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Review

Newer formulations of oral testosterone undecanoate: development and liver side effects

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Abstract

Introduction: Testosterone deficiency is a clinical disorder due to either failure of the testes to produce testosterone or failure of the hypothalamus or pituitary to produce sufficient gonadotropins. Previous formulations of oral testosterone therapy, particularly methyltestosterone, have been associated with adverse liver effects. Many different routes of testosterone delivery have been developed, each with their own administrative benefits and challenges. Newer formulations of oral testosterone undecanoate (TU) provide a convenient administration option, although their use has been limited by hepatotoxicity concerns based on older methyltestosterone data, and prescribing physicians may still be concerned about adverse liver effects.
Objectives: In this review, we discuss the history of oral testosterone development, clarify the mechanism of action of oral TU, and describe the relevant liver safety findings.
Methods: Relevant literature was allocated to present a review on the history of oral TU development and the mechanism of action of oral TU. We pooled data from individual studies of oral TU products to present a safety summary.
Results: Overall, safety results from studies of the newer formulations of oral TU showed that increased liver function test values are not generally associated with oral TU formulations and that no clinically significant liver toxicities were noted in clinical trials of oral TU.
Conclusion: Continued research into the safety of oral TU will contribute to a better understanding of the potential risks in patients receiving this therapy, an outcome that highlights the importance of providing patient education and reassurance regarding oral TU safety.

Keywords: chemical and drug-induced liver injury; methyltestosterone; oral testosterone; testosterone congeners; testosterone deficiency.

Introduction

Male testosterone deficiency is a clinical syndrome characterized by low testosterone due to malfunction of the testes or failure of the hypothalamus/pituitary to produce stimulatory hormones.[1,2] Patients with testosterone deficiency often experience symptoms such as fatigue, depressed mood, loss of lean muscle mass, and reduced sexual desire.[2,3] Testosterone therapy is used to achieve therapeutic testosterone levels and symptom improvement.[4,5] The guidelines of the American Urological Association recommend initiation of testosterone at minimal doses to achieve a normal physiologic testosterone range of 450-600 ng/dL and that signs and symptoms of testosterone deficiency be re-evaluated within 3 months to determine if dosing adjustments are necessary.[4] The guidelines also recommend that patients with testosterone deficiency who are receiving testosterone therapy undergo adjunctive testing, including measurement of serum luteinizing and follicle-stimulating hormones, prolactin, estradiol, hemoglobin, and hematocrit. At the time of this report, however, no recommendations had been reported regarding monitoring with liver function tests (LFTs).[4]

Testosterone undecanoate (TU) package inserts bear a label with a warning stating that oral methyltestosterone has been associated with serious hepatic adverse events, and long-term therapy with intramuscular testosterone enanthate has produced hepatic adenomas. While no specific recommendations for LFT monitoring are provided, prescribers are still advised to report any signs or symptoms of hepatic dysfunction (ie, jaundice), which may indicate drug-induced liver injury (DILI).[6-8]

Hepatic dysfunction due to DILI may indicate a severe liver injury or irreversible liver failure that is fatal or requires liver transplantation.[9] Because most drugs that cause DILI do so infrequently,[9] evaluation for DILI is important and includes severity categories that may be described according to liver injury descriptions in the drug label: level 1, steatosis; level 2, cholestasis and steatohepatitis; level 3, liver aminotransferases increase; level 4, hyperbilirubinemia; level 5, jaundice;

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level 6, liver necrosis; level 7, acute liver failure; and level 8, hepatotoxicity.[10] On the basis of these DILI severity classes, liver injury from DILI associated with methyltestosterone was categorized up to level 5 (jaundice).[10,11] In a study of the US Food and Drug Administration (FDA) Adverse Event Reporting System, examinations of the frequency of DILI associated with testosterone treatment resulted in a reported odds ratio <1, suggesting that there is no major concern for possible development of DILI in patients undergoing treatment with testosterone.[12]

