF scores at weeks 30 and 36. Secondary efficacy was assessed according to the changes in the AMS scores and answers to the GAQ at the same visits. Means of data were calculated for each group and were reported as mean ± 95% confidence interval of the standard deviation of the mean. Statistical

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of the two treatment groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Group II</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.3 ± 10.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.98 ± 3.1</td>
</tr>
<tr>
<td>Comorbidities (n)‡</td>
<td>12/30</td>
</tr>
<tr>
<td>HTN</td>
<td>5</td>
</tr>
<tr>
<td>DM</td>
<td>3</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>4</td>
</tr>
<tr>
<td>BPH/LUTS</td>
<td>5</td>
</tr>
<tr>
<td>Testosterone (ng/dL)</td>
<td>270.8 ± 48.5</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>14.1 ± 1.1</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>42.4 ± 3.2</td>
</tr>
<tr>
<td>PSA (ug/dL)</td>
<td>0.98 ± 0.51</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>191.2 ± 30.2</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>98.2 ± 36.2</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>53.2 ± 15.2</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>150.2 ± 70.5</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>118.3 ± 31.2</td>
</tr>
<tr>
<td>IIEF (EF)</td>
<td>13.0 ± 5.6</td>
</tr>
<tr>
<td>IIEF (OF)</td>
<td>5.0 ± 2.8</td>
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<tr>
<td>IIEF (SD)</td>
<td>4.2 ± 1.5</td>
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<td>IIEF (IS)</td>
<td>5.3 ± 2.2</td>
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<td>IIEF (OS)</td>
<td>4.0 ± 1.9</td>
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<tr>
<td>IIEF (total)</td>
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<tr>
<td>AMS (psycho)</td>
<td>12.9 ± 4.7</td>
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<tr>
<td>AMS (sexual)</td>
<td>17.2 ± 3.5</td>
</tr>
<tr>
<td>AMS (total)</td>
<td>48.9 ± 12.1</td>
</tr>
</tbody>
</table>

*P values are obtained by paired t-test (between visit 0 and visit 5)
‡Some patients had multiple comorbidities

AMS = Aging Males’ Symptoms; BMI = body mass index; BPH = benign prostatic hyperplasia; HDL = high-density lipoprotein; IIEF = International Index of Erectile Function; LDL = low-density lipoprotein; LUTS = lower urinary tract symptoms; PSA = prostate-specific antigen

Figure 1 Schedule of testosterone undecanoate injection and assessment of efficacy and safety in both groups. AMS = Aging Males’ Symptoms; BMI = Body Mass Index; GAQ = Global Assessment Question; IIEF = International Index of Erectile Function; PSA = prostate-specific antigen
analysis was conducted using the independent \( t \)-test and the chi-squared test after confirmation of normal distribution of parameters by the Kolmogorov–Smirnov test. \( P \) values less than 0.05 were considered statistically significant.

**Results**

At baseline, there were nonsignificant differences between group I and group II in terms of mean age, BMI, or comorbidities. Additionally, there were nonsignificant differences in lipid profiles or baseline serum levels of total testosterone, Hb, Hct, PSA, or glucose. Further, nonsignificant differences were observed between baseline IIEF scores or AMS scores between the two groups (Table 1).

During the treatment period, four patients in group I and eight patients in group II dropped out of the study. Four patients in group II did not continue treatment due to the expense of the medications, and the others did not visit the outpatient department during the follow-up period. No one was withdrawn from the study for not meeting the detailed exclusion criteria or complications related to treatment.

Serum total testosterone levels were significantly increased at week 12 (\( P < 0.001 \) in both groups) and remained elevated until week 24 (\( P < 0.001 \) in both groups compared with baseline) in both groups. However, a significant decrease in serum testosterone level was observed at week 36 compared with week 24 in both groups (\( P < 0.001 \) in both groups); nonsignificant differences in serum testosterone levels were observed between the two groups at these times (Figure 2).

