



Long-acting testosterone undecanoate for parenteral testosterone therapy

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Testosterone as a compound for the treatment of testosterone deficiency has been available for almost 70 years; however, the pharmaceutical formulations have been less than ideal. Injectable testosterone esters have been used traditionally for treatment, but they generate supranormal testosterone levels shortly after the 2–3-weekly injections, when testosterone levels then decline very rapidly becoming subnormal in the days before the next injection. Testosterone undecanoate is a new injectable testosterone preparation with a considerably better pharmacokinetic profile. After two initial injections with a 6-week interval, the following intervals between two injections are almost always 12 weeks. Plasma testosterone levels with this preparation are almost always in the normal range. Side effects experienced with conventional testosterone esters are almost nil with this preparation.

Soon after its chemical identification more than 70 years ago, the male hormone testosterone became pharmaceutically available. However, it has taken a considerable time for convenient and safe preparations to be developed. The low bioavailability, after both oral and parenteral administration due to the short circulating half-life of testosterone, hampered its therapeutic use [1,2]. Among ways to circumvent these limitations, chemical modifications of the testosterone molecule were developed allowing oral use, although part some these turned out to be hepatotoxic. Subsequently, various parenteral testosterone preparations were developed. Among the earliest were intramuscular injectable formulations of testosterone esterified with fatty acids dissolved in a vegetable oil vehicle [3]. These preparations remain the most cost-effective and widely used worldwide. However, injections of conventional testosterone fatty acid esters (enanthate, cypionate, decanoate and propionate) have an effective duration of action of 1–2 weeks [4], as wider or narrower spacing between injections leads to progressively more extreme excursions in serum testosterone concentrations with substantial supra- and sub-physiological serum concentrations, less well-sustained gonadotropin suppression [5] and greater subjective symptoms of these wide fluctuations [2]. Subdermal testosterone pellet implants or biodegradable microspheres allow longer application intervals, although handling of these preparations is relatively difficult [6–8].

Most forms of oral testosterone are alkylated at the 17 α -carbon position, greatly reducing their hepatic metabolism and improving their oral bioavailability. Unfortunately, these compounds, such as 17 α -methyl testosterone, are associated with an unacceptably high rate of hepatotoxic effects, including cholestatic jaundice, peliosis hepatis and even liver tumors in a third to half of long-term users [9–11]. As a result, such 17 α -alkylated forms of testosterone are not considered safe for long-term use by most experts in the field [12].

The only oral administration of testosterone that is currently safe is testosterone undecanoate (TU), which is commercially available in many countries. When administered orally, a portion of TU is absorbed via lymphatics and thereby bypasses hepatic first-pass metabolism [13–15]. TU is lymphatically absorbed due to its long lipophilic side chain. However, the absolute bioavailability of testosterone after oral TU administration is only approximately 6% [15], implying that most of an oral TU dose is absorbed via the portal circulation and metabolized by the liver. TU must be administered orally in doses of 120–240 mg/day (divided in two-to-three administrations per day).

The transdermal route for testosterone administration generates excellent pharmacokinetic profiles; however, patches can cause moderate to severe skin reaction due to the vehicles (enhancers) that facilitate testosterone absorption across the skin [16]. The newly available testosterone gels are safe and effective, but must be applied to

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a fairly large area of skin and care must be taken to avoid inadvertent exposure to women and children [17–21].

Sustained- and controlled-release testosterone buccal systems, including mucoadhesive excipients, are now available in some countries but require twice-daily administration. Venous drainage from the oral cavity flows directly to the superior vena cava and, thus, hepatic first-pass metabolism is circumvented with these preparations [22–25].

In summary, each of these modes of testosterone delivery has drawbacks. The recent discovery of steroidal and nonsteroidal selective androgen receptor modulators (SARMs) could provide a promising alternative for testosterone therapy, including hormonal male contraception. The identification of an orally bioavailable SARM with the ability to mimic the desired central and peripheral androgenic and anabolic effects of testosterone in a tissue-specific manner and simultaneously avoid the undesirable androgen effects (e.g., on prostate and skin) would represent an important step in androgen therapy [26–30]. However, most of these compounds are in very early phases of pharmaceutical development and the availability on the market is expected in the more or less distant future. That also applies to microencapsulation of Leydig cells [31] and some possibilities of stem cell technology.

In a search for medium-term solutions to key problems of testosterone therapy, TU, for intramuscular administration was developed by Jenapharm GmbH & Co. KG, a subsidiary of Schering AG in Berlin, Germany. The development of this long-acting TU (LA-TU) will now be presented and discussed.

Development of LA-TU

For the development of an intramuscular long-acting testosterone preparation for male contraception, the WHO Special Programme of Research, Development and Research Training in Human Reproduction initiated search activities for identifying suitable fatty acid side chains for esterification of testosterone [32]. It appeared that testosterone esterified with undecanoic acid shows ideal long-term kinetics [4,33–34]. The first TU preparation was developed in China [35–36]. Unfortunately, the injection volume of 8 ml for TU 1000 mg caused some problems at the local injection site. Therefore, by use of a special galenic formulation based on benzyl benzoate and refined castor oil, Jenapharm/Schering were

able to develop a suitable intramuscular testosterone preparation with a volume of 4 ml containing 1000 mg of TU. At present, the stability in climate zone II (25°C) lasts 60 months [37]. Intramuscular TU is currently not approved for use in the USA, but is prescribed in Europe, Latin America and Asia under the trade name Nebido®, and in Australia under the trade name Reandron 1000® for the treatment of male hypogonadism.