Hy's Law is a principle used to identify patients at high risk of severe liver damage from a medication and is based on observations by Hy Zimmerman, a leading researcher in DILI. Hy's Law focuses on hepatocellular injury, highlights that jaundice is a warning sign of injury, and provides threshold values for elevated liver enzymes and bilirubin that indicate a patient is at high risk for DILI. While it is a helpful tool to raise suspicion, Hy's Law is not a definitive test, and when it is used to assess a patient, further investigation by a doctor is warranted.[9,13,14] A combination of diagnostic laboratory blood tests that are used to identify a potential DILI case include the following: increased aminotransferase (AT) >3× upper limit of normal (ULN) compared to control; increased AT >5×, 10×, or 20× ULN in modest numbers of test group patients and not seen in the control group; or 1 or more cases of newly increased total serum bilirubin >2× ULN in a setting of pure hepatocellular injury, with no other explanation, accompanied by an overall increased incidence of AT >3× ULN in a test group patients compared to the control group. According to Hy's Law, a finding of 2 of the abovementioned diagnostic indicators (and probably even 1) is considered highly predictive that the drug has the potential to cause severe DILI.[9]

Multiple routes of testosterone delivery have been approved for use, including oral, buccal, intranasal, transdermal, subcutaneous, and intramuscular (Table 1).[15] The routes of administration and FDA-licensed doses of the testosterone agents presented here have not been known to cause hepatic adverse effects, although the use of androgenic anabolic steroids has been associated with hepatotoxicity.[16-22] Oral administration of testosterone offers convenient dosing without injections, skin and nasal irritation, risk of transference, or risk of pellet extrusion, and recent trends in other disease states have shown patient preference for oral therapies over other regimens.[5,15,23] Despite these benefits, prescription rates of oral testosterone have steadily declined.[5] Possible explanations for current hesitation regarding the use of oral TU include concerns for hepatotoxicity demonstrated in earlier methylated testosterone formulations and unfavorable pharmacokinetics and multiple dosing requirements of the early TU product Andriol® (Merck Canada Inc, Kirkland, QC, Canada).[5,23] Additional hesitancies among clinicians with regard to prescribing oral TU may be due to a lack of insurance coverage and/or high cost, a known issue in the United States.[24]

Oral TU products have recently been approved by the FDA. The objective of this review is to discuss the history of oral testosterone development, to clarify the oral TU mechanism of action, and to describe relevant liver safety findings to address concerns surrounding oral TU therapy.

Oral TU development

Testosterone deficiency generally requires long-term treatment, making it essential that patients receive individualized therapy that ensures satisfaction and compliance.[25] Oral testosterone, while convenient, was not an option in the early stages of testosterone drug development due to its metabolism in the gut, first-pass metabolism in the liver, and subsequent hepatotoxicity.[25] It took many years and various chemical modifications to develop an oral formulation of testosterone with acceptable safety and efficacy (Fig. 1).[26]

In 1935, Ruzica and Butenandt synthesized 17α-methyltestosterone, the first orally active testosterone treatment.[5] This formulation was found to be associated with liver toxicity, including abnormal LFTs, cholestasis, and jaundice.[2,4,15,26] Because native testosterone had poor oral absorption and methyltestosterone was associated with liver toxicity, other routes were explored that are now approved for use, including buccal, intranasal, transdermal, subcutaneous, and intramuscular.[15,26] Alternative chemical modifications of testosterone were explored including esterification at the 17β-hydroxy group of the molecule rendering testosterone suitable for intramuscular injection, thus leading to short-acting testosterone propionate and long-acting testosterone enanthate and cypionate.[26] In the mid-1990s transdermal testosterone patches were developed.[26] To circumvent unpleasant skin reactions, transdermal gels were introduced in the 2000s.[26] Additionally, during the course of testosterone therapy's development, other parenteral routes were explored, including buccal and nasal routes.[26]

TU was first introduced in Europe in the 1970s as Andriol, an esterified form of testosterone that bypassed first-pass metabolism in the liver and, when coupled with an oleic acid vehicle, increased lymphatic absorption in the gut.[25,27] Andriol was approved in many countries but never in the United States due in part to high dependence of concentration on dietary fat intake.[28–31] The oleic acid vehicle used to increase absorption required Andriol to be refrigerated to maintain stability.[25] The Andriol formulation was updated to a castor oil and propylene glycol vehicle in a new formulation (Andriol Testocaps), which increased the shelf life of the medication, improved the consistency in drug concentration, and reduced the effect of dietary fat.[23,25,32] This necessitated multiple capsules throughout the day to maintain adequate drug levels.[23]

Advancements to the self-emulsifying drug delivery system (SEDDS) allowed for the development of novel oral TU formulations (JATENZO®, Clarus Therapeutics, Northbrook, IL, United States; TLANDO®, Antares Pharma, Inc., San Diego, CA, United States) that produced physiologic concentrations of testosterone without concern for meal fat content.[33–36] Another oral formulation of TU uses a phytosterol carrier vehicle (KYZATREX™, Marius Pharmaceuticals, Raleigh, NC, United States).[7,25]

