Original Article
Hormonal regulation and hypogonadism

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health 2024 Oct 42(4): 762-771
https://doi.org/10.5534/wjmh.230164

The World Journal of MEN's HEALTH

Patient Satisfaction with Oral Testosterone Undecanoate in Men Who Received Prior Testosterone Therapy: An Open-Label, Single-Center Clinical Trial

Marco-Jose Rivero[1], Rohit Reddy[1], Akhil Muthigi[1], Raghuram Reddy[2], Sunwoo Han[3], Isildinha M. Reis[3,4], Mehul Patel[1], Ranjith Ramasamy[1]

[1]*Desai Sethi Urology Institute, University of Miami Miller School of Medicine,* [2]*Herbert Wertheim College of Medicine, Florida International University,* [3]*Biostatistics and Bioinformatics Shared Resource, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine,* [4]*Department of Public Health Sciences, University of Miami Miller School of Medicine, Miami, FL, USA*

Purpose: To evaluate patient satisfaction and symptom control in hypogonadal men transitioning from other testosterone therapies to oral testosterone undecanoate (TU).

Materials and Methods: In this open-label clinical trial, men aged 18 to 75 years with hypogonadism were switched to oral TU after a sufficient washout of previous testosterone therapies. Treatment satisfaction and symptom control were primarily measured using the 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9) and quantitative androgen deficiency in aging males (qADAM) questionnaires, respectively. Secondary outcomes included changes in serum testosterone (T), estradiol (E2), hematocrit (HCT), and prostate-specific antigen (PSA) levels.

Results: Forty-one men participated, with significant improvements in all TSQM-9 scores observed over 6 months. Symptom control as measured by qADAM remained consistent. There was a significant increase in serum T and E2 levels, but HCT and PSA levels remained stable.

Conclusions: Switching to oral TU from other testosterone therapies is associated with increased patient satisfaction and stable hypogonadal symptom control.

Keywords: Clinical trial; Hypogonadism; Patient satisfaction; Testosterone

INTRODUCTION

Hypogonadism is characterized by low serum testosterone (T) levels associated with clinical symptoms such as fatigue, decreased muscle mass, decreased libido, depressed mood, and sexual dysfunction [1,2]. This condition exhibits a prevalence of 6%–12% in men between the ages of 40 and 70 years, escalating to 15%–30% among individuals who are either obese or diagnosed with diabetes [3]. Testosterone therapy (TTh) has been

Received: Jul 23, 2023 **Revised:** Sep 9, 2023 **Accepted:** Sep 27, 2023 **Published online** Jan 2, 2024
Correspondence to: Ranjith Ramasamy https://orcid.org/0000-0003-1387-7904
Desai Sethi Urology Institute, University of Miami Miller School of Medicine, 1120 NW 14th st, 15th fl, Miami, FL 33136, USA.
Tel: +1-305-243-6260, **Fax:** +1-305-243-3381, **E-mail:** ramasamy@miami.edu

made accessible through a broad range of delivery systems, including intramuscular injections, topical solutions, transdermal patches, and subcutaneous pellets. Each of these comes with their unique advantages and drawbacks [4].

Previously, oral T formulations were not available within the United States due to concerns about low bioavailability and hepatotoxicity risks associated with first-pass metabolism. However, following FDA approval in 2019, oral testosterone undecanoate (TU) emerged on the scene and has demonstrated its capability to restore serum T to normal levels [5]. This was made possible, in part, through a self-emulsifying drug delivery system that circumvents first-pass metabolism [4,6-8]. Oral TU has displayed efficacy and safety in phase III clinical trials, with significant improvements in sexual function, body fat reduction, and increases in lean mass and bone density over a 12-month period. While a modest increase in systolic blood pressure (SBP) was observed, the side effect profile resembled that of other forms of TTh, without evidence of liver toxicity [5,8,9]. Despite the demonstration of efficacy and safety of oral TU, data on patient satisfaction in comparison to other TTh forms are lacking. Hence, we designed a clinical trial to assess patient satisfaction in men who transition to oral TU from other TTh formulations, hypothesizing comparable satisfaction levels to other forms of TTh.

MATERIALS AND METHODS

This single-arm clinical trial was conducted at the University of Miami from June 2021 to April 2023 (IRB No. 20200971, ClinicalTrials.gov Identifier NCT04983940). Informed consent was obtained by all enrolled subjects.

1. Patient population

In this study, we enrolled men aged 18 to 75 years previously diagnosed with hypogonadism and treated with various forms of TTh. Hypogonadism was identified if the T level was less than 350 ng/dL, accompanied by at least one symptom such as fatigue, low libido, depressed mood, and/or erectile dysfunction, in line with the guidelines from multiple international associations, including the International Society for Sexual Medicine [10]. To ensure the reliability of our study, we insisted that patients completed an adequate washout period after stopping their prior TTh (4 weeks for gels and injection-based therapies and 16 weeks for subcutaneous pellets). We deemed a single T measurement during the washout period sufficient for inclusion in the trial. Exclusion criteria included body mass index >40 kg/m^2; SBP >150 mmHg or diastolic blood pressure (DBP) >90 mmHg; abnormal results for prostate exam or prostate-specific antigen (PSA); hemoglobin >16 g/dL; hematocrit (HCT) <35% or >50%; history of stroke or myocardial infarction in the past 5 years; untreated, severe obstructive sleep apnea; history of seizures; or history of breast or prostate cancer.