In both group I and group II, mean total IIEF scores were significantly improved at week 6 (\( P < 0.001 \) in both groups), and the improvements were maintained until week 30 (\( P < 0.001 \) in both groups at weeks 12, 18, 24, and 30 compared with baseline). Similarly, the total scores on the AMS questionnaire significantly decreased at week 6 (\( P = 0.009 \) in group I, \( P = 0.007 \) in group II), and the improvements were maintained until week 30 (\( P < 0.001 \) in both groups at weeks 12, 18, 24, and 30 compared with baseline). When IIEF scores were compared between the two groups, there were significant differences at week 6 (\( P = 0.02 \) and week 30 (\( P = 0.04 \) (Figure 3). There was also a significant difference in AMS scores between the two groups at week 6 (\( P = 0.045 \); Figure 4). Six weeks after the treatment cessation (week 36), both groups showed changes in IIEF (\( P < 0.001 \) in group I, \( P = 0.041 \) in group II) and AMS scores (\( P = 0.011 \) in group I, \( P = 0.083 \), in group II) that indicated worsened symptoms compared with week 30. Overall, IIEF and AMS scores at week 36 in group II indicated greater symptom improvement than in group I (\( P = 0.015 \) and \( P = 0.03 \), respectively; Figures 3 and 4).

According to the response to the GAQ at week 6, 60% (15/25) of patients in group I and 77.3% (17/22) in group II reported improvement in erectile function compared with the pretreatment...
phase; the difference between the two groups was significant ($P = 0.015$). At week 30, 76.0% (19/25) of patients in group I and 90.9% (20/22) in group II reported improvement in erectile function; the difference between the two groups was significant ($P = 0.037$). Six weeks after the treatment cessation, the proportion of patients in each group who reported improved erectile function decreased to 48.0% (12/25) and 72.7% (16/22), respectively. This also revealed a significant difference between the groups ($P = 0.032$; Figure 5).

Nonsignificant change in BMI was observed during the 30 weeks of treatment in either group. A significant decrease in plasma total cholesterol was noted in both groups ($P = 0.023$, $P = 0.035$). Low-density lipoprotein and triglyceride levels were decreased, and high-density lipoprotein levels were slightly increased in both groups, but these changes were not statistically significant. Plasma glucose levels showed a tendency to improve after treatment in both groups, but no statistical significance was observed (Table 2).

Hg and Hct levels, which had increased during the first 12 weeks of testosterone administration ($P < 0.001$ in both groups), remained stable until week 36, and no values were observed above the upper limit of the normal range in either group. PSA levels were significantly increased at week 12 in both groups ($P = 0.04$, $P = 0.02$); however, nonsignificant changes in PSA level were observed during the last 18 weeks of treatment or the 6 weeks of treatment cessation (Figures 6 and 7). No disorders or abnormalities were identified by follow-up DRE or clinical symptoms.

During the treatment period, 19 patients in group I were prescribed on-demand tadalafil 10 or 20 mg from day 1 through week 30 due to ED that responded poorly to TU. In comparison of baseline data between subgroups of group I according to

**Table 2** Changes in BMI, lipid profile, and glucose levels in the two groups during the treatment period

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>$P^*$</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 30th week</td>
<td>Baseline 30th week</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.98 ± 3.10 24.85 ± 4.01</td>
<td>25.01 ± 3.60 24.95 ± 3.65</td>
<td>0.802 0.815</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>191.2 ± 30.2 181.8 ± 39.2</td>
<td>189.1 ± 41.2 180.1 ± 45.2*</td>
<td>0.023 0.035</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>98.2 ± 36.2 97.5 ± 38.5</td>
<td>100.1 ± 32.1 98.9 ± 34.1</td>
<td>0.610 0.270</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>53.2 ± 15.2 54.2 ± 19.2</td>
<td>54.3 ± 13.2 54.9 ± 14.0</td>
<td>0.860 0.225</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>150.2 ± 70.5 146.2 ± 70.5</td>
<td>151.3 ± 69.5 147.3 ± 69.5</td>
<td>0.108 0.115</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>118.3 ± 31.2 116.8 ± 33.2</td>
<td>119.2 ± 28.9 116.6 ± 32.9</td>
<td>0.350 0.180</td>
</tr>
</tbody>
</table>

*P value < 0.05 by paired t-test between baseline and week 30 in each group

HDL = high-density lipoprotein; LDL = low-density lipoprotein

There was no significant difference between two groups at baseline and 30th week by independent t-test
to the use of on-demand tadalafil, there was no significant difference in BMI, comorbidities, serological parameters including testosterone, and baseline AMS scores. However, the group that did not receive on-demand tadalafil was younger \((P=0.043)\) and had higher baseline IIEF scores \((P=0.015)\) than the group that received on-demand tadalafil.

Five patients (20%) in group I and four patients (18.2%) in group II experienced an adverse event, including dyspepsia, hot flushing, headache, myalgia, and acne. However, symptoms of all adverse events were mild, and patients recovered without sequelae. There was nonsignificant difference in the incidence of adverse events between the two groups.