Oral TU mechanism of action

After oral administration, the TU molecule is primarily absorbed into the intestinal lymphatic system by chylomicrons, improving solubility in fat.[36,37] It is released into systemic circulation by the thoracic duct and converted to testosterone, predominantly avoiding absorption into the portal vein and circumventing first-pass metabolism in the liver (Fig. 2). This mechanism is supported by evidence describing TU lymphatic absorption rates of 93.0% to 99.8% in a thoracic lymph duct–cannulated dog model.[38] Further research has demonstrated that lymphatic drug transport in humans is similar to transport in species with higher body

Table 1. Overview of testosterone therapies.

Route	Benefits	Challenges
Gel	Noninvasive, simple application	Transference; skin irritation
Patches	Noninvasive, simple application	Skin irritation
Buccal	High bioavailability, simple and self-administration; quick reversal	Gum or mouth irritation; effects on taste, cost -prohibitive
Oral	Improved compliance; modifiable dosage; quick reversal	Multiple administrations daily; food-dependent absorption; cost prohibitive
Injection	Cost-effective, SC less painful	Pain considerations for IM vs SC; multiple injections
Pellet	Infrequent dosing, no risk of transference	Invasive administration (surgical incision); local hematoma; spontaneous extrusion
Intranasal	High bioavailability; simple and self-administration; quick reversal	Multiple administrations daily; rhinorrhea, nosebleed; nasal discomfort

Abbreviations: IM, intramuscular; SC, subcutaneous.

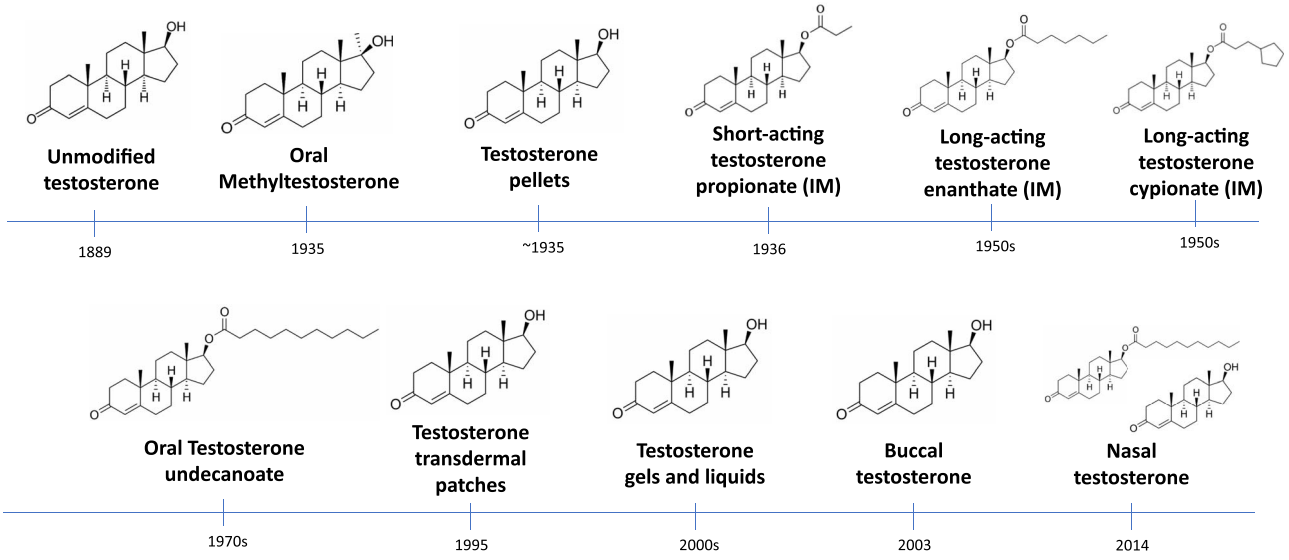

Figure 1. Historical chemical modifications of testosterone development. Between 1889 and 2014, various chemical modifications were developed. An oral formulation of testosterone with acceptable safety and efficacy was not developed until the 1970s.[15,26,36] IM, intramuscular.