2. Intervention and data collection

Patients initially completed the 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9) and the quantitative androgen deficiency in aging males (qADAM) questionnaire to record their experiences with previous TTh. After completion of the washout period, patients were started on oral TU (Jatenzo®) 237 mg twice daily (BID, morning and evening) with food. Serum total T, estradiol (E2), HCT, and PSA were measured after completion of the washout period and at each subsequent follow-up visit. At the 1-month follow-up visit, the oral TU dosage was titrated based on total serum T in accordance with FDA prescribing guidelines [11]. The 3-month and 6-month follow-up visits included a physical examination, repeat laboratory studies, and completion of the TSQM-9 and qADAM questionnaire with regards to their experience with oral TU. Throughout the study, patients were required to remain off all forms of TTh except for the study medication. Therapeutic T range was defined as ≥350 ng/dL. Patients with polycythemia (HCT >52%) at 3- or 6-month follow-up were referred for therapeutic phlebotomy.

3. Outcomes

The primary outcomes were 3- and 6-month changes in patient satisfaction, as measured by the TSQM-9 (score range 0–100); and in hypogonadal symptom control, as measured by the qADAM questionnaire (score range 10–50) [12,13]. The secondary outcomes were 3- and 6-month changes in serum total T, E2, HCT, and PSA. As oral TU carries a black box warning for blood pressure increases, we also monitored SBP and DBP at each visit.

The World Journal of MEN's HEALTH

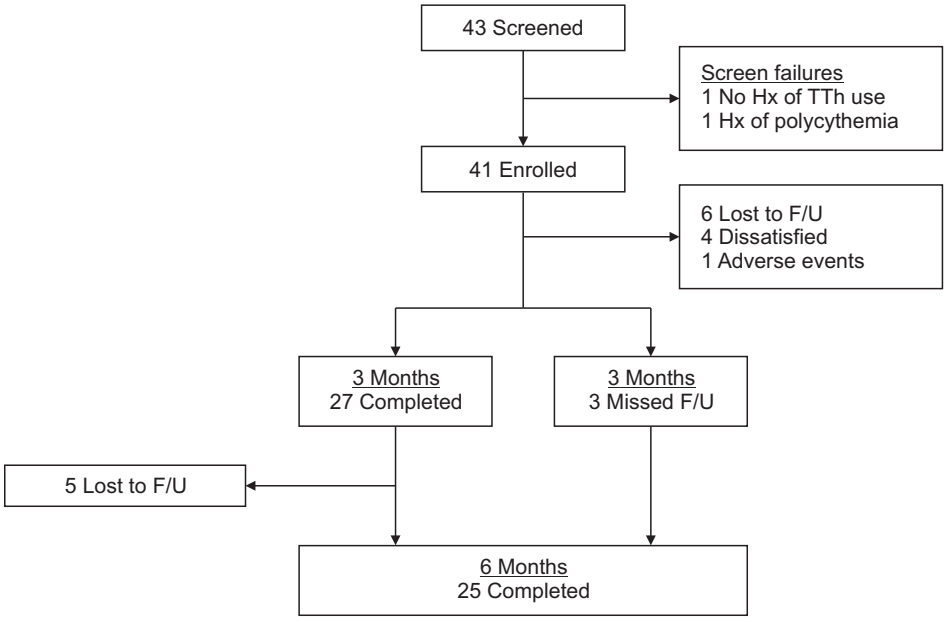

Fig. 1. Study process diagram. Hx: history, TTh: testosterone therapy, F/U: follow-up.

4. Statistical analysis

We used descriptive statistics to succinctly summarize demographic and baseline characteristics of the sample. Outcome measures at the 3- and 6-month evaluations were presented as means with a 95% confidence interval (CI). To decipher mean changes over time, we executed longitudinal data analyses using a linear mixed model. We assumed that any missing data are missing at random. When the overall changes were significant, we performed pairwise comparisons using Bonferroni correction. Statistical significance was considered at a p-value of less than 0.05. All our analyses were performed in SAS 9.4.

RESULTS

A total of 41 men were enrolled, all of whom received the intended treatment. Twenty-seven men (65.8%) returned to 3-month visit and 25 (61.0%) to 6-month visit (Fig. 1). Trial recruitment and follow-up proceeded from June 2021 to April 2023. The trial intended to evaluate 40 patients at 6 months, but it was ended due to limited funding from the trial sponsor. Men completing at least one follow-up evaluation were analyzed for baseline characteristics, primary and secondary outcomes. The mean age was 49 years, and mean baseline T and HCT were 200.3 (standard deviation [SD]: 60.4) and 44.9 (SD: 3.8), respectively (Table 1). Of the patients enrolled in the study, 14 (34.1%) were previously on intramuscular T cypionate, 4 (9.8%) on topical gels, 5 (12.2%) on intranasal gels, 15 (36.6%) on subcutaneous pellets, and 3 (7.3%) on intramuscular T undecanoate. Twelve out of 30 (40.0%) patients required up titration from 237 mg BID to 316 mg BID at 1-month follow-up.