Toxicology & pharmacology

The active pharmacological principle of LA-TU is testosterone itself. After entering the peripheral circulation, TU (molecular weight 456.7 Da) is hydrolyzed to testosterone, which exerts its androgenic activity [14,38]. Therefore, the toxicology of TU is the same as for other cleavable testosterone fatty acid esters, such as testosterone propionate (three carbon atoms), testosterone enanthate (TE; seven carbon atoms) or testosterone cypionate (eight carbon atoms). In contrast to these fatty acid esters, the kinetics for side-chain cleavage of the saturated aliphatic fatty acid undecanoic acid with 11 carbon atoms turned out to be considerably longer, permitting much longer injection intervals and at the same time preventing supra- or subphysiological serum testosterone levels.

Nahrendorf and colleagues evaluated the influence of LA-TU treatment on left ventricular remodeling following experimental myocardial infarction in male rats, as assessed by magnetic resonance imaging and *in vivo* hemodynamics [39]. The authors found no evidence for cardiac toxicity of testosterone administration, despite a tenfold increase in testosterone serum levels, after TU administration compared with placebo administration. Neither infarct size nor procedure-related mortality was influenced by TU. On the contrary, there was a tendency to an improved hemodynamic outcome: left ventricular end diastolic pressure was reduced significantly in TU-treated animals together with wall stress without differences in diastolic filling rates following myocardial infarction.

Despite the fact that, after oral administration, TU is well tolerated, the bioavailability leaves much to be desired. Täuber and colleagues reported that the mean absolute bioavailability of testosterone after oral administration of TU to women was $6.83 \pm 3.32\%$, whereas the mean absolute bioavailability of orally administered free testosterone was $3.64 \pm 2.45\%$ [15]. The absorption of TU by the gut is erratic, resulting

in a great inter- as well as intra-individual variability in serum levels. TU is metabolized partly in the intestinal wall [14].

With the present state of available testosterone preparations, the parenteral administration of TU will receive growing interest.

Pharmacokinetics

The relationships between intramuscular TU dose (31, 62.5, 125, 250 and 500 mg/kg body weight subcutaneously) and testosterone serum levels was investigated in male rats [40]. A single injection of TU 125 mg/kg body weight is effective in inducing physiological testosterone levels in orchietomized rats for a minimum of 4 weeks. High-dose TU (500 mg/kg body weight) administered as a single injection results in supraphysiological testosterone serum concentrations for up to 6 weeks in nonorchietomized animals. TU was superior to other preparations releasing testosterone (subcutaneous testosterone pellets, testosterone-filled subcutaneous Silastic® implants and subcutaneous testosterone propionate).

In five long-term orchidectomized cynomolgus monkeys (*Macaca fascicularis*), Partsch and colleagues compared the testosterone serum levels after single intramuscular injections of TU or TE 10 mg/kg body weight [41]. With respect to pharmacokinetic characteristics, such as AUC (4051 vs 1771 nmol × h/l), residence time (41 vs 12 days), terminal half-life (26 vs 10 days), maximal testosterone concentration (73 vs 177 nmol/l) and time to maximal testosterone concentration (11 vs 1 days), TU showed pharmacokinetic and pharmacodynamic properties clearly superior to those of TE. Animals treated with TU also demonstrated a significantly longer ejaculatory response (14 weeks) than those treated with TE (7 weeks).

A group headed by Eberhard Nieschlag in Germany, together with the National Research Institute for Family Planning in China, examined the pharmacokinetics of parenteral TU dissolved in soybean oil, castor oil or tea seed oil. Five castrated male cynomolgus monkeys (*Macaca fascicularis*) received a single intramuscular injection of TU 10 mg/kg body weight (nonesterified testosterone 6.3 mg/kg body weight for all preparations). After injection, supraphysiological testosterone levels were induced. There were no significant differences in the pharmacokinetics of the three TU preparations with regard to plasma testosterone and estradiol. The suppression of gonadotropin levels showed

highly individual variations. Prostate volumes increased equally in all groups after administration and declined to castrate levels after withdrawal. The results suggest that TU in soybean oil produces similar effects as TU in other vehicles. The authors conclude that this study in nonhuman primates warranted testing of this new preparation in humans [42].

Pharmacokinetics in men

Zhang and colleagues presented the first detailed pharmacokinetic investigation of the injectable Chinese TU preparation administering two single doses in hypogonadal men [43]. Eight patients with Klinefelter's syndrome received either TU 500 or 1000 mg by intramuscular injection; and 3 months later, the other dose was administered to each of the participants. Every week or second week after the injections, the serum total testosterone concentrations were measured. The whole observation period was only 8–9 weeks. The single-dose injections maintained serum testosterone levels within the normal range for at least 7 weeks, without immediately apparent side effects. Of considerable interest was the observation that the pharmacokinetic profiles of testosterone were different when TU 500 mg was administered as the first injection or when it was given as the second. Somewhat unexpectedly, the peak testosterone values obtained were lower when the 500 mg dose given as the second injection, compared with when the 500 mg dose was administered first. The authors speculate that long-term hypogonadism of these men may have induced faster cleavage or clearance mechanisms for TU and testosterone by the time of the second injection. Another explanation proposed was that the residual endogenous testosterone is suppressed by the first injection (decreasing of luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) and that, after the second injection, only exogenous testosterone is measured.