mass, such as dogs, suggesting that lymph flow and lipid transport in humans may be predicted from animal models via allometric scaling.[39]

Chylomicrons are lipid spheroids formed in enterocytes that facilitate the transport of lipids, especially entities of high lipophilicity.[36] Chylomicrons are necessary for the absorption of oral TU and are released in response to lipid ingestion and digestion, and thus, the administration of oral TU with a meal is required.[36] Historically, evidence has suggested unreliable oral bioavailability, fluctuating serum levels, and short half-life when oral TU was not taken with food. However, current evidence suggests that meal fat content does not influence the bioavailability of novel formulations of oral TU.[15,25,36] Therefore, oral TU requires administration with food, but there is no evidence to support improved absorption with increased meal fat.[33,34]

In a phase 3, open-label study of hypogonadal men undergoing testosterone replacement therapy (NCT02722278), patients receiving JATENZO demonstrated a trend toward higher free testosterone levels and a greater decrease in sex hormone–binding globulin (SHBG) compared to patients receiving Axiron.[40] Higher free testosterone and decreased SHBG in patients receiving oral testosterone have been further corroborated by the results of a phase 3, randomized, active-controlled study of patients with testosterone deficiency (SOAR, ClinicalTrials.gov: NCT02081300), in which patients receiving TLANDO demonstrated a noticeable decrease in SHBG and increased free testosterone compared to those receiving topical AndroGel 1.62%.[41] Patients treated with oral TU or with topical or injectable testosterone may experience some small but noticeable first-pass metabolism that may reduce the concentration of the active drug, as evidenced by a decrease in SHBG and high-density lipoprotein and increase in free testosterone.[33,42,43] Understanding more about the safety aspect of oral TU liver metabolism will help determine real-world implications for this effect.

TU safety

Oral formulations of TU bear a warning citing possible hepatic adverse effects following prolonged use of 17-alpha-alkyl androgens (methyltestosterone).[6-8] Although oral TU therapies have demonstrated a lack of hepatic AEs in clinical studies and evidence supports the lymphatic absorption of oral TU, these therapies are still regarded with trepidation concerning the potential for hepatic adverse events.[33,34,39] In the following section, we discuss safety findings pertaining to the liver from studies of currently available oral TU products (Table 2).

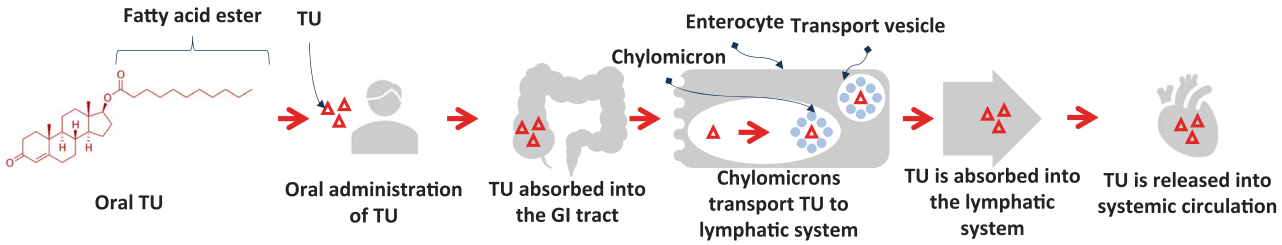

Figure 2. Oral TU absorption mechanism. TU is a lipophilic molecule primarily absorbed into the intestinal lymphatic system by chylomicrons after oral administration, improving solubility in fat.[36,37] TU is released into systemic circulation by the thoracic duct and converted to testosterone, predominantly avoiding absorption into the portal vein and circumventing first-pass metabolism in the liver. GI, gastrointestinal; TU, testosterone undecanoate.

Table 2. Description of JATENZO, TLANDO, and KYZATREX studies.