1. Primary outcomes

Patient satisfaction with oral TU as measured by the TSQM-9 was significantly higher at 3 and 6 months relative to baseline. From longitudinal analyses, overall time effect was significant in all three domains of the TSQM-9 ($p<0.05$). Effectiveness scores increased from an estimated mean of 63.0 (95% CI: 51.2–74.7) at baseline to 78.2 (95% CI: 71.1–85.3, p=0.025) at 3 months and 78.1 (95% CI: 70.8–85.5, p=0.028) at 6 months. Convenience scores increased from an estimated mean of 62.4 (95% CI: 50.4–74.4) at baseline to 84.5 (95% CI: 77.5–91.5, p=0.002) at 3 months and 86.6 (95% CI: 79.9–93.2, p=0.001) at 6 months. Global Satisfaction scores increased from an estimated mean of 66.7 (95% CI: 55.0–78.3) at baseline to 83.3 (95% CI: 77.1–89.4, p=0.015) at 3 months and 83.0 (95% CI: 74.9–91.1, p=0.026) at 6 months. Finally, there was no significant change in hypogonadal symptom control as measured by the qADAM questionnaire (p=0.060) (Table 2, Fig. 2).

2. Secondary outcomes

With oral TU treatment, overall time effect supporting improvement of outcome was significant for

Table 1. Baseline patient characteristics

Characteristic	Total
Total patients	30 (100)
Age (y)	
Mean (SD)	49 (11.5)
Median (P25, P75)	49.9 (43.5, 56.9)
Race	
White	26 (86.7)
Black	2 (6.7)
Unknown	2 (6.7)
Hispanic ethnicity	23 (76.7)
BMI (kg/m^2)	
20–24.9 (healthy)	6 (20.0)
25–29.9 (overweight)	14 (46.7)
≥30 (obese)	10 (33.3)
Mean (SD)	28.5 (3.7)
Median (P25, P75)	28.5 (25.8, 32.1)
Not current smoker	29 (96.7)
CAD	1 (3.3)
HTN	15 (50.0)
HLD	8 (26.7)
DM	5 (16.7)
OSA	7 (23.3)
No. of comorbidities	
0	12 (40.0)
1	7 (23.3)
2+	11 (36.7)
Baseline T-level (ng/dL)	
Mean (SD)	200.3 (60.4)
Median (P25, P75)	195.3 (150, 243)
Baseline HCT (%)	
Mean (SD)	44.9 (3.8)
Median (P25, P75)	44.6 (42.1, 46.8)
Systolic blood pressure	
Mean (SD)	126.8 (13.1)
Median (P25, P75)	125 (120, 137)
Diastolic blood pressure	
Mean (SD)	77.6 (8.7)
Median (P25, P75)	76.5 (71, 83)

BMI: body mass index, CAD: coronary artery disease, HTN: hypertension, HLD: hyperlipidemia, DM: diabetes mellitus, OSA: obstructive sleep apnea, T: total testosterone, HCT: hematocrit, SD: standard deviation, P25, P25: 25th and 75th percentiles.

serum total T (p<0.0001) and E2 (p=0.004). Serum total T increased from an estimated mean of 200.3 (95% CI: 177.5–223.1) at baseline to 485.2 (95% CI: 399.5–571.0, p<0.0001) at 3 months and 649.2 (95% CI: 507.1–791.2, p<0.0001) at 6 months. Therapeutic T levels were attained in 66.7% (18/27) of patients at 3 months and 76.0% (19/25) of patients at 6 months. Serum E2 increased from an estimated mean of 14.4 (95% CI: 10.9–17.9) at baseline to 21.8 (95% CI: 17.3–26.2, p=0.008) at 3 months and 21.2 (95% CI: 15.8–26.6, p=0.040) at 6 months (Fig. 3). During the trial, two patients were started on anastrozole, dosed at 0.25 to 1 mg twice per week. For both HCT and PSA, there were no significant changes over time (overall time effect p=0.340 for HCT and p=0.816 for PSA, Fig. 3). One patient had polycythemia at 3 months and was thus referred for therapeutic phlebotomy. There were no significant changes over time in mean SBP or DBP (Table 3).

3. Losses and adverse events

As illustrated in Fig. 1, among 41 enrolled patients, there were 11 patient dropouts before 3-month visit, including 6 lost to follow-up, 4 dissatisfied with treatment, and 1 adverse event. Among 30 patients with baseline evaluation, 27 and 25 completed evaluations at 3 and 6 months, respectively. The one adverse event-related dropout was due to worsening chronic kidney disease requiring transplant, which preceded the trial in onset. Other adverse events include 3 patients with hypertension, 2 with polycythemia, and 1 with new-onset nocturia (Table 4).

DISCUSSION

The recent FDA approval of oral TTh capsules presents an exciting opportunity to treat hypogonadism in a manner that benefits from the ease of oral medication administration. Previous studies have found that treatment with oral TU has been associated with improvements in serum T, psychosexual function, bone density, and body composition [5,8,9]. Despite these documented improvements, there is a lack of data on patient-reported outcome measures, prompting the need for this prospective clinical trial assessing treatment satisfaction in patients who switched to oral TU from other TTh formulations.