Behre and colleagues, from the group in Muenster, compared the Chinese preparation (TU 125 mg/ml in tea seed oil) with TU 250 mg/ml in castor oil [44]. TU 125 mg/ml in tea seed oil was injected in two volumes of 4 ml at two sites, while TU 250 mg/ml in castor oil was a single injection of 4 ml. It appeared that TU 250 mg/ml in castor oil had a longer half-life than the tea seed preparation (33.9 ± 4.9 vs 20.9 ± 6.0 days). This observation is in agreement with an interesting study on the possible

influence of injection volume on the pharmacokinetics of nandrolone esters. Comparing intramuscular 1000 mg nandrolone decanoate in 1 vs 4 ml oily solution, the bioavailability of the steroid in the smaller injection volume was larger than in the larger volume [45]. This underlines the relevance of an injection volume of this type of drug. In the case of LA-TU the well-established injection volume of 4 ml should not be modified, for example, by administering 2 ml twice at different sites at the same time.

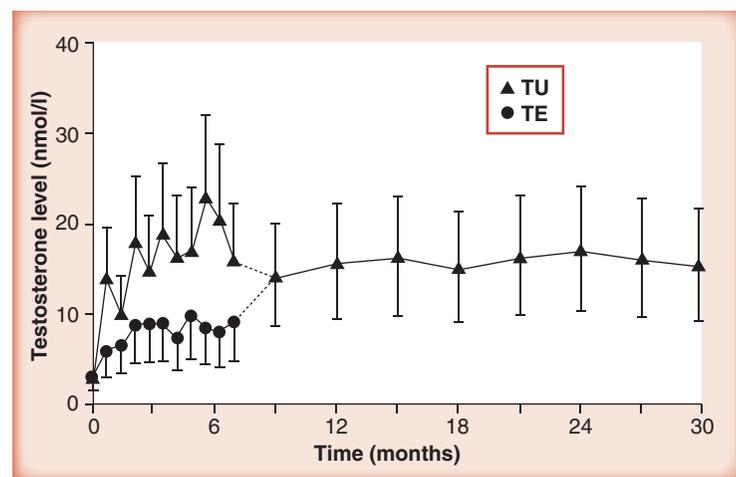
In the next study from the Muenster group, 13 hypogonadal men received four intramuscular injections of LA-TU at 6-week intervals [46]. Testosterone serum levels were never found to lie below the lower limit of normal, and only briefly after the third and fourth injections were testosterone serum levels above the upper limit of normal, while peak and trough values increased over the 24-week observation period. Serum estradiol and dihydrotestosterone (DHT) followed this pattern, not exceeding the normal limits. The same group performed a study for finding suitable injection intervals for LA-TU [47]. In seven hypogonadal men, injections were administered at gradually increasing intervals between the fifth and tenth injections (starting with a 6-week injection interval) and from then on every 12 weeks. Steady-state kinetics were assessed after the thirteenth injection. C_{max} was 32.0 ± 11.7 nmol/l and the half-life was 70.2 ± 21.1 days. The mean C_{max} of 32 nmol/l seen during steady-state with LA-TU administration was lower than that achieved by Testogel® 100 mg/day (37.5 nmol/l); however, it was higher than with Testogel 50 mg/day (28.8 nmol/l) and Androderm® patch 5 mg/day (26.5 nmol/l). Prior to the next injection, the serum levels for testosterone and its metabolites, DHT and estradiol, were mostly within the normal (eugonadal) range and showed a tendency to decrease with increasing injection intervals. The study concluded that, after initial loading doses at 0 and 6 weeks, injection intervals of 12 weeks establish eugonadal values of serum testosterone in almost all men. Also, Yassin and Saad analyzing 58 hypogonadal men on LA-TU treatment every 3 months, and did not notice any elevation of DHT levels exceeding the physiological threshold [48].

In an open-label, randomized, prospective study, Saad and colleagues compared LA-TU (TU 1000 mg three-times every 6 weeks, thereafter every 9 weeks) with TE (250 mg every 3 weeks) in 40 hypogonadal men (Figure 1) [49].

In contrast to the group treated with TE, trough testosterone levels (measured immediately before the new injection) in patients receiving LA-TU remained within the physiological (eugonadal) range. This study was extended as a follow-up study for approximately 2.5 years of treatment [50]. All the patients in this study phase received TU 1000 mg every 12 weeks (the former LA-TU patients) or TU 2×1000 mg every 8 weeks, followed by TU 1000 mg every 12 weeks (the former TE patients). This regimen resulted in stable mean serum trough levels of testosterone (ranging from 14.9 ± 5.2 to 16.5 ± 8.0 nmol/l) and estradiol (ranging from 98.5 ± 45.2 to 80.4 ± 14.4 pmol/l). For testosterone therapy with LA-TU, the authors recommended an initial loading dose of TU 3×1000 mg every 6 weeks, followed by TU 1000 mg every 12 weeks. It was demonstrated that patients receiving TE could be switched to LA-TU without interruption in therapy, but with an additional loading dose of LA-TU 2×1000 mg every 8 weeks after switching from the short-acting TE to TU.