Study ID	Study design	No. of patients enrolled	Duration	Study drug and administration	Summary of liver effects
JATENZO studies					
CLAR-15012	Open-label, repeat-dose, dose-titration, phase 3 clinical trial	JATENZO 166 Axiron 55	3-4 mo	237 mg twice daily Active control: Axiron 2%	No clinically significant changes in LFTs were observed in either treatment group
CLAR-09007	Open-label, randomized, phase 3 clinical trial	JATENZO 161 AndroGel 160	12 mo	316 mg twice daily Active control: AndroGel 1%	No clinically significant changes to LFTs in patients receiving either therapy One patient receiving JATENZO experienced episodes of elevated ALT and AST 2× to 3× ULN, bilirubin remained normal
CLAR-12010	Phase 3, 12-mo open-label extension study to the CLAR-09007 Study	JATENZO 86	24 mo	316 mg twice daily Active control: AndroGel 1%	No clinically significant changes from baseline in LFTs were observed in those with JATENZO exposure
TLANDO studies					
LPCN 1021-18-001	Multicenter, open-label, single-arm study	TLANDO 138	4 mo	225 mg twice daily	Patients receiving TLANDO demonstrated no changes from baseline in LFTs at 4 mo
LPCN 1021-16-002	Multicenter, open-label, single-arm study	TLANDO 95	24 d	225 mg twice daily	Patients receiving TLANDO demonstrated no hepatic adverse events after 4 mo
LPCN 1021-13-001	Randomized, multi-center, open-label, active controlled, phase 3 study	TLANDO 210 AndroGel 105	13 weeks	225 mg twice daily Active control: AndroGel 1.62%	Both treatment groups demonstrated a decrease in LFTs (ALT, AST, ALP, and GGT) from baseline at week 52 No hepatic AEs or incidences of Hy's Law were observed
LPCN 1021-18-001	Subanalysis of a prospective, open-label, multicenter, single-arm, phase 3 study	TLANDO 36	4 mo	225 mg twice daily	Approximately 90% of patients receiving TLANDO demonstrated liver fat improvement on MRI Reductions in liver fat were greatest in patients with higher baseline liver fat NAFLD resolved in 33% of patients following 8 weeks of therapy and 48% following 16 weeks
KYZATREX studies					
MRS-TU-2019EXT	Open-label, multicenter, single-arm study	KYZATREX™ 155	6 mo	200 mg twice daily	Liver assessments not reported
MRS-TU-2019	12-mo, open-label, active-controlled, randomized, phase 3 study	KYZATREX™ 214 AndroGel 100	12 mo	400 mg in the morning and 200 mg in the evening Active control: AndroGel 1.65%	Those on KYZATREX™ showed greater change from baseline in LFTs compared to AndroGel for ALP, ALT, and bilirubin There was no improvement in AST seen No liver-related AEs were identified

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; LFT, liver function test; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease.

Testosterone undecanoate

Studies have shown that the first form of oral TU, Andriol, was rarely associated with decreased liver function. In a study of 33 men with testosterone deficiency treated for 10 years with doses of oral TU between 80 and 200 mg/d, no impairments in LFTs were observed.[27] In a double-blind study of 120 patients randomized to receive a 6-month course of oral TU 160 mg/d or placebo, 1 patient exhibited increased LFTs >3× ULN; however, this patient was discontinued from oral TU, and LFTs returned to normal. There were no differences in mean LFTs between baseline and final visit for patients receiving oral TU and no difference between study participants taking oral TU and those taking a placebo.[44] In a study of 322 men randomized to placebo or oral TU at doses of 80, 160, or 240 mg/d for 1 year, there were no adverse effects of oral TU on LFTs.[45] In a multicenter study of 2693 patients who received 1 of 6 different testosterone formulations, of whom 1016 patients received oral TU (Testocaps), all LFTs remained normal at each 6-month visit for those receiving oral TU and for other testosterone formulations.[46]

JATENZO

JATENZO (Clarus Therapeutics), the first FDA-approved oral TU formulation, was approved in 2019 for testosterone replacement therapy in adult men for conditions associated with a deficiency or absence of endogenous testosterone.[8] JATENZO capsules are administered once in the morning and once in the evening with food.[8] Studies have shown that treatment with JATENZO has not led to increased LFTs or clinically significant liver toxicities. In a phase 3 clinical trial of 221 patients, no clinically significant changes in LFTs were observed between men with testosterone deficiency who took JATENZO 237 mg twice daily and those who took Axiron. Two patients receiving oral TU exhibited increased aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <2× ULN, and 1 patient exhibited transient increased AST <2× ULN that returned to normal following continued oral TU.[33] Additionally, a phase 3 trial of JATENZO 316 mg twice daily compared to AndroGel 1% in men with testosterone deficiency found no clinically significant changes to LFTs in the 321 patients receiving either therapy. One patient receiving JATENZO experienced 2 transient episodes of elevated ALT and AST that were 2× to 3× ULN, yet, during these episodes, bilirubin remained normal.[40] Finally, in a 2-year study of men with testosterone deficiency receiving JATENZO, no clinically significant changes from baseline in LFTs were observed in the 81 evaluable patients.[47]