1. Primary outcomes

Patients treated with oral TU demonstrated significantly increased scores in the Effectiveness, Convenience, and Global Satisfaction domains of the TSQM-9, indicating a positive perception of the treatment's effectiveness in alleviating symptoms and improving overall satisfaction. The observed improvements in

The World Journal of MEN's HEALTH

Table 2. Patient satisfaction measured by TSQM-9 and qADAM

	Baseline	3 months	6 months
TSQM-9 Effectiveness			
Number	30	27	25
Observed mean (95% CI)	63.0 (51.7, 74.3)	78.0 (70.7, 85.3)	78.2 (70.6, 85.9)
Estimated mean (95% CI)[a]	63.0 (51.2, 74.7)	78.2 (71.1, 85.3)	78.1 (70.8, 85.5)
Est. mean diff. from baseline (95% CI)	N/A	15.2 (3.5, 27.0)	15.1 (3.2, 27.1)
Adjusted p	N/A	0.025	0.028
TSQM-9 Convenience			
Number	30	27	25
Observed mean (95% CI)	62.4 (50.7, 74.1)	84.4 (77.1, 91.6)	86.9 (80.2, 93.6)
Estimated mean (95% CI)[a]	62.4 (50.4, 74.4)	84.5 (77.5, 91.5)	86.6 (79.9, 93.2)
Est. mean diff. from baseline (95% CI)	N/A	22.1 (9.6, 34.6)	24.1 (11.8, 36.5)
Adjusted p	N/A	0.002	0.001
TSQM-9 Global			
Number	30	27	25
Observed mean (95% CI)	66.7 (55.3, 78.1)	83.1 (76.8, 89.3)	83.7 (75.5, 91.9)
Estimated mean (95% CI)[a]	66.7 (55.0, 78.3)	83.3 (77.1, 89.4)	83.0 (74.9, 91.1)
Est. mean diff. from baseline (95% CI)	N/A	16.6 (4.7, 28.5)	16.3 (3.7, 29.0)
Adjusted p	N/A	0.015	0.026
qADAM			
Number	30	27	25
Observed mean (95% CI)	36.6 (35.7, 37.5)	34.4 (32.9, 36.0)	35.5 (33.5, 37.6)
Estimated mean (95% CI)	36.6 (35.7, 37.5)	34.4 (32.8, 36.0)	35.5 (33.5, 37.6)
Est. mean diff. from baseline (95% CI)	N/A	-2.2 (-4.0, -0.4)	-1.1 (-3.3, 1.2)

TSQM-9: the 9-item Treatment Satisfaction Questionnaire for Medication (score: 0–100 [best] for each domain, qADAM: quantitative androgen deficiency in aging males; score 10–50 [best], Estimated mean: from a linear mixed model assessing time effect. 95% CI: 95% confidence interval, Adjusted p: Bonferroni adjusted p-value for multiple comparisons *versus* baseline, N/A: not applicable.
[a]Overall time effect was significant at $p<0.05$ for TSQM-9 Effectiveness ($p=0.030$), TSQM-9 Convenience ($p=0.001$), and TSQM-9 Global Satisfaction ($p=0.021$). Overall time effect was not significant for qADAM ($p=0.060$).

these domains suggest that oral TU is effective in addressing the concerns and needs of the study population. However, no significant change was observed in hypogonadal symptom control as measured by the qADAM questionnaire. This finding suggests that while patients reported increased satisfaction with oral TU, it may not have led to significant improvements in specific hypogonadal symptoms relative to previous TTh. These results highlight the multifaceted nature of patient satisfaction, wherein subjective perceptions of effectiveness and convenience play a crucial role but may not correlate with control of symptoms. The increased patient satisfaction observed in the present study is likely, in part, associated with the route of administration [14]. Oral medications are easy to administer and often more convenient for patients to incorporate into their daily routines compared to parenteral routes of administration [15,16].

2. Secondary outcomes

The trial demonstrated a significant increase in serum total T levels at both the 3- and 6-month time points, indicating the effectiveness of oral TU in raising T levels in patients with hypogonadism. Additionally, there were significant increases in serum E2 levels, consistent with aromatization of circulating T [17]. No significant changes were observed in HCT levels or PSA levels during the treatment period, suggesting that oral TU did not significantly affect red blood cell count or prostate health. Mean HCT increased 0.8% over 6 months, but this change was not statistically significant. It should be noted that patients in the present study may have had residually increased HCT at baseline secondary to previous TTh, thereby "masking" the full impact of oral TU on HCT levels. Nevertheless, these results contribute to a better understanding of the hormonal effects of oral TU treatment and provide

