

# Expert Opinion

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## Nebido: a long-acting injectable testosterone for the treatment of male hypogonadism

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Over the last six decades, tremendous strides have been made in the development of safe, efficacious and 'patient-friendly' modalities of testosterone replacement therapy in men. The most recent forms of androgen replacement that are in widespread use include testosterone patch and gel. These preparations are convenient in their use and deliver a physiological amount of testosterone. Although these transdermal preparations are gaining popularity, many hypogonadal men still receive treatment with intramuscular esters. Testosterone enanthate remains the most commonly prescribed ester. Although testosterone esters are efficacious in terms of improving bone and muscle mass, they possess unfavourable pharmacokinetics that result in fluctuations in the mood, energy and sexual function of patients. Furthermore, these esters need to be injected every 2 – 4 weeks. Hence, there has been a need to develop long-acting esters that can be administered infrequently and deliver a physiological amount of testosterone without major fluctuations. Recently, injectable testosterone undecanoate (Nebido®) has become available in Europe and will soon be marketed in south America, Asia and Australia. In this paper, the structure, pharmacokinetics, efficacy and side-effect profile of testosterone undecanoate will be reviewed and also compared with other existing testosterone esters.

**Keywords:** male hypogonadism, testosterone enanthate, testosterone undecanoate

*Expert Opin. Pharmacother.* (2005) 6(10):1751-1759

### 1. Introduction

#### 1.1 Male hypogonadism

Male hypogonadism affects an ~ 4 – 5 million men in the US. It is defined as a failure of the testes to produce an adequate amount of testosterone and/or conduct normal spermatogenesis. Hypogonadism can be primary (testicular failure) or secondary (hypothalamic or pituitary disorders) [1]. The production of an adequate amount of testosterone is necessary for the development of external genitalia and secondary sexual characteristics in children and adolescents. In adults, androgen production is necessary for the maintenance of lean body mass (LBM), bone mass, libido, sexual function and spermatogenesis. The phenotype of testosterone deficiency depends on the timing of the onset of the disease. When present *in utero*, hypogonadism results in ambiguous genitalia. Clinical characteristics of prepubertal testicular failure include small testis and penis, lack of development of secondary sexual characteristics, eunuchoidal body habitus and delayed bone age. When onset is in adulthood, the features of hypogonadism are loss of libido, infertility, decreased LBM, decreased sense of well being and osteoporosis.

Primary hypogonadism (hypergonadotropic hypogonadism) results in low serum testosterone and elevated gonadotropins, luteinising hormone (LH) and follicle stimulating hormone (FSH). Genetic disorders such as Klinefelter's syndrome or any testicular

## Nebido

damage (surgery, radiation, chemotherapy) are examples of hypergonadotropic hypogonadism. In secondary hypogonadism (hypogonadotropic hypogonadism), LH and FSH levels are low or inappropriately normal in the presence of low testosterone levels. Involvement of the hypothalamus or the pituitary gland (malformation, tumour, infiltrative diseases, trauma, radiation) results in hypogonadotropic hypogonadism.

In addition to pathological hypogonadism, another clinical entity gaining popularity is 'Andropause' (i.e., age-related decline in testosterone levels). Of men aged > 65 years ~ 20% have hypogonadal serum testosterone levels. Hypogonadism in the elderly male is associated with osteoporosis, decreased LBM, impaired sexual function, poor cognition and fatigue. This type of hypogonadism is multifactorial and is due to a combination of primary testicular failure and pituitary insufficiency.

### 1.2 History of testosterone replacement

In today's world, the physicians have the luxury to choose from various modalities of testosterone replacement available in the market for their hypogonadal patients. However, the history of testosterone replacement has evolved over a period of half a century where it began in the 1940s with the development of subdermal testosterone implants. This was followed by the development of testosterone esters in the 1950s. These esters are still popular and remain the most common form of intramuscular androgen replacement modality.

In the 1970s, oral testosterone undecanoate (TU) became available outside the US (where it is still being used). Finally, in the 1990s, testosterone patch became available and in 2000, testosterone gel was launched in the US. Hence, there remains a quest for the development of a long-acting testosterone replacement modality that provides physiological levels of circulating androgens.

