Initial Clinical Experience With Testosterone Undecanoate Therapy (AVEED) in Men With Testosterone Deficiency in the United States

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OBJECTIVE To report our initial experiences with testosterone undecanoate (TU 750) mg (AVEED) in men with testosterone deficiency.

METHODS All patients receiving TU 750 mg at our center between July 1, 2014, and August 1, 2016, were identified. Clinical response was assessed through structured interviews and laboratory evaluations. Adverse events were documented, including increase in prostate specific antigen (PSA), increase in hematocrit (Hct), and the development of postinjection cough.

RESULTS More than 2 injections were received by 147 men, with mean age 63.2 years. Mean baseline total testosterone (T) and free T were 305 ng/dL and 0.69 ng/dL, respectively. Nadir mean results during treatment were higher for total and free T, at 413.2 ng/dL and 0.81 ng/dL, respectively ($P < .001$ for each). Symptomatic improvement was reported by 97 of 147 patients (66.0%). Thirty patients (20.4%) discontinued therapy. Return of symptoms before the next injection was noted by 34%, managed by reduced interval between injections and/or supplemental injections of T cypionate. Three patients (2%) experienced transient cough immediately after TU injection, none requiring intervention. Mean Hct rose from 45.6% to 47.2%. Mean PSA rose from 1.7 ng/mL to 2.0 ng/mL. There were no strokes, myocardial infarctions, or deaths, and no new cases of prostate cancer.

CONCLUSION This initial clinical experience with TU 750 mg provides evidence for good patient satisfaction and persistence with treatment, together with a favorable safety profile. Optimal dosing may be less than 10 weeks for some individuals.

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In 2014 the Food and Drug Administration (FDA) approved testosterone undecanoate (TU) 750 mg (AVEED) for the treatment of testosterone deficiency (TD) in the United States. Outside of the United States, TU at a higher dose of 1000 mg (Nebido) has been available since 2003. Although TU 750 mg was shown to provide acceptable pharmacokinetics and safety for regulatory approval,[1] we are unaware of any reports on its clinical use.

The 11-carbon side chain of TU provides a longer half-life than testosterone cypionate or enanthate, allowing for less frequent injections and therefore greater convenience for patients.[2] Whereas T cypionate and T enanthate are typically injected every 1-2 weeks, the recommended intervals for AVEED and Nebido are 10 weeks and 10-14 weeks, respectively. The decreased frequency of treatment allows patients to reduce their yearly injections from 26-52 injections per year to approximately 5 injections per year. In addition to the convenience of fewer injections, studies have also demonstrated improved biochemical responses to TU when compared with shorter-acting T formulations, in particular absence of rapidly alternating high and low T concentrations, called the "roller coaster effect," that can cause symptomatic distress.[3] One concern regarding TU raised by the FDA in the United States is an injection-related cough believed due to pulmonary oil microembolism (POME). This concern led to a box warning

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for AVEED, with recommendation to manage this through a risk evaluation and mitigation strategy program. This warning does not appear on TU 1000 mg products outside the United States.

A substantial literature has demonstrated clinical benefits of TU 1000 mg on a number of end points in men with TD, including sexual function and desire, metabolic parameters, and bone density.[4-6] However, studies on the clinical benefits and risks of TU 750 mg are lacking. Here we present our experience with TU 750 mg for the treatment of TD in a cohort of men with symptomatic TD.

METHODS

Patients who received TU (AVEED) at our center between July 1, 2014, and August 1, 2016, were identified by search of electronic medical records. Patients who had incomplete medical records or who were lost to follow-up after their initial injection were excluded. Indications for testosterone therapy at our center include the presence of characteristic symptoms or signs of TD together with documented low levels of serum total testosterone (T) or free T demonstrated on at least 2 occasions. Biochemical criteria for TD were total T less than 350 ng/dL or free T less than 1.5 ng/dL by analog assay or less than 100 pg/mL by equilibrium dialysis or as calculated free T.[7] Total T was measured by immunoassay performed by Quest Diagnostics LLC, and free T was measured by immunochemiluminescence assay performed by Quest Diagnostics LLC. Decisions regarding the choice of T therapy delivery including the use of TU are influenced greatly by patient choice, convenience, and medical insurance coverage.