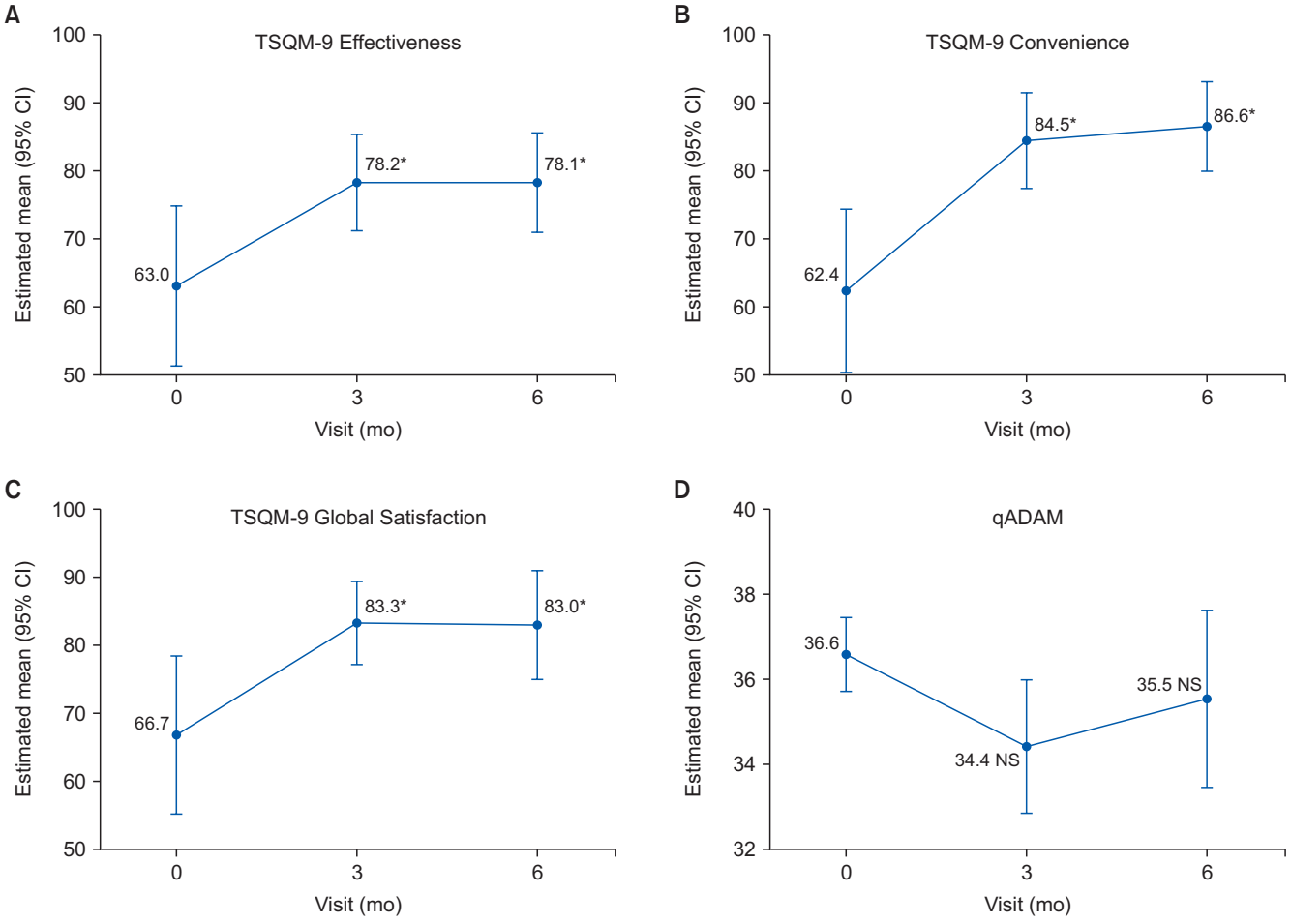

Fig. 2. Mean TSQM-9 scores for (A) Effectiveness, (B) Convenience, (C) Global Satisfaction, and (D) qADAM with 95% confidence intervals. TSQM-9: the 9-item Treatment Satisfaction Questionnaire for Medication, qADAM: quantitative androgen deficiency in aging males. *Significant difference from baseline (Bonferroni adjusted $p<0.05$, NS indicate $p\geq0.05$).

reassurance regarding its safety profile. With attention to oral TU's black box warning, enrolled patients developed new-onset hypertension at a rate comparable to that of a previous trial [9]. However, the overall mean SBP and DBP experienced no significant changes.

3. Losses

The patient dropouts may have potential implications for practical use of oral TU. The high rate of loss to follow-up, amounting to 26.8% (11/41) of patients, is likely specific to this single center study population, as higher follow-up rates were achieved in a 2-year multicenter study [9]. A total of 4 patients (9.8%) dropped out due to dissatisfaction—lack of symptom relief—with oral TU. Of these patients, 1 was previously on short-acting intramuscular injections, 1 on intranasal gel, and 2 on subcutaneous pellets. These findings suggest that alternative forms of TTh may offer advantages in terms of patient adherence and satisfaction [4]. Oral TU is dosed frequently (BID), which may lead to decreased compliance with missed scheduled doses. Yet other patients may be adherent with BID dosing, but have inadequate co-intake with food, resulting in poor absorption, another possible reason for lack of symptom relief with oral TU [7,18]. It is crucial for healthcare providers to consider these factors when making treatment decisions and discussing the practical use of TTh options with patients, accounting for individual preferences, lifestyle, and the potential impact on treatment outcomes [19]. Regarding adverse events, only one led to dropout, namely chronic kidney disease requiring kidney transplantation, which preceded the trial in onset and is thus not attributable to the study treatment.

