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Research Article

Testosterone Therapy: Injectable Androgens

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Pharmacology and Toxicology of Injectable Testosterone

Studies looking at the mode of action of LA-TU (molecular weight 456.7 Da) have shown that upon entry into the peripheral circulation, TU is hydrolyzed to T, which may then exert its androgenic role [1]. It is therefore believed that the toxicology of TU is the same as for other cleavable testosterone fatty acid esters such as T propionate (3 carbon atoms), -enanthate (7 carbon atoms), -cypionate (8 carbon atoms), and -undecanoic acid (11 carbon atoms). The use of T-undecanoic acid, which presents with a saturated aliphatic fatty acid, in contrast to using the fatty acid esters enumerated above, significantly improves the kinetics for side chain cleavage, thus permitting much longer intervals of injections, while at the same time maintaining balanced serum T levels [2]. Animal studies focusing on the use of injectable TU as T replacement have shown that, in orchiectomized male rats, a single injection of 125 mg/kg body weight can induce physiological T levels for a minimum of 4 weeks, while a maximum injection of 500 mg/kg body weight resulted in supraphysiological T serum concentrations for up to 6 weeks in non-orchiectomized rats. When compared to other T-releasing formulations, such as subcutaneous T pellets, T-filled subcutaneous Silastic® (Dow Corning Corp.) implants or subcutaneous T-propionate, TU was clearly superior regarding pharmacokinetic profile, safety, efficacy, and reduced side-effect profile [3].

Independent studies using cynomolgus monkeys (Macaca fascicularis) have addressed the pharmacokinetics of TU following administration of injectable TU 10 mg/kg body weight. One study revealed that with respect to pharmacokinetic and pharmacodynamic characteristics such as Area Under The Curve (AUC), residence time, terminal half-life, maximal T concentration, and time to maximal T concentration, in contrast to the administration of TE 10 mg/kg body weight, TU showed clear superiority [4]. A second study, comparing TU dissolved in soybean oil, castor oil or tea seed oil, showed no significant differences in the pharmacokinetics of the three TU formulations regarding plasma T and estradiol. The suppression of gonadotropin levels varied between individuals and despite increased prostate volumes after administration, these declined back to castrate levels after withdrawal [5]. In humans, several independent research groups have reported findings looking at pharmacokinetics of injectable TU in a variety of concentrations and using several delivery vehicles. The first pharmacokinetic investigation, lasting over 8–9 weeks, by Zhang and colleagues, concluded that, in hypogonadal men, administration of 500 mg injectable TU as first injection, followed by a 1000 mg injection 3 months later, provided more favorable peak testosterone values than when the 500 mg dose was administered as a second injection. The authors speculated that either long-term hypogonadism may induce faster cleavage or a clearance mechanism for TU and T by the time of the second injection or that residual endogenous T is suppressed by the first injection and that following the second injection, only exogenous T is measured [6]. Many pharmacokinetics studies of TU demonstrate that, after intramuscular injection of 1000 mg TU, serum T concentrations are still in the physiological range. One exception, a study of 10 hypogonadal men reported that 500

mg TU every 6 weeks always provided physiological androgen replacement with T levels within the normal range, while administration of 1000 mg TU every 12 weeks and 750 mg TU every 9 weeks was reported to cause periodical supraphysiological plasma T levels. These findings with TU have not been replicated by other groups, and treatment with 1000 mg TU every 10–14 weeks post-loading period is now used as the gold standard [7, 8]. With a view to establishing the most efficient vehicle of administration of TU in humans, Behre and colleagues, compared the Chinese preparation (TU 125 mg/mL in tea seed oil) injected in 2 volumes of 4 mL each at 2 sites, with TU 250 mg/mL in castor oil as a single 4 mL injection [9].