Clinical long-term experience up to 120 weeks was also published in 2004 by another group [51]. A total of 26 hypogonadal patients received LA-TU (TU 1000 mg/4 ml) in a first stage of the study in weeks 0, 6, 16, 26 and 36, followed by an additional stage of up to 120 weeks with injections every 12 weeks. The supranormal peak concentrations of total and free testosterone occurred 2 weeks after the first injection, then decreased to within the physiological range. At the end of the study, during washout period, serum testosterone levels declined to the low pretreatment levels 14 weeks after the final injection. A parallel increase of 17β -estradiol levels was seen, but there was an earlier decrease to pre-treatment levels by 4 weeks after the last injection. Serum LH and FSH were suppressed during the treatment period, while sex hormone-binding globulin (SHBG) remained stable. Serum prostate-specific antigen (PSA) rose from 0.660 to 0.976 ng/ml ($p < 0.01$) after 120 weeks, but did not exceed the normal range. Prostate volume increased from 19.6 to 26 ml ($p < 0.05$). Osteocalcin rose from 0.734 to 1.049 nmol/l ($p < 0.01$). Bone mineral density (BMD) did not change. Standard laboratory tests and uroflow did not change. Sexual interest (assessed by use of the aging males' symptom [AMS] questionnaire) increased.

Figure 1. Trough levels of testosterone after repeated injections of testosterone enanthate and testosterone undecanoate in 40 hypogonadal men.



Mean age: 41 years; range: 18–74 years.

TE: Testosterone enanthate; TU: Testosterone undecanoate.

Long-term experience (up to more than 8 years) with LA-TU in 22 hypogonadal men has been presented by Zitzmann and Nieschlag [52]. Individual dosing intervals ranged from 10 to 14 weeks. Serum trough levels of testosterone were generally within the low normal range, indicating sufficient substitution. In contrast to short-acting testosterone esters, sensations of fluctuations in androgen serum concentrations were rarely observed. If this was the case, it occurred during the last 2 weeks before the next injection, indicating loss of androgenic psychotropic effects. Summarizing the two key studies by Zitzmann and Nieschlag [52] and Schubert and colleagues [50], the following administration regimen is recommended for LA-TU therapy in hypogonadal men: after the first injection of TU 1000 mg, the second injection of TU 1000 mg is to be administered 6 weeks after the first injection (loading dose), followed by injections every 12 weeks (Figure 2). An individualization of the LA-TU therapy is recommended by Zitzmann and Nieschlag [52]. If before the fourth injection the testosterone serum concentration lies between 10 and 15 nmol/l, the injection interval should be every 12 weeks. Should the testosterone serum concentration at this time be lower than 10 nmol/l, the injection interval is shortened to every 10 weeks. If the testosterone level is greater than 15 nmol/l, the injection interval should be extended to every 14 weeks. Additionally, clinical symptoms should be considered for individualization of

injection intervals with LA-TU therapy. The loading dose of TU achieved by the first two injections with an interval of 6 weeks is also recommended for patients who are being transferred from short-acting testosterone injections (e.g., testosterone enanthate 250 mg) to treatment with LA-TU.

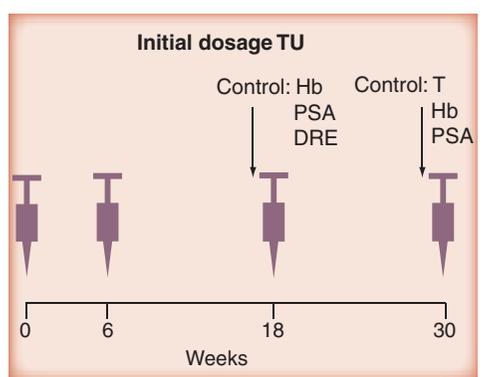
Whereas all known papers on the pharmacokinetics of LA-TU show that, after intramuscular injection of TU 1000 mg, serum testosterone concentrations are still in the physiological (eugonadal) range, Hay and Wu report that administration of TU 1000 mg every 12 weeks and TU 750 mg every 9 weeks causes periodical supraphysiological excursions of testosterone levels in ten hypogonadal men [53,54]. TU 500 mg every 6 weeks provided the most physiological androgen replacement, with testosterone levels within the normal range at all time points. However, these findings with LA-TU were not replicated by other groups.

Therapy of hypogonadism with LA-TU

Several treatment options exist for hypogonadal patients. The most commonly used include injectable intramuscular testosterone esters, such as TE, administered at injection intervals of 2–3 weeks, which is associated with supraphysiological peak values shortly after the injection and to subphysiological levels in the days before the new injection. This often leads to mood swings or emotional instability. Another important consequence of the supraphysiological testosterone levels treatment with TE is the periodic elevation in hematocrit. From 70 older men with low serum testosterone receiving TE 200 mg every 2 weeks, 30% developed a hematocrit greater than 52%. In another study of 32 hypogonadal men receiving TE 200 mg every 2 weeks, 14 patients (43.8%) had at least one occurrence of an elevated hematocrit value [59]. Elevated hematocrit values may lead to thromboembolic events. It is now clear that LA-TU is at least as effective and safe as the standard injectable formulation and requires only four injections per year in long-term treatment while maintaining serum testosterone levels within the physiological range. The data confirm the safety and efficacy of long-term LA-TU therapy in hypogonadal patients treated over a period of more than 8 years.