4. Strengths and limitations

The study demonstrates several strengths, including

The World Journal of MEN's HEALTH

Table 3. Testosterone, HCT, Estradiol, PSA, and blood pressure outcomes

	Baseline	3 months	6 months
Testosterone			
Number	30	27	24
Observed mean (95% CI)	200.3 (177.7, 222.9)	486.8 (398.9, 574.7)	649.3 (504.0, 794.7)
Estimated mean (95% CI)[a]	200.3 (177.5, 223.1)	485.2 (399.5, 571.0)	649.2 (507.1, 791.2)
Estimated mean difference from baseline (95% CI)	N/A	284.9 (203.1, 366.8)	448.9 (311.4, 586.4)
Adjusted p	N/A	<0.0001	<0.0001
HCT			
Number	30	27	24
Observed mean (95% CI)	44.9 (43.5, 46.4)	45.0 (43.6, 46.5)	45.2 (43.9, 46.5)
Estimated mean (95% CI)	44.9 (43.5, 46.4)	45.0 (43.6, 46.3)	45.7 (44.4, 47.1)
Estimated mean difference from baseline (95% CI)	N/A	0.1 (-1.1, 1.2)	0.8 (-0.4, 2.0)
Estradiol			
Number	23	21	17
Observed mean (95% CI)	14.4 (11.0, 17.8)	21.6 (16.9, 26.3)	21.2 (15.8, 26.7)
Estimated mean (95% CI)[a]	14.4 (10.9, 17.9)	21.8 (17.3, 26.2)	21.2 (15.8, 26.6)
Estimated mean difference from baseline (95% CI)	N/A	7.4 (2.8, 12.0)	6.8 (1.5, 12.2)
Adjusted p	N/A	0.008	0.040
PSA			
Number	23	21	17
Observed mean (95% CI)	1.06 (0.71, 1.41)	1.14 (0.80, 1.49)	0.95 (0.53, 1.37)
Estimated mean (95% CI)	1.06 (0.71, 1.41)	1.10 (0.77, 1.43)	1.04 (0.69, 1.39)
Estimated mean difference from baseline (95% CI)	N/A	0.04 (-0.15, 0.23)	-0.02 (-0.23, 0.18)
Systolic blood pressure			
Number	30	23	22
Observed mean (95% CI)	126.8 (121.9, 131.7)	127.8 (121.7, 133.9)	125.5 (120.1, 130.8)
Estimated mean (95% CI)	126.8 (122.0, 131.6)	127.7 (122.0, 133.3)	125.1 (120.2, 129.9)
Estimated mean difference from baseline (95% CI)	N/A	0.9 (-4.0, 5.7)	-1.8 (-6.3, 2.8)
Diastolic blood pressure			
Number	30	23	22
Observed mean (95% CI)	77.6 (74.4, 80.9)	75.3 (71.2, 79.5)	76.4 (72.4, 80.4)
Estimated mean (95% CI)	77.6 (74.4, 80.8)	76.4 (72.4, 80.3)	76.2 (72.8, 79.7)
Estimated mean difference from baseline (95% CI)	N/A	-1.3 (-4.2, 1.6)	-1.4 (-4.1, 1.3)

HCT: hematocrit; PSA: prostate-specific antigen, Estimated mean: from a linear mixed model assessing time effect, 95% CI: 95% confidence interval, Adjusted p: Bonferroni adjusted p-value for multiple comparisons *versus* baseline, N/A: not applicable.
[a]Overall time effect was significant at p<0.05 for Testosterone (p<0.0001) and Estradiol (p=0.004). Overall time effect was not significant for HCT (p=0.340), PSA (p=0.816), systolic blood pressure (p=0.575), and diastolic blood pressure (p=0.505).

Table 4. Adverse events during treatment period

Adverse event	Number (%)
Hypertension	3 (7.3)
Polycythemia	2 (4.8)
Nocturia	1 (2.4)
Chronic kidney disease	1 (2.4)

high medication adherence, adequate follow-up rates, diverse patient backgrounds, positive primary outcomes, significant improvement in hormone levels, and minimal adverse events. Despite some dropouts before the 3-month visit, a substantial number of patients (65.8%) returned for the 3-month visit, and a majority (61.0%) completed the 6-month visit. These follow-up rates suggest good retention and cooperation from the patients. The results demonstrate that patient satisfaction with oral TU, as measured by the TSQM-9, significantly increased at both the 3-month and 6-month marks compared to baseline. The improvements were observed across all three domains of the TSQM-9 (Effectiveness, Convenience, and Global Satisfaction). These findings highlight the favorable impact of oral