**Discussion**

Several clinical studies have been conducted to evaluate the efficacy of testosterone replacement therapy using various treatment methods. Specifically, Moon et al. [14] investigated the efficacy and safety of injectable TU in 133 Korean patients. The authors reported significant improvements in IIEF and AMS scores. No serious adverse reactions were reported. A 4-year follow-up study of 25 men who received injectable TU confirmed the safe and steady effect of injectable TU [15]. In addition to the improvements in symptom scores and minimal side effects of injectable TU, Yassin et al. [2] showed its ability to recover or rehabilitate erectile function in patients who have venous leakage as the etiology of ED with TDS. We selected injectable TU as the modality of testosterone replacement in the present study owing to its convenience in maintaining a steady therapeutic effect that is not influenced by an individual’s medication compliance and its proven efficacy and safety in Korean populations.

Several studies have shown improved erectile function following monotherapy with injectable TU. According to Zitzmann et al. [16], patients with some degree of ED who did not receive concomitant therapy with PDE5Is reported decreased severity of ED after TU therapy. Aversa et al. [17] also showed that 6 months of treatment with injectable TU increased testosterone levels, improved metabolic parameters, and improved erectile function, as indicated by scores on the IIEF-5 and the AMS questionnaire. However, many studies have also shown that monotherapy with testosterone or PDE5Is is not sufficient to achieve satisfactory erectile function in many hypogonadal men with ED. According to Yassin et al. [18], only 58% of ED patients responded to injectable TU monotherapy, and 88.2% of nonresponders showed response after the addition of on-demand vardenafil to injectable TU. Buvat et al. [19] showed that the addition of transdermal testosterone to daily tadalafil treatment was beneficial in patients with testosterone levels below 300 ng/dL. These data indicated that combination therapy with testosterone and PDE5Is may be appropriate for patients who do not respond to monotherapy. Still, controversies exist regarding the benefits of combination therapy [18,20].

![Figure 6](image1.png)

**Figure 6** Changes in serum PSA levels (ug/dL). A significant increase in PSA levels was observed at week 12 compared with baseline \((P=0.04\) in group I, \(P=0.02\) in group II); the increase was maintained until week 36 in both groups, and no significant differences were observed between the groups. \(^1P<0.05\), compared with baseline testosterone levels in each group.

![Figure 7](image2.png)

**Figure 7** Changes in hematocrit (Hct [%]). A significant increase in Hct was observed during the first 12 weeks of treatment in both groups \((P<0.001\) in both groups); a significant decrease was observed after cessation of treatment \((P=0.04\) in group I, \(P=0.03\) in group II). No significant differences were observed between the groups. \(^1P<0.001\), compared with baseline testosterone levels in each group. \(^2P<0.05\), compared with week 24 testosterone levels in each group.
Therefore, we designed the present study to evaluate combination therapy with injectable TU and PDE5Is in hypogonadal men with ED.

With respect to the use of PDE5Is combined to testosterone replacement, chronic use of PDE5Is can be considered. In several animal studies, chronic treatment with PDE5Is such as tadalafil was shown to have beneficial effects on pathologic findings of the tunica albuginea and corpus cavernosum, even though the inducible nitric oxide synthase was insufficient [21,22]. A study in rats pretreated with chronic PDE5Is evaluated the effects of regular treatment with PDE5Is on cavernous tissue endothelial reactivity and examined frequency response curves generated by electrical cavernosal nerve stimulation. The rats treated with PDE5Is showed enhanced endothelial-mediated relaxation and frequency-dependent erectile responses compared with untreated control rats [23].

The data from several clinical studies, as well as animal studies, have also shown that chronic PDE5Is can improve or preserve erectile function. McMahon [6] demonstrated that the group of men who received a daily dose of tadalafil 10 mg showed significantly higher IIEF erectile function domain scores and completions of successful intercourse compared with the group that received on-demand tadalafil 20 mg [6]. Aversa et al. [24] also showed that tadalafil 20 mg on alternate days for 4 weeks was better than on-demand dosing for improving endothelium-dependent vasodilatation of cavernous arteries, and improvements were maintained for 2 weeks after the discontinuation of treatment.