The two key studies on TU have been performed in Muenster, Germany, by the group headed by Nieschlag, and in Cologne, Germany, headed by Jockenhoevel and Schubert. The results

Figure 2. Dosage scheme of intramuscular testosterone undecanoate 1000 mg.



The second injection should be administered after an interval of 6 weeks, and thereafter every 12 weeks. Recommended scheme of checks in patients aged over 45 years.
 DRE: Digital rectal examination; Hb: Hemoglobin; PSA: Prostate-specific antigen; T: Testosterone; TU: Testosterone undecanoate.

have been presented by Zitzmann [52] and Schubert [58] at the Fifth World Congress on the Aging Male, 2006, in Salzburg, Austria. These studies are summarized by Schubert and colleagues [Schubert M, Zitzmann M. Unpublished Data]. LA-TU was generally well tolerated. Local irritation at the site of injection was moderate, did not last longer than 3 days and could be minimized by administering LA-TU slowly over a period of approximately 1 min. No patients discontinued treatment due to problems of local discomfort. LA-TU should be injected deeply into the gluteal muscle with the patient in a prone position. During the first year of LA-TU treatment, erythropoiesis parameters, prostate size and serum PSA should be monitored for safety reasons in men above the age of 45 years at quarterly intervals and then yearly thereafter.

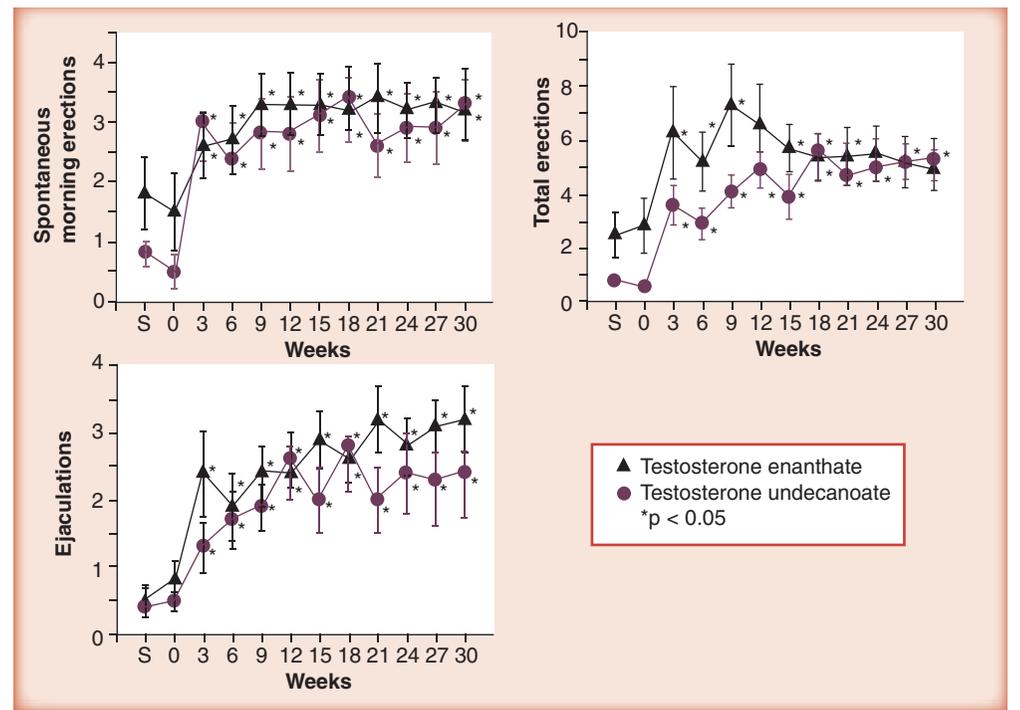
Muenster study

The study included 14 patients who received LA-TU up to 8.5 years at injection intervals of approximately 12 weeks. Patients reported restoration of sexual function and positive changes in mood patterns. In contrast to short-acting TE preparations, patient-reported perception of fluctuations in androgen concentrations were rarely reported. Over the whole treatment period, PSA concentrations did not exceed the normal range and prostate size remained below 30 ml in all patients. Hemoglobin and hematocrit increased initially during treatment, but

remained within the normal range over the entire treatment period. Computed tomography of the lumbar spine showed that bone density improved in all patients during the first 2 years and remained stable thereafter. Body mass index (BMI) decreased during the first 2 years of treatment. Serum total cholesterol levels did not change over the treatment period and serum LDL levels decreased slightly, concurring with the decrease of BMI, and serum HDL levels increased slightly over time. There were no relevant changes in blood pressure or heart rate. Overall, treatment with intramuscular TU demonstrated beneficial effects on body composition and lipid profile [58].