It appeared that when castor oil was used as a delivery vehicle, TU had a longer half-life than the tea seed preparation, an observation supported by another study showing that the bioavailability of the steroid in smaller injectable volumes (1000 mg nandrolone decanoate in 1 mL oily solution) was larger than in the larger volume (1000 mg nandrolone decanoate in 4 mL oily solution) [10]. A study by von Eckardstein and Nieschlag, examining suitable LA-TU injection intervals, concluded that, after initial loading doses at 0 and 6 weeks, injection intervals of 12 weeks established eugonadal values of serum T [11]. Consequently, in an open-label, randomized, prospective study, Saad and colleagues compared LA-TU (TU 1000 mg 3 times every 6 weeks, thereafter every 9 weeks) with TE (250 mg every 3 weeks) in 40 hypogonadal men [12]. Trough T levels, measured prior to every injection, remained within the physiological range in patients treated with LA-TU in contrast to the group treated with TE. 2.5-year follow-up data from this study demonstrated that both the group administered TU 1000 mg every 12 weeks (former LA-TU group) and the group administered 2× 1000 mg every 8 weeks followed by 1000 mg every 12 weeks (former TE group), resulted in stable mean serum concentrations of T and estradiol [13]. In summary, use of injectable TU has demonstrated a considerably better pharmacokinetic profile requiring only 2 initial 1000 mg 4 mL with a 6-week interval followed by injections every 10–14 weeks when T serum concentrations decrease to a range between 10 and 15 nmol/L. Another major advantage of LA-TU is that it requires only a few injections per year compared to 26 injections per year for testosterone esters taken at a dose of 200 or 250 mg every 2–3 weeks or orally administered TU which requires careful dosing at least twice a day, and a requirement to be taken with fatty meals in order to achieve acceptable plasma T levels [14].

Efficacy of Injectable TU and Comparative Studies

Though several T replacement therapies are currently available to patients, with varying degrees of efficacy and safety, the preferred T preparations include T gel and injectable T (TE and TU). A limited number of comparator studies exist. One such study examined T gel vs. injectable TU, in 27 hypogonadal men aged 47–74 years, indicated that while both preparations meet the requirements of present-day androgen treatment, higher plasma T levels are achieved with TU compared to T gel [15]. These include improved positive effects on the International Index Of Erectile Function (IIEF), the Aging Males' Symptoms Scale (AMS), and International Prostate Symptoms Score (IPSS) in patients with Metabolic Syndrome (MS). Similarly, another comparative study showed that TU treatment generates higher plasma levels of T in contrast to treatment with T gel, which may explain the greater improvement in sexual and metabolic syndrome symptoms [16]. In comparison to TU injections, intramuscular TE administered at injection intervals of 2-3 weeks is the most used form of therapy for hypogonadism. As previously discussed, this treatment is often associated with supraphysiological and sub-physiological values of serum T shortly after and in the days before an injection, leading to mood swings and emotional instability. Additionally, elevated hematocrit values that may lead to thromboembolic events have been reported in 14 of 32 hypogonadal men receiving TE every 2 weeks [17]. Similarly, 30% of older men with low serum T receiving 200 mg TE developed hematocrit values of greater than 52% [18,19]. Sommer et al. compared the efficacy of intramuscular administration of TU vs. TE (250 mg) in a randomized, controlled, prospective, parallel group study for a 30-week period followed by a long-term open-label study over 5 years [18]. During the first 30 weeks comparative phase, 40 hypogonadal men were randomly assigned to either 250 mg TE intramuscularly every 3 weeks (n = 20) or TU three times in 6-week intervals followed by a 9-week interval. Patients then received TU every 12 weeks in a 1-arm follow-up study over an additional 30 months. The authors reported that TU treatment had no serious side-effects, and the slightly increased Prostate-Specific Antigen (PSA) levels and prostate volumes observed in the first 30 weeks of treatment with either TE or TU remained stable over an additional 30 months on TU treatment. Additionally, both preparations improved sexual parameters of spontaneous morning erections, total erections, and ejaculations.Several independent studies have examined the effects of T therapy on anthropometric, endocrine, and metabolic parameters, and have reported a sustained and clinically meaningful weight loss in hypogonadal men, though most of these studies are of short duration [20-22]. A prospective registry study of 261 men treated with T has, however, provided long-term data on metabolic parameters following testosterone replacement [20,23]. A significant weight loss of approximately 11 kg in 96% of subjects over the 5-year duration of the study was reported [21], possibly due to an increase in the overall level of vitality and physical activity after T treatment as also indicated by another study of more than 1400 hypogonadal men from 155 centers in 23 countries [22].