Based on the findings from these studies, testosterone replacement and chronic dosing of PDE5Is for penile rehabilitation is thought to be a promising combination in “disease modification” or a “cure” for ED with TDS based on the synergistic effects of the two treatments. In fact, several animal studies have shown the efficacy of this combination therapy [1,25]. However, few clinical studies have been conducted in humans that evaluate the efficacy of combination therapy with testosterone and chronic PDE5Is. Kim et al. [26] demonstrated that the combination of testosterone replacement and chronic PDE5Is was more beneficial to patients with severe testosterone deficiency. The patients received an intramuscular testosterone enanthate injection every 4 weeks for 12 weeks; they received a combination of testosterone enanthate injection and daily tadalafil 5 mg for the next 12 weeks. However, the optimal therapeutic interval of intramuscular testosterone enanthate injection is known to be 2–3 weeks, and therefore, sufficient testosterone replacement was not achieved in that study. Additionally, the period of combination therapy was only 12 weeks, which was not sufficient to show a synergistic effect of testosterone and daily tadalafil. Also, the therapeutic effect of combination therapy was not fully determined because this study was not a randomized controlled study.

In the present study, patients received long-acting injectable TU in combination with daily tadalafil 5 mg. We compared the effects of combination therapy with the effects of testosterone plus on-demand tadalafil. The treatment was discontinued at week 30, and the symptom severity was evaluated at week 36 to assess the efficacy of combination therapy in penile rehabilitation. The results showed that the combination of testosterone replacement and daily tadalafil had better efficacy and satisfaction than testosterone replacement plus on-demand tadalafil. The symptom scores of both the IIEF and AMS questionnaires, and the response to GAQ were better in the group that received daily tadalafil (group II) compared with the group that received on-demand tadalafil (group I) at 6 weeks. These findings reflect the more rapid improvement of erectile function in group II compared with group I. This may be related to infrequent use of on-demand tadalafil during the first 6 weeks in group I due to low libido, which is one of the main symptoms of late-onset hypogonadism. On the contrary, group II could maintain constant serum levels of tadalafil regardless of their libido. Then, the scores of both the IIEF and AMS questionnaires and the responses to GAQ in group I were improved to the levels of group II at 18 weeks as libido increased. The differences between the two groups in IIEF scores and responses to the GAQ at 30 weeks reflect the synergistic effects of combination therapy with testosterone and daily tadalafil. According to Francomano et al. [27], withdrawal of long-acting injectable TU therapy provokes a return to hypogonadism in all cardiac and hormonal parameters within 6 months. In the present study, serum testosterone levels in both groups showed a similar pattern after treatment cessation. However, the improved symptom scores of both the IIEF and AMS questionnaires and the responses to the GAQ at week 36 (6 weeks after stopping treatment) in group II confirmed that combination treatment that included daily tadalafil therapy demonstrated a distinct benefit in penile rehabilitation.
There are several limitations to the present study. First, this was a pilot study, and the size of the study population was relatively small, so the statistical power is limited. Second, the follow-up period was too short to evaluate the maximal effects. One year or more may be required to achieve maximum treatment effects in erectile function [28,29]. Nonsignificant changes in BMI and other metabolic parameters after treatment were also related to the short treatment period [28,29]. Third, there were several patients who did not complete the entire study due to the economic burden of the price of the medications. Fourth, the absence of a daily tadalafil-only group or a testosterone replacement-only group limits the interpretation of our results. Finally, because our analysis of symptom severity of ED and TDS relied on self-assessment questionnaires, biased reporting is a concern; the lack of objective parameters, such as the results of penile Doppler ultrasound, is also a limitation of this study. However, our approach had clinical significance, and one of its strengths was its ability to show a synergistic effect of the combination of testosterone and chronic PDE5I treatment. An increase in the duration of response following treatment cessation was also evident. All the parameters related to erectile function, testosterone deficiency, and patient satisfaction indicated improved symptom severity after cessation of all treatment in the combination group compared with the group that received only on-demand PDE5Is.

Conclusions

The combination of long-acting injectable TU and once-daily tadalafil 5 mg resulted in a significant improvement in erectile function compared with long-acting injectable TU with on-demand tadalafil. Moreover, the improvement in erectile function was sustained in the group with once-daily dosing of tadalafil 5 mg compared with those with on-demand tadalafil, even after the cessation of treatment. Therefore, the combination of injectable TU and once-daily tadalafil 5 mg can be considered a primary treatment modality for ED patients with TDS. Long-term follow-up of a large population is needed to confirm and expand on our findings.

Acknowledgments

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