TLANDO

TLANDO (LPCN 1144/LPCN1021; Halozyme) was the second FDA-approved oral TU formulation in the United States. It was approved March 2022 for testosterone therapy in adult men for conditions associated with a deficiency or absence of endogenous testosterone.[6,48] TLANDO capsules are to be taken twice daily with food without dose titration.[6] In a single-arm ambulatory blood pressure–monitoring study of TLANDO 225 mg twice daily to assess blood pressure and heart rate, 138 patients receiving TLANDO demonstrated no changes from baseline in LFTs at 4 months.[49] In a single-arm study of TLANDO 225 mg twice daily to assess the safety and efficacy of this agent without dose titration, 95 patients receiving TLANDO demonstrated no hepatic adverse events after 4 months.[34] In a phase 3, randomized study (SOAR) of 315 patients, both treatment groups (TLANDO 225 mg twice daily vs AndroGel 1.62%) demonstrated a decrease of normal LFTs (ALT, AST, alkaline phosphatase [ALP], and gamma-glutamyltransferase [GGT]) from baseline at week 52.[41] Additionally, no hepatic AEs or incidences of Hy's Law were observed. In a pooled analysis of 10 clinical studies and 720 total patients (Table 3), no clinically meaningful changes were observed in mean values over time for serum ALT, AST, ALP, GGT, or bilirubin in patients receiving TLANDO, and mean values remained within normal limits despite outliers for some measurements. Among patients receiving TLANDO, shifts from normal baseline LFTs to high LFTs at exit occurred in 3% of patients for ALT (conventional high = 40 U/L), 1% of patients for AST (conventional high = 43 U/L), 0.3% of patients for ALP (conventional high = 115 U/L), and 3% of patients for GGT (conventional high = 49 U/L).[50]

Studies with TLANDO have shown that oral TU is not associated with increased LFTs and may demonstrate a positive liver effect. TLANDO has also been studied in a single-arm 16-week study of nonalcoholic fatty liver disease (NAFLD) in hypogonadal men, and the impact of hypogonadism correction on NAFLD by TLANDO was evaluated using a subcohort of patients from the ambulatory blood pressure–monitoring study of TLANDO.[49,51] In this study, approximately 90% of patients receiving TLANDO with baseline liver fat ≥5% as measured by a magnetic resonance imaging–estimated proton density fat fraction test demonstrated liver fat improvement, and reductions in liver fat were greatest in patients with higher baseline liver fat.[51] The measured liver fat fractions were validated based on comparison to reference values that were measured using fat fraction phantom vials, and a Bland–Altman analysis with 95% limit of agreement was performed between quantitative measures and reference values.[51] Resolution of NAFLD occurred in 33% of patients following 8 weeks and in 48% of patients following 16 weeks of therapy. This study was the first to suggest a favorable association between NAFLD and liver fat improvements and oral TU in men with testosterone deficiency, although additional studies using a placebo comparator are necessary to investigate causation and to determine the clinical significance of these observed improvements in NAFLD.[51] The term metabolic dysfunction–associated steatohepatitis (MASH) is being increasingly used to describe the diverse metabolic abnormalities seen in individuals with fatty liver deposition.

KYZATREX

KYZATREX (Marius Pharmaceuticals) is the most recently approved oral TU therapy. KYZATREX is formulated with phytosterols with a goal of maximizing lymphatic absorption and minimizing liver toxicity.[7] It was FDA approved in October 2022 for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.[7] Similarly to JATENZO and TLANDO, KYZATREX is to be taken twice daily with food.[7] In a single-arm study of KYZATREX 200 mg twice daily titrated based on plasma testosterone, patients with testosterone deficiency demonstrated small increases in clinical and ambulatory blood pressure and minimal increases in ambulatory HR that were not related to ambulatory blood pressure changes after 120 and 180 days of therapy. Liver assessments were not reported.[49] In a randomized study of

Table 3. Description of TLANDO pooled analysis.