Cologne study

The efficacy of LA-TU was compared with the gold standard of TE 250 mg intramuscularly in a 30-week controlled, prospective, randomized, parallel-group study that was followed by a long-term open-label study over 5 years. During the first 30 weeks of the comparative phase, 40 hypogonadal men with testosterone levels below 5 nmol/l were randomly assigned to either TE 250 mg intramuscularly every 3 weeks (n = 20) or LA-TU three times in 6-week intervals, followed by a 9-week interval. Following the first 30 weeks of the comparative part of the study, all patients received LA-TU every 12 weeks in a one-arm follow-up study over an additional 30 months. In the first 30 weeks, there were no differences in sexual parameters (spontaneous morning erections, total erections and ejaculations) between the two groups (Figure 3). After 30 weeks, serum PSA levels in both treatment groups had risen slightly, but remained stable during long-term LA-TU administration and stayed within the normal range over the entire observation period. Prostate volume increased during the first 30 weeks but then remained stable until the end of the follow-up study (Figure 4) [59]. Comparing the mean baseline levels with the mean levels after follow-up, there was an increase in serum testosterone (from 3.9 to 16.2 nmol/l), PSA serum levels (from 0.27 to 0.75 ng/ml) and prostate volume (from 14.5 to 20.2 ml), whereas a decline of serum total cholesterol (from 235.3 to 202.4 mg/dl), LDL cholesterol (from 158.8 to 134.9 mg/dl), HDL cholesterol (from 46.1 to 42.8 mg/dl) and triglycerides (from 199.9 to 161.2 mg/dl) was observed. Taken together, there were no serious side effects of LA-TU treatment.

Figure 3. Sexual parameters in 40 hypogonadal men treated with testosterone or testosterone undecanoate.

Mean age: 41 years; range: 18–74 years.

Using a standardized self-evaluation questionnaire for assessing psychosexual effects of LA-TU treatment [60], it was found that scores for sexual thoughts/fantasies and sexual interest/desire doubled. Also, the score for satisfaction of sex life increased. Improvements were seen for waking erections, total number of erections and ejaculations. The psychological parameters for depression, fatigue and anxiety decreased within the first 3–6 weeks and remained stable. There were no statistically significant differences between TE and TU. No significant change was observed in the score for aggressiveness in either group, indicating that this parameter was not affected by the treatment provided. These results obtained in hypogonadal men are paralleled in some respects in the study by O'Connor and colleagues showing that a single injection of TU 1000 mg to 28 eugonadal young men, elevating mean testosterone levels above normal, was associated with significant increases in anger/hostility from baseline to week 2 after the injection [60]. It was accompanied by an overall reduction in fatigue/inertia and did not increase aggressive behavior or induce any changes in nonaggressive or sexual behavior.

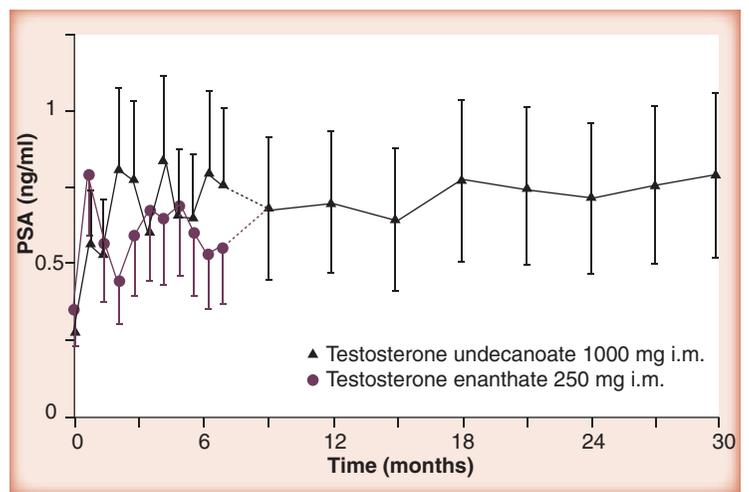
The Muenster and Cologne studies were confirmed recently by a study conducted by Jacobeit and colleagues [61]. A total of 33 hypogonadal men with primary, secondary or late-onset hypogonadism between the ages of 45 and 79 years, were treated with LA-TU. Serum testosterone levels increased from 9.0 ± 3.8 nmol/l at baseline to 13.5 ± 4.6 nmol/l after 6 weeks and to 16.4 ± 6.4 nmol/l after 30 weeks of treatment. DHT levels increased from 0.98 ± 0.48 to 3.1 ± 1.0 nmol/l. Serum PSA levels fluctuated minimally in the normal range. In two patients, the length between two injections could be prolonged from 12 to 14 weeks. All patients reported improved mood, sexual function and quality of life.

In contrast to the short-acting testosterone esters with LA-TU, the gonadotropins FSH and luteinizing hormone LH are permanently suppressed. This suppression of gonadotropins is desired for male contraception, for which LA-TU is a potential candidate.

Treatment of erectile dysfunction with LA-TU

The influence of LA-TU on erectile dysfunction (ED) has been investigated extensively by Yassin and colleagues [62–66]. In a study assessing the

Figure 4. Effect of testosterone undecanoate (intervals of 12 weeks) on prostate-specific antigen in 40 hypogonadal men.