## 2. Modalities of testosterone replacement/overview of the market

As native testosterone is rapidly degraded, modified analogues have been developed to obtain a better pharmacokinetic profile [2]. Table 1 summarises the testosterone replacement modalities currently available. Esterification of the 17 $\beta$ -hydroxyl group of testosterone produces derivatives that are less polar and more slowly absorbed than native testosterone. Testosterone enanthate (TE; e.g., Delatestryl® 200 mg, Testoviron® 250 mg) and testosterone cypionate (TC; Depo-Testosterone®) are commonly used in the treatment of male hypogonadism [3]. Both are administered as intramuscular injections at a dose of 150 – 200 mg at 2 – 4 week intervals. Following injection, serum testosterone levels increase to the upper limit of normal or supraphysiological range, followed by a gradual decline to hypogonadal values within 2 weeks. This wide variation in serum testosterone levels (described as roller-coaster pharmacokinetics) produces unwanted fluctuations in mood, energy, libido and sexual function. The frequent need for injections

**Table 1. Testosterone esters currently on the market.**

Drug	Route of delivery	Dose
<b>Testosterone esters</b>		
<b>Testosterone propionate</b>	<b>Intramuscular</b>	<b>10 – 25 mg two- to three-times a week</b>
<b>Testosterone enanthate</b>	<b>Intramuscular</b>	<b>200 – 250 mg every 2 – 4 weeks</b>
<b>Testosterone cypionate</b>	<b>Intramuscular</b>	<b>200 mg every 2 – 4 weeks</b>
<b>Testosterone undecanoate</b>	<b>Intramuscular</b>	
<b>Nebido®</b>		<b>1000 mg in 4 ml every 12 weeks</b>
<b>Chinese TU preparation</b>		<b>1000 mg in 8 ml every 12 weeks</b>
<b>Testosterone patch</b>		
<b>Androderm®</b>	<b>Topical</b>	<b>5 mg/day</b>
<b>Testosterone gel</b>		
<b>Androgel®/ Testogel®, Testim®</b>	<b>Topical</b>	<b>5 g/day</b>
<b>Buccal testosterone</b>		
<b>Striant®</b>	<b>Buccal</b>	<b>30 mg b.i.d.</b>
<b>Testosterone pellets</b>	<b>800 mg (4 pellets, 200 mg each)</b>	<b>Every 4 – 6 months</b>

TU: Testosterone undecanoate.

(26 injections/year) is another drawback of these agents. Another intramuscular agent is testosterone propionate, which has a shorter half-life and requires injections three-times per week. An implantable pellet system (Tesopel®) results in physiological testosterone levels with little fluctuations over 4 – 6 months. However, it requires a minor surgical procedure with potential risks of infection and extrusion of the pellet. Oral TU (Andriol®), although convenient, has to be taken three times daily and results in variable serum testosterone levels.

Transdermal testosterone patches (Androderm®) have been developed to attain a steady-state testosterone value. They are more expensive than the intramuscular forms and cause skin irritations at the site of application in more than one-third of the patients. Two transdermal gels (Androgel®/ Testogel® and Testim®) are currently available. The gel is applied daily and delivers a physiological concentration of testosterone. However, they are also substantially more

expensive than intramuscular testosterone esters. Recently, buccal testosterone has become available (Striant®). It has to be applied to the gums twice daily and its disadvantages include problems in adherence and bad taste.

As the currently available modalities have their limitations, there is need for a testosterone product that provides physiological androgen levels with fewer injections and at a reasonable cost to the patients.

### 3. Chemistry of testosterone undecanoate

TU (Nebido®) is a semisynthetic systemic androgen with a molecular weight of 456.7 Da. It is a fatty acid ester, which makes it more lipophilic and results in slow absorption. TU has a prolonged half-life in comparison with other testosterone preparations due to its longer and hydrophobic side chain (consisting of 11 carbon atoms compared with 7 in other esters; Figure 1) [4]. TU is currently not approved for use in the US, but is prescribed in Europe for the treatment of male hypogonadism.

### 4. Pharmacokinetics and metabolism

#### 4.1 Metabolism of testosterone

At the target tissues, testosterone crosses the cell membrane via passive diffusion due to its highly lipophilic nature [5]. Testosterone may directly activate its receptor or may first be metabolised to dihydrotestosterone (DHT) by the enzyme 5 $\alpha$ -reductase. DHT has a much higher binding affinity for the androgen receptor. Testosterone or DHT binds a cytoplasmic receptor that crosses the nuclear membrane and associates with a hormone-specific receptor and modulates DNA transcription. Testosterone is also converted to oestradiol by aromatase, an enzyme that is abundant in adipose tissue. The effect of androgen-induced transcriptional modulation depends on the target tissue. Testosterone is 98% bound to plasma proteins. Hence, only 2% circulates in free form (biologically active). Of the 98% bound testosterone, ~ 40% is bound to sex hormone binding globulin (SHBG) and 60% is bound to albumin. The affinity of testosterone for SHBG is 1000-fold that of albumin; hence, it is tightly bound to SHBG. In contrast, testosterone is loosely bound to albumin and is readily available to the tissues. This albumin-bound testosterone, along with the free form, is called biologically available testosterone.