Clinical assessment of response was performed through structured interviews covering sexual function, psychological well-being, and physical function. Patients underwent a thorough physical examination at baseline including a digital rectal examination. Baseline laboratory evaluation included prostate-specific antigen (PSA), hematocrit (Hct), total T, free T, sex hormone-binding globulin, luteinizing hormone, and follicle-stimulating hormone.

Treatment consisted of intramuscular injection of 750 mg TU, followed at 4 weeks by a booster injection and injections at 8–10-week intervals thereafter. Injections were given by slow push in the upper outer quadrant of the buttocks alternating sides with each injection. In accordance with the FDA Risk Evaluation and Mitigation Strategy for TU 750 mg, patients were advised to remain within the office for 30 minutes following each TU injection to monitor for POME or anaphylaxis.

After the initial booster injection, blood tests were routinely obtained 1 week before each treatment, consisting of total T, free T, Hct, PSA, luteinizing hormone, and follicle-stimulating hormone. Subjective response to treatment was assessed through structured interviews covering sexual function, psychological well-being, and physical function. Because of our experience with other long-term therapies such as pellets in which there is considerable interindividual variation in duration of symptomatic response,[8] patients were specifically questioned at follow-up visits regarding return of symptoms at the end of the injection cycle. Although not previously reported in the literature, patients who experienced return of symptoms together with documented low nadir T levels were offered a 100-mg intramuscular injection of T cypionate before their next scheduled TU treatment to alleviate their symptoms. At each visit patients were offered the choice of continuing treatment, discontinuing treatment, or choosing a different T delivery method. Bone densitometry was not routinely performed.

In our practice, therapeutic phlebotomy is routinely offered to men whose Hct exceeded 54%. Those patients also undergo a discussion about dose adjustments and alternative options for T delivery. Prostate biopsy was recommended to men whose PSA rose to above 4.0 ng/mL or demonstrated a worrisome rise in PSA from baseline, even if the value was less than 4.0 ng/mL.

RESULTS

Complete electronic records were available for 147 patients. Baseline characteristics are presented in Table 1. Mean age was 63.2 years ± 11.0. A large majority of patients (86.4%) had previously undergone treatment with another form of T therapy and 13.6% received TU as their initial form of T therapy. The most frequent mode of

Table 1. Demographics of TU patients (n = 147)

Patient Demographics	
Mean age (years)	63.2 (±11.0)
T naïve	13.6%
Previous T exposure	86.4%
Baseline TT	305 ng/dL (±80.6)
Baseline FT	0.69 ng/dL (±0.28)
Baseline PSA	1.7 ng/dL (±1.5)
Baseline Hct	45.6% (±4.7)
Comorbidities	
Hypertension	42.8%
Diabetes	13.6%
SHIM Score	10.1 (±6.0)
Reasons for Switching to TU From Previous Therapy*	
Desired longer acting	22.1%
Pain without previous therapy	21.3%
Poor response to previous therapy	21.3%
Polycythemia with previous therapy	5.5%
Cost of previous therapy	7.9%
Previous Methods of TTh†	
Short-acting injections	53.5%
Pellets	37.0%
Topicals	29.1%

Hct, hematocrit; FT, free testosterone; PSA, prostate-specific antigen; SHIM, Sexual Health Inventory for Men; T, testosterone; TT, total testosterone; TU, testosterone undecanoate; TTh, testosterone therapy.

* Values >100% due to some patients endorsing multiple reasons for switching to TU.

† Values >100% due to patients previously on multiple different modalities.

previous T therapy was weekly self-injections with T cypionate (53.5%). Multiple forms of previous T therapy had been used by 21.1% of the cohort. The most frequently stated reason for switching to TU was a desire for less frequent injections. The interval between previous T therapy and TU was 8.6 weeks (±0.8) and was influenced by insurance requirements and patient's personal decisions of when to start therapy. Mean baseline total and free T were 305 ng/dL (±80.6) and 0.69 ng/dL (±0.28), respectively. Mean baseline values were 1.7 ng/mL for PSA and 45.6% for Hct. The prevalence of hypertension and diabetes in this population was 42.8% and 13.6%, respectively. Baseline Sexual Health Inventory for Men score 10.1 (±6.0).

The mean amount of time between injections after the initial booster injection was 8.5 weeks (±0.7). The range of TU injections was 3-12 total injections. The mean total duration of TU treatment was 9.3 months (±4.6, range 2-25 months), during which time there was a mean of 6.9 (±2.3) injections per patient.