In a recent controlled study, Francomano et al. examined the effects of TRT on metabolic and hormonal parameters in hypogonadal

men with metabolic syndrome. The group reported improvements in anthropometric parameters, such as BW and WC, in a stepwise yearly manner [22]. More interestingly, a continuous decrease in anthropometric parameters in these patients was observed when compared to the control group in whom no modification occurred [22]. Data from two previous independent studies observing more than 500 hypogonadal men, reported a significant weight loss in over 95% of patients and changes in body composition, including a decrease in body fat concomitant with an increase in lean body mass [19,23]. Finally, when TU administration was compared to the use of short-acting testosterone esters, the gonadotropins FSH and LH appeared permanently suppressed. Suppression of gonadotropins is desired for male contraception, for which TU is a potential candidate. However, further studies are required to establish a definitive regimen for male hormonal contraception.In two long-term studies by Muenster et al., and Cologne et al., hypogonadal men were followed on TU (1000 mg) for up to 8.5 years or on a mixed TE and TU or TU regimen over 5 years, respectively [17,24]. Muenster et al. reported that PSA concentrations did not exceed the normal range and that the 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. Overall, treatment with intramuscular TU demonstrated beneficial effects on body composition and lipid profiles that account for an observed decrease in Body Mass Index (BMI) during the first 2 years of treatment that also concurred with slightly increased High-Density Lipoprotein (HDL) serum concentrations and decreased Low Density Lipoprotein (LDL) serum concentrations over time.

There were no relevant changes in blood pressure or heart rate. Similarly, Cologne et al. demonstrated that while serum PSA levels in both treatment groups had risen slightly, these values remained stable and within the normal range over the entire observation period. Decreases in total cholesterol, LDL, HDL, and triglycerides were observed. Extending the Muenster study, Cologne and colleagues reported that compared to TE treatment, TU treatment improved sexual parameters (spontaneous morning erections, total erections, and ejaculations) and psychological parameters for depression, fatigue, and anxiety. In addition, an independent study of 33 hypogonadal men treated with TU confirmed some of these findings where patients presented normal serum PSA levels and improved mood, sexual function, and quality of life [25]. Furthermore, in a study of 22 hypogonadal men treated with individualized injection regimens of 1000 mg TU, based on T serum concentrations, were followed for up to 8 years [26]. Consistently and in contrast to short-acting TE, TU treatment fluctuations in T serum concentrations were rarely observed and if so, it occurred during the last 2 weeks before the next injection. The authors recommend that transfer of hypogonadal patients on short-acting T injections (e.g., testosterone enanthate 250 mg) to treatment with TU be initiated with two injections of TU at an interval of 6 weeks, followed by injections every 10–14 weeks depending on T serum concentrations.

Conclusion

All testosterone preparations have, to varying degrees, favorable physical and metabolic effects. In view of its pharmacology, LA-TU presents with significantly improved efficacy and safety when compared to other conventional injectable T Preparations (e.g., TE). Its advantages are obvious, from the reduced injection frequency to a significant improvement in side-effects associated with fluctuations of plasma T seen with conventional TE. As of January 2014, the FDA stated they are investigating the potential link between T therapy and several comorbidities, “FDA-approved testosterone treatment increases the risk of stroke, heart attack, or death,” but have not yet concluded. Available evidence indicates that TU is largely considered to be safe in most hypogonadal men, with a small inherent risk of adverse events in some high-risk men with multiple comorbidities. T therapy has been associated with occasional modest increases in serum PSA and prostate size, yet within clinical safety limits, and without compelling evidence to support an increased risk of prostate cancer.Indeed, when given to appropriately selected patients with vigilant monitoring, injectable T can produce improvements in QoL, energy level, libido, muscle mass, cognition, and bone density. Future research should focus on the evaluation of large, multiethnic cohorts of men through prospective trials to better elucidate both risk and hazard ratios of T as it relates to CVD and MS, prostate cancer, LUTS, OSA, erythrocytosis, and other yet-to-be-determined theoretical risks in men both with and without CV risk.In parallel, progress is being made with respect to research looking at the use of SERMs and SARMs, as TU alternatives in the treatment of male hypogonadism. Larger randomized clinical trials are required to determine the proper use, safety, and efficacy of SARMs, but preliminary studies suggest that this is a cost-effective suitable alternative to T supplementation.

For more information on the effect of TTh on different organ systems and/or prevention even in older men, we can refer to the recent published literature in this concern [27-32]. For the question: how long should TTh continue? Data suggest that interruption could cause recurrence in symptoms and signs of hypogonadism. So researchers agree to continue as lifetime treatment such as with Thyroxine or Insulin [33].

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