The hepatic cytochrome P450 3A enzymes convert testosterone and DHT to inactive products. Oxidation of the D-ring produces the 17-ketosteroids androsterone and etiocholanolone, which are secreted in the urine and bile. Testosterone and its metabolites can also be hydroxylated by glucuronyltransferases and sulfotransferases to produce water-soluble conjugates that are excreted in the urine and bile. Of testosterone ~ 2% is excreted unchanged in the urine.

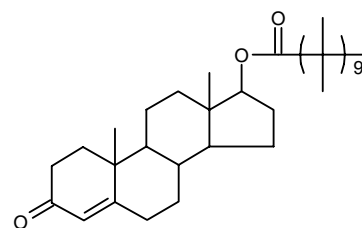
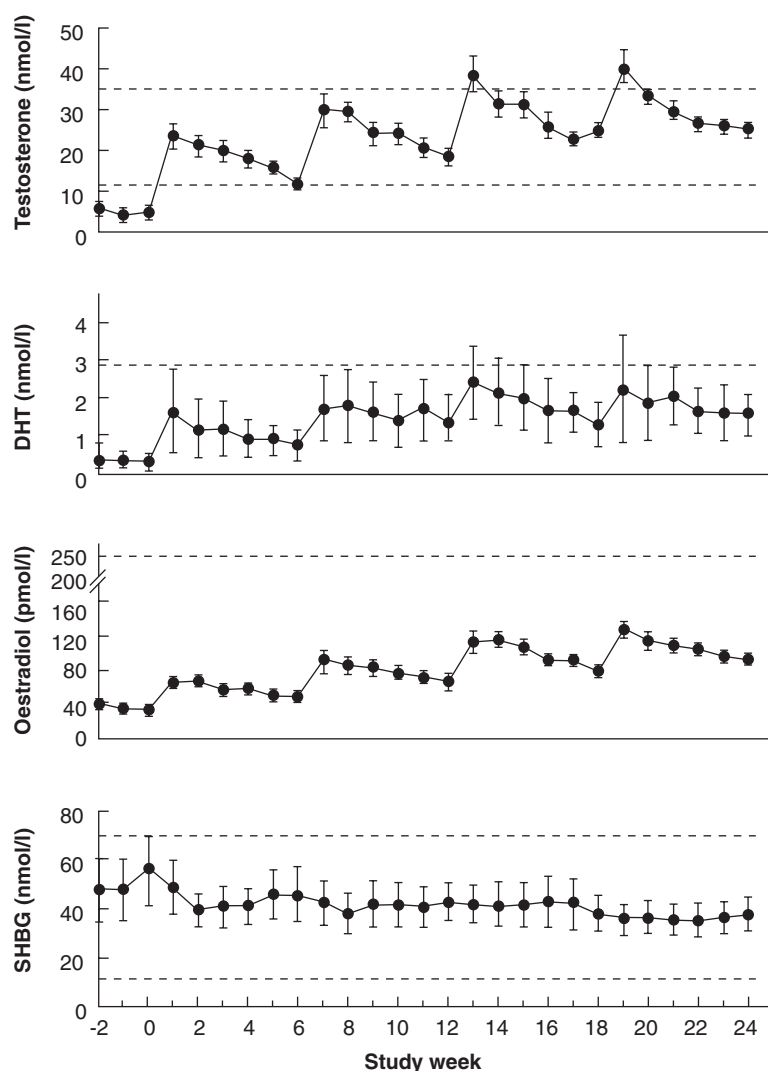


Figure 1. Structure of testosterone undecanoate.

#### 4.2 Testosterone undecanoate

Oral TU is dissolved in oil and encapsulated in soft gelatin; each capsule containing TU 40 mg. Because of the aliphatic side chain, TU is absorbed from the gut with lipids in the lymphatic system, bypassing hepatic metabolism and deactivation [6]. Maximal serum testosterone values are reached 2 – 6 h after ingestion, and 85% of oral TU is eliminated in the urine or faeces within 3 – 4 days. Doses of 120 – 240 mg/day (divided three-times daily) of oral TU results in normal serum testosterone values in most patients [7,8].