Mean age: 41 years; range: 18–74 years.
i.m.: Intramuscular; PSA: Prostate-specific antigen. From [59].

impact of testosterone therapy only on ED, 22 hypogonadal men with ED received injections of LA-TU on day 1, again after 6 weeks and then in intervals of 12 weeks. Sexual function was assessed using the International Index of Erectile Function (IIEF) [65]. While in all patients testosterone therapy alone significantly improved the sexual desire domain of the IIEF (from 4.5 to 8.4 on a scale of 10), in 12 out of 22 patients (54%) the erectile function domain score increased from 12 at baseline (moderate ED) to 25 (indicating normal erectile function) at week 24. It is of note that the effect of testosterone on erectile function may appear as late as after 12–24 weeks of administration of testosterone.

Evaluation of the role of testosterone therapy on veno-occlusive dysfunction showed cavernosographic changes in hypogonadal patients with severe ED, diabetes mellitus, obesity and/or metabolic syndrome who did not respond to phosphodiesterase (PDE)5 inhibitors and alprostadil injections [64–66]. One patient who had venous leakage prior to testosterone received treatment with LA-TU at 12–14-week intervals following a loading dose of 6 weeks. The patient showed improved sexual function after 9 weeks of treatment and repeated cavernosography after 12 weeks revealed that the venous leakage had receded (Figure 5) [66]. The results from this case study suggest that LA-TU has a positive impact on the veno-occlusive properties of penile trabecular tissues in hypogonadal ED patients. The

disappearance of venous leakage suggests that LA-TU treatment may have beneficial effects on penile anatomical/physiological substrate, facilitating the veno-occlusive mechanism. This finding has been replicated in five out of 12 hypogonadal patients [64]. These results confirm data obtained from animal studies showing that androgen insufficiency leads to veno-occlusive dysfunction that cannot be restored with PDE5 inhibitor treatment alone [67].

Suitability of LA-TU for the management of transgender patients

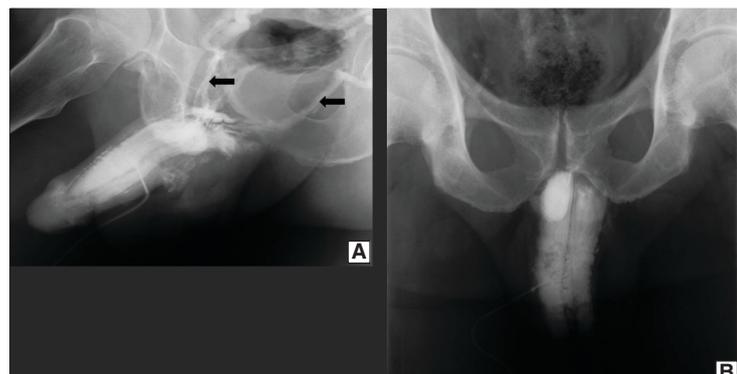
Despite the current limited experience (13 patients), the treatment of female-to-male transgender individuals with LA-TU appears to be a safe and effective therapy. Undesirable side effects have not been observed. Total cholesterol and LDL were lowered and HDL remained unchanged. The use of LA-TU did not lead to acne, seborrhoea and balding. In two patients it was possible to prolong the injection interval from 12 to 14 weeks [68,69].

Use of LA-TU for male contraception

Exogenous administration of testosterone functions as a contraceptive in the male by suppressing the secretion of LH and FSH from the pituitary. After 2–3 months of treatment, low levels of FSH and LH lead to markedly decreased sperm concentrations. This approach to contraceptive development appears safe and fully reversible; however, sperm concentrations are not suppressed to zero in all men. Therefore, researchers have combined testosterone with progestins to further suppress pituitary gonadotropins and optimize contraceptive efficacy [70–79]. Surprisingly, studies in Chinese men show that intramuscular TU alone affords better suppression of spermatogenesis and protection against pregnancy than male condom use and, thus, use of TU alone could suffice for contraceptive use in Chinese men and may receive registration in China [80].

In contrast to East Asians, only approximately 50% of Caucasian volunteers exhibited azoospermia following treatment with LA-TU alone administered every 6 weeks [81]. However, these results with LA-TU, which are comparable to those obtained following weekly injections of TE [82], offer the advantage of longer injection intervals and, therefore, TU is the most promising androgen preparation for further development as a male contraceptive if combined with potent progestins [83–87]. To increase long-term

Figure 5. Cavernosography images before and after testosterone undecanoate treatment.



(A) Cavernosography before testosterone undecanoate treatment clearly showing venous leakage (arrows). **(B)** Repeat cavernosography after 12 weeks testosterone undecanoate treatment showing no signs of venous leakage. From [66].

acceptability of the regimen, TU injection intervals might even be prolonged to 8 or 12 weeks. Merigiola and colleagues demonstrated that injections of LA-TU every 8 weeks, combined with 200 mg of the long-acting parenteral norethisterone enanthate (NETE), very effectively suppresses spermatogenesis in normal men [86].

For many years, the lack of suitable testosterone formulations, in terms of pharmacokinetics and convenience of administration, has hampered the development of male hormonal contraceptives. The recent studies with LA-TU represent a turning point in the development of male hormonal contraceptives [87]. Despite the requirement of regular injections, the acceptability of this regimen (LA-TU combined with NETE) is high [87]. Although there are now many studies showing the suitability of LA-TU combined with a progestin for male contraception, it is currently too early to recommend a definitive regimen for male hormonal contraception. Further studies are required.