Follow-up nadir blood test obtained 1 week before the next injection revealed a mean total T of 413.2 ng/dL and a mean free T of 0.81 ng/dL. These values were significantly higher than baseline laboratory values for total T (P = .0001) and free T (P = .0006).

Symptomatic Response

Symptomatic improvement was reported by 97 of 147 patients (66.0%) during treatment. Thirty patients (20.4%) discontinued therapy. The most frequently stated reasons for discontinuation were related to the cost and/or efficacy of the treatment (see Table 2). Of the patients who discontinued therapy only 6 patients (20.0%) had not been on a previous modality of T therapy.

Twenty patients (13.6% of the cohort) began TU as their initial form of T therapy. Nadir testosterone levels in this cohort was 436.2 ng/dL (±190.1). Six of those patients (30%) discontinued TU. Three of those patients switched to T cypionate because of insurance issues; 2 switched to pellets because of poor symptomatic response; and 1 discontinued therapy altogether.

A return of TD symptoms before the next injection was reported by 50 patients (34.0%). Of these only 8 patients (16.0%) had been testosterone-naïve before starting TU. Mean nadir total T was 333.4 ng/dL (±136.7) for men who reported a return of symptoms and 435.0 ng/dL (±179.3) for men without a return of symptoms (P = .0006). Twelve patients (8.2% of the cohort) received an injection of T cypionate toward the end of their treatment interval to ameliorate the return of their symptoms before their next TU injection.

Table 2. Discontinuation rates

Discontinuation of TU Therapy (n = 147)	
Yes	30 (20.4)
No	117 (79.6)
Reason for Discontinuation (n = 30)	
Insurance issue/cost of treatment	12 (41)
Dissatisfaction with/lack of efficacy of therapy	14 (47.5)
Unknown/other	4 (11.5)

Data are presented as n (%).

Table 3. Side effects of TU treatment (n = 147)

Side Effects	n (%)
Cough	3 (2.0)
Bruising	3 (2.0)
Injection site soreness	2 (1.4)
Polycythemia (Hct >54%)	2 (1.4)
Other	2 (1.4)
Headaches	1 (0.68)
Insomnia, racing heart, facial flush	1 (0.68)
Experienced symptoms at nadir visit	50 (34)
Safety	
Mean PSA increase	+0.31 ng/dL
Mean Hct increase	+3.2%

Adverse Events (Table 3)

Cough. Three patients (2%) experienced cough immediately after TU injection. In all instances the cough lasted less than 5 minutes and did not require intervention. All 3 men continued treatment with TU with no recurrence of cough at subsequent injections.

Injection Site. Bruising was reported in 3 patients.

Hct. Mean Hct rose from 45.6% to 47.2%. The mean individual increase in hematocrit was 1.6%. Two men (1.4%) developed Hct greater than 54% while on therapy, and both underwent therapeutic phlebotomy.

Prostate. Mean PSA rose from 1.7 ng/mL to 2.0 ng/mL. The mean individual change in PSA was an increase of 0.3 ng/mL. Nine transrectal prostate biopsies were performed for patients with rising PSA and 3 were performed for men on active surveillance for low-risk prostate cancer. No patient developed prostate cancer or demonstrated disease progression while on treatment.

Cardiovascular. There were no strokes, myocardial infarctions, or deaths.

DISCUSSION

This study presents our initial clinical experience with TU 750 mg. Overall, TU 750 mg appeared to offer good symptomatic benefit, with a favorable safety profile. The observed discontinuation rate of 20.4% compares favorably with discontinuation rates for topical T therapies, which exceed 50% at 9 months.[9] This result may not be generalizable to broader populations. The decision by a large majority to continue with TU 750 mg must be regarded in light of previous experience with at least 1 other mode of therapy in 86% of the cohort, with the option of returning

to their previous treatment if they were dissatisfied with TU 750 mg. The longer duration of action of TU injections over the short-acting injection formulations, primarily T cypionate in our practice, was the most commonly given reason for switching to TU and presumably for continuing with treatment.