Study ID	Study design	No. of patients enrolled	Duration	Study drug and administration
LPCN 1021-13-001	Multicenter, randomized, open-label, active-control, parallel-group, multiple-dose, efficacy and safety study	Fixed-dose TU: 210 Testosterone gel: 105	52 weeks	225 mg oral TU titrated to 150 mg or 300 mg bid as needed Active control: testosterone gel 1.62%; topical
LPCN 1021-09-001	Randomized, open-label, single- and multiple-dose pilot bioavailability and pharmacokinetic study	Fixed-dose TU: 36 Dose-adjusted TU: 36	5 d	50 and 100 mg oral TU (qd on d 1 and 8; bid on d 3-7) Active control: dose-adjusted TU
S361.1.001	Single-dose, open-label, bioavailability and pharmacokinetic study	24	1 d	75, 150, and 225 mg oral TU
M12-778	Randomized, double-blind, placebo-controlled multiple-dose-escalating study of safety, tolerability, and pharmacokinetics	84	14-28 d	75, 150, 225, and 300 mg oral TU bid Placebo
M13-298	Single- and multiple-dose relative bioavailability study	32	14 d	225 mg oral TU bid
LPCN 1021-14-001	Randomized, open-label, 4-period, 4-treatment, crossover, single-dose bioavailability and pharmacokinetics study	14	1 d	225 mg oral TU
LPCN 1021-16-002	Multicenter, open-label, 1-treatment, multiple-dose study evaluating efficacy	95	24 d	225 mg oral TU bid
LPCN 1021-16-003	Multicenter, open-label, 1-treatment, multiple-dose study evaluating efficacy	100	24 d	150 mg oral TU tid
LPCN 1021-18-001	Multicenter, open-label, single-arm, multiple-dose study evaluating change from baseline in ABPM	138	107 d	225 mg oral TU bid
LPCN 1021-18-003	Open-label, single-dose study	12	1 d	225 mg oral TU bid

Abbreviations: ABPM, ambulatory blood pressure monitoring; bid, twice daily; qd, every day; tid, three times a day; TU, testosterone undecanoate.

KYZATREX (NCT03198728), 314 patients were randomized to receive KYZATREX 400 mg in the morning and 200 mg in the evening titrated based on plasma testosterone or AndroGel 1.65%.[52] Patients were assessed for change from baseline to end of treatment (time of early withdrawal or at day 365) LFTs (ALT, AST, total bilirubin, and ALP).[52] Results showed greater change from baseline in LFTs for KYZATREX compared to AndroGel for ALP, ALT, and bilirubin, and no improvement in AST: mean (SD) change from baseline: ALP, −4 (11.31) vs −1.5 (10.37) U/L; ALT, −0.4 (19.84) vs 0.9 (14.64) U/L; bilirubin, −0.032 (0.2157) vs 0.026 (0.2117) mg/dL; and AST 2.4 (27.18) vs 1.0 (9.69) U/L. No liver-related AEs were identified.[52] Further research into the effect that KYZATREX has on liver safety is needed to assess whether there is concern for Hy's law and DILI.

Overall, oral TU studies have shown that contrary to concerns about the previous formulations of oral TU therapy, which contained methylated testosterone, the newer formulations of oral TU are safer in relation to liver assessments.

Summary of clinical findings for oral TU

Taken together, these results suggest that increased LFTs are not generally associated with oral testosterone formulations, and no clinically significant liver toxicities were noted in clinical trials of oral TU. These medications are in the early stages of development, making it crucial to monitor liver events in larger populations of clinical practice. If signs or symptoms of liver dysfunction do arise, such as increased LFTs, it is imperative that clinicians report these signs or symptoms of hepatic dysfunction. To prevent the development of DILI and a cumulative effect on the liver, clinicians should advise caution in the use of oral TU combined with drugs known to cause hepatotoxicity, including isoniazid, labetalol, and the anti-convulsant felbamate, and use in patients with pre-existing liver disease.[9]

Safety results for oral TU products do not indicate a concern for DILI, and continued efforts to evaluate the safety of oral TU will be beneficial in determining the risk of DILI in patients receiving this therapy. Clinical trials have shown that oral TU may be used safely in men without an observed increase in LFTs, and results from a single-arm study using MRI studies, suggest a possible beneficial effect of oral TU on liver fat improvement. However, further research is necessary to fully understand these findings in patients with testosterone deficiency and NAFLD/nonalcoholic steatohepatitis, and real-world evidence demonstrating the liver effect of oral TU is needed. The data outlined in this review could be reassuring for clinicians and patients who are thinking about using oral TU.

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Conflicts of interest

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Data availability

The data used for the analyses in this manuscript are available on request from the corresponding author.

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