Safety & tolerability

No major adverse effects were encountered in the clinical trials of TU. This is not surprising since the pharmaceutically active component is testosterone itself. Common side effects of testosterone administration, such as gynecomastia, breast tenderness and acne, were reported in only a minority of patients, which is probably to be ascribed to the largely normal physiological levels achieved with LA-TU. Adverse effects observed in the initial studies were less frequent when the dosing frequency was decreased from 6 and 8 weeks to 12 weeks, generating more

physiological testosterone levels. Very few patients reported irritation or pain at the sight of injection despite the large volume of injection (4 ml). Significant increases in PSA and prostate size were noted in some of these trials; however, this is probably due to the fact that hypogonadal men have subnormal PSA values and small prostate size at baseline and is observed with every kind of testosterone administration that normalizes plasma testosterone levels. Furthermore, PSA levels and prostate size remained within the normal range. Similarly, increases of parameters of erythropoiesis to the eugonadal values were observed, but there was no occurrence of polycythemia as observed in studies with the more traditional testosterone esters. Only one study demonstrated a transient decline in serum HDL cholesterol; however, its value remained within the normal range [88].

Expert commentary

Most medical conditions requiring androgen therapy are irreversible. As a consequence, androgen-replacement therapy often extends over many decades. Therefore, patient compliance is of utmost importance. Treatment with the unmodified testosterone molecule is preferred by opinion leaders, with a treatment modality and in a dose that maintains serum testosterone in the physiological range for the full 24 h of the day. To date, studies show that LA-TU represents an effective, safe and well tolerated means of androgen treatment in hypogonadal men. At present, clinical experience is available with LA-TU treatment over 9 years [89].

After a recommended loading dose of two injections with a 6-week interval, LA-TU is the first intramuscular agent that can be administered every 12 weeks, thus maintaining physiological plasma testosterone levels. Depending on the trough plasma testosterone level immediately before the next injection and clinical symptoms of the patient, adjustment of the injection interval is desirable, rarely by shortening (every 10–11 weeks), or more often by prolonging (every 13–14 weeks) the interval between two injections. LA-TU produces fewer peaks and troughs in serum testosterone levels in comparison to the traditional testosterone esters. Hypogonadal men treated with LA-TU report a general sense of well-being and normal sexual function during treatment. These parameters were not different when evaluated at the

half point of injection intervals compared with the end of the injection interval period. This suggests that normal physiological testosterone values were maintained throughout the 12-week period, without major fluctuations. As a result, patients did not report mood swings or emotional instability, which is a common complaint with other testosterone preparations.

A major advantage of LA-TU is that it only requires four injections per year compared with 26 injections per year for TE (if taken at a dose of 200 or 250 mg every 2 weeks). Every 12 weeks, the physician sees the patient for safety and efficacy monitoring. The clinical experience with LA-TU meets the requirements spelled out in the consensus on testosterone as well as other recommendations regarding safety and efficacy monitoring of testosterone administration. Therefore, LA-TU is also well suited for elderly men since these patients will be examined four times per year and a prostate malignancy and other reasons for the discontinuation of the therapy can be timely diagnosed.

LA-TU treatment is indicated for all forms of hypogonadism. Men with ED and low testosterone may also benefit from LA-TU administration, and the combination of PDE5 inhibitors and LA-TU may be indicated in men who do not respond sufficiently to PDE5 inhibitors alone. The results of use of LA-TU for male contraception, for example, in combination with progestins, are quite encouraging. However, this subject needs further study.

The open questions are related to testosterone therapy in general and also apply to other testosterone preparations. Larger, longer-term clinical studies with more patients are required to find definitive answers regarding the inter-relationships between testosterone serum levels and the pathophysiology of prostate cancer. However, experts agree that it is responsible clinical practice to treat elderly hypogonadal men with testosterone provided the existing guidelines for monitoring are followed. Specific questions with regard to LA-TU are related to the different pharmacokinetics after single and multiple injections in comparison to other testosterone preparations.

Outlook

In view of its favorable pharmacokinetic profile, LA-TU has been well received. Its advantages over the more conventional injectable testosterone preparations are obvious. The injection frequency is as little as four per year. The large fluctuations of plasma testosterone with the conventional testosterone esters are subjectively experienced as unpleasant by many patients. LA-TU, with its more favorable pharmacokinetic profile, did not have these side effects in clinical trials. Thus, the merits of LA-TU have manifested themselves. The traditional testosterone esters developed some 50–60 years ago are relatively cheap. Health economics may delay a wide introduction of LA-TU in the short-term in spite of the improvements in comparison to the traditional testosterone esters.

Highlights

- Traditional testosterone preparations have been available for more than 50 years, although their pharmacokinetic properties have been less than ideal.
- Injectable testosterone esters, to be administered at 2–3-week intervals, have been traditionally used but they generate supranormal testosterone levels shortly after the injection and then testosterone levels decline very rapidly, becoming subnormal in the days before the next injection.
- Testosterone undecanoate is a new injectable testosterone preparation with a considerably better pharmacokinetic profile. After two initial injections with a 6-week interval, the following intervals between two injections is usually 12 weeks.
- Plasma testosterone levels with testosterone undecanoate treatment are almost always in the range of normal men.
- Side effects experienced with the conventional testosterone esters are almost nil with this preparation.

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