Intramuscular TU is administered in a castor oil depot in order to decrease absorption rate. TU has a longer aliphatic side chain than other testosterone esters (11 versus 7 carbons), further slowing its absorption and increasing its half-life. Treatment with testosterone 1000 mg in 4 ml castor oil has been evaluated in several studies in order to determine half-life, maximum concentration ( $C_{max}$ ) and dosing frequency. A trial by Nieschlag evaluated the effect of TU 1000 mg injection every 6 weeks for 4.5 months [9]. Serum testosterone values remained above the lower limit of normal throughout the trial and showed a trend toward increased serum testosterone levels.  $C_{max}$  was seen following the final injection, and was slightly supraphysiological at  $40.8 \pm 3.8$  nmol/l (Figure 2). A trial by Schubert *et al.* comparing TU with TE showed TU to result in significantly higher trough testosterone values than TE, with a mean serum testosterone level of 16.17 nmol/l with 12-week injection intervals [4]. In addition, it was demonstrated that patients receiving TE could be transitioned to TU without interruption in therapy, but with an additional loading dose of TU  $2 \times 1000$  mg every 8 weeks after switching from the short-acting TE to TU. Based on these findings a dosing regimen of 1000 mg every 12 weeks has been suggested and evaluated to be effective and safe over a 3-year period [10]. This study evaluated the use of 9 doses of TU at gradually increasing intervals from 6 to 12 weeks. Patients were then maintained on the 12-week regimen for 60 weeks.  $C_{max}$  was  $32.0 \pm 11.7$  nmol/l and half-life was  $70.2 \pm 21.1$  days. These steady-state pharmacokinetic values are considerably higher than those calculated based on a single dose and more comparable to clinical outcomes. Values remained within the normal range without severe oscillations at 12-week dosing intervals.



**Figure 2. Serum testosterone, DHT, oestradiol and SHBG levels (mean  $\pm$  SEM) in 13 hypogonadal men before and during substitution therapy with intramuscular testosterone undecanoate.** Injections of 1000 mg were given at weeks 0, 6, 12 and 18. Reproduced from NIESCHLAG E, BCHTER C, VON ECKARDSTEIN S *et al.*: Repeated intramuscular injection of testosterone undecanoate for substitution therapy in hypogonadal men. *Clin. Endocrinol.* (1999) **51**:757-763 [9] with permission from Blackwell Publishing. DHT: Dihydrotestosterone; SEM: Standard error of measurement; SHBG: Sex hormone binding globulin.

In order to reach steady-state conditions as soon as possible, it is recommended to begin therapy with a shorter interval of 6 weeks as a loading dose and then, from the second injection onwards, administer TU every 12 weeks.

## 5. Efficacy and safety of testosterone undecanoate

### 5.1 Preclinical trials of testosterone undecanoate

Animal studies have shown TU to produce serum testosterone values within the normal range in orchietomised models of hypogonadism and has a more favourable pharmacokinetic profile and efficacy than TE. Nonhuman primates treated with a single intramuscular injection of TU

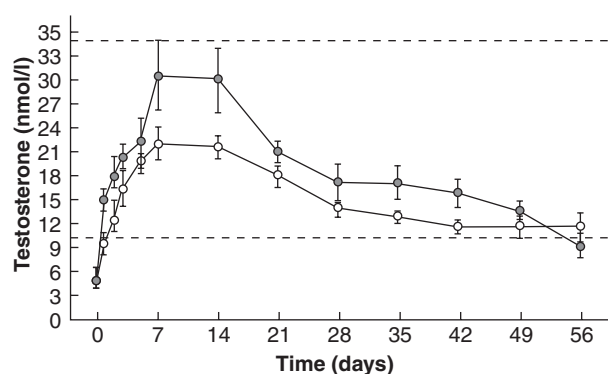
10 mg/kg body weight developed moderately supraphysiological testosterone levels for 4.5 weeks, with maximal testosterone values on day 11. Thereafter, serum testosterone values remained in the physiological range for an additional 10 weeks [11]. The same study found that TE 10 mg/kg body weight produced significant supraphysiological testosterone levels for 1 week, with a peak at day 1.2. However, serum testosterone values declined rapidly reaching lower limit of normal after 31 days (4.5 weeks). The mean elimination half-life was 25.7 days in the TU group versus 10.3 days in the TE group. Pharmacokinetic analysis showed that TU had a much higher area under the curve (AUC), longer residence time, longer terminal half-life and a lower maximal testosterone concentration than TE. Animals treated with

TU also showed a significantly longer ejaculatory response (14 weeks) than those treated with TE (7 weeks).