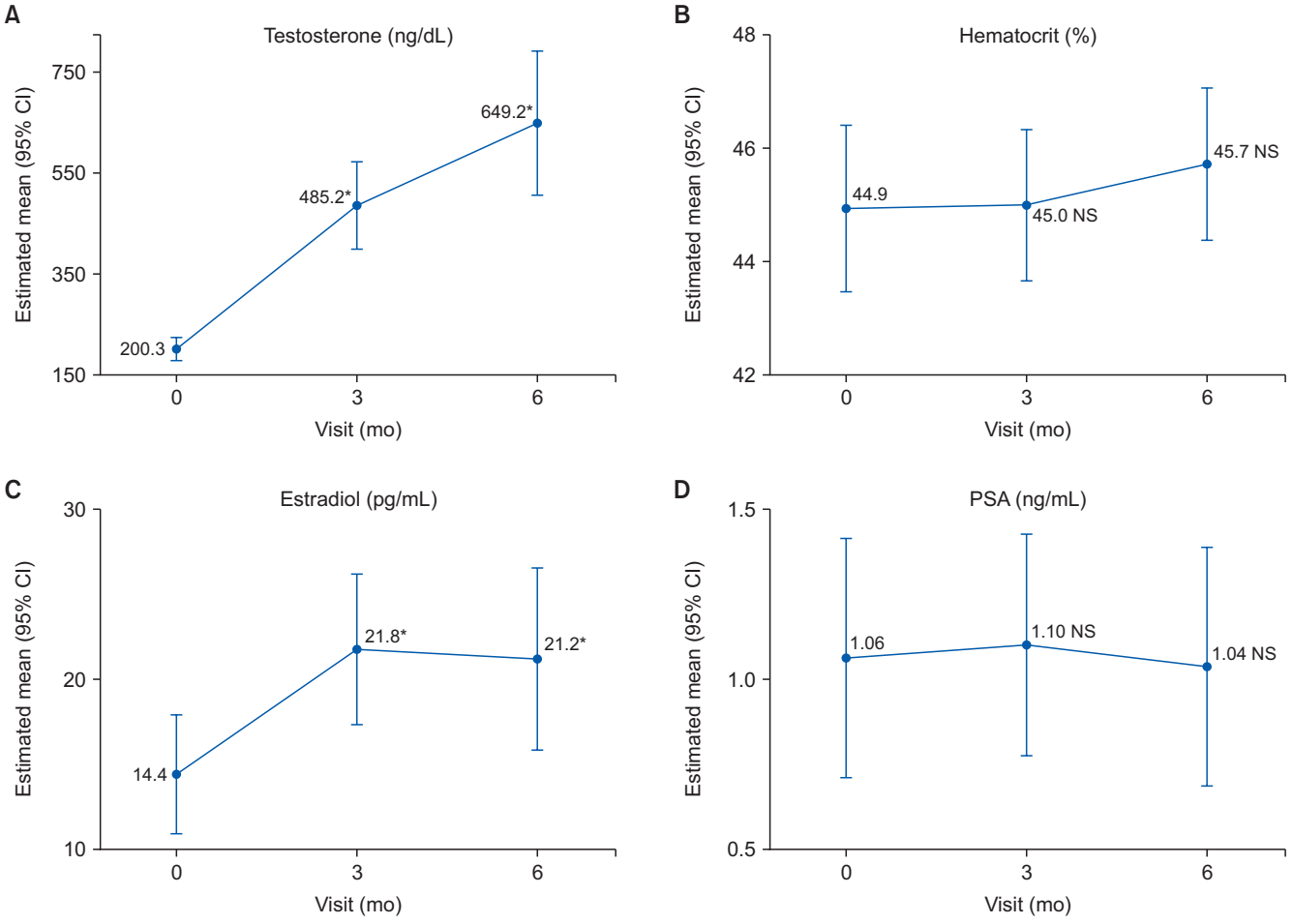

Fig. 3. Mean values for (A) serum total testosterone, (B) hematocrit, (C) estradiol, and (D) PSA with 95% confidence intervals. PSA: prostate-specific antigen. *Significant difference from baseline (Bonferroni adjusted $p<0.05$, NS indicate $p\geq0.05$).

TU on patient-reported outcomes. The study revealed a substantial increase in serum total T levels after treatment with oral TU. The improvements were observed at both the 3-month and 6-month assessments, with most patients (66.7% at 3 months and 76.0% at 6 months) achieving therapeutic T levels. These results emphasize the efficacy of oral TU in restoring T levels in hypogonadal men.

This study is not without its limitations. Firstly, this is an open-label trial with no comparison group. Without a control group receiving an alternative treatment or a placebo, it is likely that the observed patient satisfaction scores are influenced by other factors, such as the consumption of TTh at no cost [19]. Future studies may seek to investigate the effect of the cost of TTh on patient satisfaction. In addition, men in this trial may have been inherently dissatisfied with their prior form of TTh therapy, leading to their willingness to enroll and higher satisfaction with a new formulation. The trial suffers from a small sample size at a single center, which can compromise the generalizability and statistical power of the findings. The TSQM-9 is a Likert scale-based questionnaire that is subject to response bias and lacking validation in this specific study population, which may diminish the reliability and validity of the collected data. As men completed blood draw appointments independently at external laboratories, we were unable to control for the timing of T measurements. Men were instructed to complete blood draws at set intervals from their last dose (4–6 hours post dose). But adherence to this timing was not enforced, nor was medication adherence enforced via collection of medication bottle or other methods. Finally, there is a possibility of overestimating patient satisfaction scores due to patient dropouts. At least 4 (9.8%) patients discontinued the trial due to dissatisfaction with the treatment, and their exclusion from the analysis may lead to an inflated perception of patient satisfaction.

CONCLUSIONS

To our knowledge, this is the first prospective clinical trial evaluating patient satisfaction with oral TU. Patients switching from other TTh formulations to a 6-month course of oral TU experienced increased measures of effectiveness, convenience, and global satisfaction relative to previous TTh. Hypogonadal symptom control with oral TU was like patients' previous TTh, with an increase in serum total T to therapeutic levels in >75% of patients. Despite its frequent dosing and high cost, oral TU has been shown to be a safe, effective, and convenient TTh modality.

Conflict of Interest

Dr. Ramasamy is a consultant and grant recipient of Acerus Pharmaceuticals, Boston Scientific, Coloplast, and Endo Pharmaceuticals. Other authors have no potential conflicts of interest to disclose.