Testosterone levels were higher at nadir than at baseline, confirming the efficacy of TU 750 mg in raising serum T for the group over the injection cycle. Although the product label indicates that injections should be given every 10 weeks after the booster injection, the mean duration between injections for this group was 8.5 weeks. This shorter duration follows from pharmacokinetic data in which peak serum T concentrations are achieved at approximately day 7, declining thereafter with a terminal tail at T concentrations that are less than robust.[1] This information, coupled with early clinical experience in which some men reported return of bothersome symptoms before the next injection, led us to shorten the duration of injections to less than the recommended 10 weeks.

The return of symptoms before the next injection appears to have been directly related to a drop in serum T concentrations. Nadir T concentrations in men who reported symptom recurrence were lower than nadir concentrations in men who did not. The treatment options for these men with premature return of symptoms include supplementing testosterone with other means, such as injections of short-acting agents or topicals, or simply tolerating the symptoms until the next injection of TU 750 mg. A number of our patients elected to receive an injection of T cypionate toward the end of their cycle for this reason. Interestingly, this experience indicates that the threshold at which symptoms of TD appear is well above the value of 300 ng/mL, which is recommended by some groups as the lower limit of normal.

Our initial experience indicates a very satisfactory safety profile for TU 750 mg. In more than 1000 total injections there were no severe adverse events of any type. A minor, transient cough was noted in 3 men and all 3 continued with TU 750 mg treatment without recurrence of cough. The risk of cough in this population was less than 0.3%. It is worth noting that we have also observed rare cases of transient cough immediately after injections with testosterone cypionate. There were no cases of anaphylaxis, and no patient required medical attention for any adverse event. It is important to note that our study is limited to a homogenous group of 147 patients. Although our set of safety data is interesting, there is not sufficient evidence to suggest removing established safety protocols that have been set for TU usage.

Increases in Hct (1.6%) and PSA (0.3 ng/mL) were comparable with other reported studies. A trial in 2008 of 130 patients treated with a total of 3 TU 750 mg injections over 24 weeks demonstrated a mean Hct increase of 2.4 %.[1] Wang et al reported a mean Hct increase of 4.2% and mean PSA increase of 0.4 ng/mL in an 84-week study of TU 750 mg.[10]

Although there are no head-to-head studies comparing the US formulation (TU 750 mg administered every 10 weeks) with the higher dose available in more than 80 countries worldwide (1000 mg administered every 10-14 weeks), the reported results for the higher dose appear similar to those described here. In a study population of 122 men, Haider reported no significant change in mean prostate volume and PSA, with 4 men developing elevations of Hct greater than 52%.[11] POME was first reported in 1995 in a study of intramuscular T enanthate in 1.5% of injections given[12] and first reported as a complication of TU in 2009.[13] Middleton reported POME in 12.4% of men, none of whom required medical intervention.[14] In 0.9% of patients, an increase in Hct to above 54% was noted, and none of these patients underwent therapeutic phlebotomy. Hackett et al[15] randomized 199 patients to placebo or TU 1000 mg given at baseline, week 6, and week 18. They found significant sexual benefits in men with baseline total T less than 8 nmol/L (approximately 240 ng/dl). Safety monitoring demonstrated mean increases in Hct of 2.1% and PSA of 0.3 ng/mL. A review of 120 T-deficient men who received TU 1000 mg every 10-14 weeks revealed a Hct increase of 2.85% and a mean PSA increase of 0.2 ng/dL.[16] Francomano et al demonstrated no change in post-void residual, urinary symptoms, or prostate size when comparing obese men on TU 1000 mg with matched controls,[17] consistent with previous studies demonstrating no relationship between serum testosterone and lower urinary tract symptoms.[18-20]

Our study has a number of limitations. This was a retrospective study describing the experience from only a single center. A large majority of our patients had been previously treated with testosterone therapy in some form, and all patients had insurance coverage for TU therapy. These population features may not be reflective of the general population.

In summary, the results demonstrate that TU 750 mg is a reasonable treatment choice for many men with TD. Significantly fewer injections per year are needed than with short-acting injectables, such as T cypionate or enanthate, and the persistence rate (continued use of treatment) was considerably higher in our small, homogenous population compared with historical data regarding topical testosterone formulations. Safety data regarding increases in Hct and PSA were consistent with rates reported for other T therapies. Episodes of POME were rare and of minimal medical consequence when they occurred. One observation not previously reported, to our knowledge, was the premature return of symptoms in some men before the next scheduled injection. We attempted to address this by reducing the injection interval to 8 weeks and, in some cases, by offering a short-acting injection.

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