Funding

This study was supported by an investigator-initiated grant provided by Clarus Therapeutics (FundRef ID: GR017931).

Acknowledgements

OpenAI's ChatGPT-4 was used for grammar and sentence refinement in this manuscript. Its role was limited to text edits and did not influence research or original content generation.

Author Contribution

Conceptualization: R Ramasamy. Data curation: MJR, R Reddy, AM, MP. Formal analysis: SH, IR. Funding acquisition: R Ramasamy. Investigation: MJR, R Reddy, MP. Methodology: R Ramasamy. Project administration: MJR, R Reddy. Resources: SH, IR, R Ramasamy. Software: SH, IR. Supervision: R Ramasamy. Validation: MJR, R Reddy, AM, MP, R Ramasamy. Visualization: MJR, R Reddy, AM. Writing – original draft: MJR, R Reddy. Writing – review & editing: MJR, R Reddy, AM, SH, IR, R Ramasamy.

Data Sharing Statement

The data analyzed for this study have been deposited in HARVARD Dataverse and are available at https://doi.org/10.7910/DVN/MIBSTZ.

REFERENCES

1. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2018;103:1715-44.
2. Mulhall JP, Trost LW, Brannigan RE, Kurtz EG, Redmon JB, Chiles KA, et al. Evaluation and management of testosterone deficiency: AUA guideline. J Urol 2018;200:423-32.
3. Erenpreiss J, Fodina V, Pozarska R, Zubkova K, Dudorova A, Pozarskis A. Prevalence of testosterone deficiency among aging men with and without morbidities. Aging Male 2020;23:901-5.
4. Patel M, Muthigi A, Ramasamy R. JATENZO®: challenges in the development of oral testosterone. Int J Impot Res 2022;34:721-4.
5. Swerdloff RS, Wang C, White WB, Kaminetsky J, Gittelman MC, Longstreth JA, et al. A new oral testosterone undecanoate formulation restores testosterone to normal concentrations in hypogonadal men. J Clin Endocrinol Metab 2020;105:2515-31. Erratum in: J Clin Endocrinol Metab 2020;105:e4984.
6. Yin AY, Htun M, Swerdloff RS, Diaz-Arjonilla M, Dudley RE, Faulkner S, et al. Reexamination of pharmacokinetics of oral testosterone undecanoate in hypogonadal men with a new self-emulsifying formulation. J Androl 2012;33:190-201.
7. Yin A, Alfadhli E, Htun M, Dudley R, Faulkner S, Hull L, et al. Dietary fat modulates the testosterone pharmacokinetics of a new self-emulsifying formulation of oral testosterone undecanoate in hypogonadal men. J Androl 2012;33:1282-90.
8. Swerdloff RS, Dudley RE. A new oral testosterone undecanoate therapy comes of age for the treatment of hypogonadal men. Ther Adv Urol 2020;12:1756287220937232. Erratum in: Ther Adv Urol 2021;13:17562872211036391.
9. Honig S, Gittelman M, Kaminetsky J, Wang C, Amory JK, Rohowsky N, et al. Two-year analysis of a new oral testosterone undecanoate (TU) formulation in hypogonadal men: efficacy, impact on psychosexual function, and safety. J Sex Med 2022;19:1750-8.
10. Salter CA, Mulhall JP. Guideline of guidelines: testosterone therapy for testosterone deficiency. BJU Int 2019;124:722-9.
11. Clarus Therapeutics. Jatenzo® [Internet]. U.S. Food and Drug Administration; c2019 [cited 2023 May 16]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206089s000lbl.pdf
12. Bharmal M, Payne K, Atkinson MJ, Desrosiers MP, Morisky DE, Gemmen E. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life

Outcomes 2009;7:36.
13. Mohamed O, Freundlich RE, Dakik HK, Grober ED, Najari B, Lipshultz LI, et al. The quantitative ADAM questionnaire: a new tool in quantifying the severity of hypogonadism. Int J Impot Res 2010;22:20-4.
14. Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, et al. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes 2004;2:12.
15. Edel Y, Sagy I, Pokroy-Shapira E, Oren S, Dortort Lazar A, Egbaria M, et al. A cross-sectional survey on the preference of patients with rheumatoid arthritis for route of administration of disease-modifying anti-rheumatic drugs: oral target-specific versus parenteral biologic. Isr Med Assoc J 2020;22:154-9.
16. Sánchez Martínez I, Cerdán Sánchez M, López Román J, Iniesta Martínez F, Carreón-Guarnizo E, Meca Lallana JE, et al. Possible influence of the route of treatment administration on treatment adherence in patients with multiple sclerosis. Clin Ther 2020;42:e87-99.
17. Drago F, Lo Presti L, Nardo F, Panella I, Matera M, Scapagnini U. Aromatization of testosterone by adipose tissue and sexual behavior of castrated male rats. Biol Reprod 1982;27:765-70.
18. Schnabel PG, Bagchus W, Lass H, Thomsen T, Geurts TB. The effect of food composition on serum testosterone levels after oral administration of Andriol Testocaps. Clin Endocrinol (Oxf) 2007;66:579-85.
19. Khera M. Testosterone therapies. Urol Clin North Am 2016;43:185-93.