Another trial evaluated the effect of intramuscular testosterone propionate (Tprop), time-released implanted testosterone pellets (TP) and intramuscular TU (Nebido) in two study arms [12]. Study 1 consisted of orchiectomised rats treated with one dose of TP, Tprop or TU. Tprop produced increased serum testosterone levels for < 2 weeks, with a decline to subnormal levels by day 14. TP demonstrated a dose-dependent increase in testosterone levels with peak at week 2 and a return to baseline values by week 4. It was noted that there was very high interindividual variability of testosterone concentration observed at week 2. In comparison, a single injection of TU at doses of 125 and 62.5 mg/kg showed a dose-dependent effect with low interindividual variability. Maximum testosterone concentrations were reached at 3 weeks and stable testosterone values were maintained through to week 4. Study 2 evaluated the effect of TP and TU in non-orchiectomised rats in order to determine the pharmacokinetics of each drug as anabolic agents in healthy animals. Testosterone pellets (100 mg/90 days) produced the desired supraphysiological testosterone levels, with a trend toward decreasing levels at 6 weeks; high interindividual variability was again noted. A single TU injection (Nebido) of 250 or 500 mg/kg showed low variability with a peak at week 2 and stable testosterone levels for 6 weeks. This trial showed that TU produces a more gradual increase in serum testosterone levels and a longer duration of action than TP. At both replacement and supraphysiological levels, TU proved to be more predictable amongst individual animals in its effect than TP.

## 5.2 Phase I trials

Two trials have evaluated the pharmacokinetic profile of TU in humans. TU was shown to have a significantly longer half-life than TE and produced fewer peaks and troughs in serum testosterone levels. The effect of various vehicles on TU administration were also evaluated (i.e., comparing tea seed oil, more commonly used in China, with castor oil). The first trial consisted of two arms; the first arm using TU 1000 mg in tea seed oil (125 mg/ml; 8ml) in 7 hypogonadal men and the second arm using TU 1000 mg in castor oil (250 mg/ml; 4 ml) in 14 hypogonadal men [13]. The patients were diagnosed with either primary or secondary hypogonadism. A 4-week washout phase was implemented in patients who were on other forms of replacement. Patients received TU 1000 mg intramuscularly into the gluteus medius muscle. Serum hormone determinations were carried out on postinjection days 1, 2, 3, 5 and 7 and then weekly up to day 56 (week 8). In the first arm, testosterone values increased from a baseline of  $4.8 \pm 0.9$  to  $14.9 \pm 1.4$  nmol/l after the first day of injection. A  $C_{max}$  of  $30.5 \pm 4.3$  nmol/l was seen on day 7. Three of seven patients showed a  $C_{max}$  in the supraphysiological range, which returned to normal levels by day 14. Normal serum testosterone values were maintained for 7 weeks, after which levels



**Figure 3. Serum concentrations (mean  $\pm$  SEM) of testosterone after single dose intramuscular injections of TU 1000 mg in tea seed oil in 7 hypogonadal men (first arm, squares) or castor oil in 14 hypogonadal men (second arm, circles).** Broken lines indicate normal range of testosterone. Reprinted from BEHRE HM, OETTEL AM, HBLER D *et al.*: Intramuscular injection of testosterone undecanoate for the treatment of male hypogonadism: Phase I studies. *Eur. J. Endocrinol.* (1999) **140**:414-419 [13], © Society of the European Journal of Endocrinology (1999). Reproduced by permission. SEM: Standard error of measurement.

returned to the hypogonadal range (Figure 3). Serum half-life was  $20.9 \pm 6.0$  days. In the second arm, injection of TU 1000 mg in castor oil produced a normal serum testosterone value of  $12.3 \pm 1.7$  nmol/l on day 2. A  $C_{max}$  of  $19.3 \pm 2.1$  nmol/l was reached between day 7 and 14, and 1 of 14 patients developed a  $C_{max}$  in the supraphysiological range. Up to week 8, serum testosterone values were in the normal range at  $11.5 \pm 1.5$  nmol/l, with a half-life of  $33.9 \pm 4.9$  days. In the second arm, serum DHT levels also increased significantly, with two patients developing supraphysiological levels of DHT. Both studies showed an increase of oestradiol within the physiological range. Comparison of the results from both arms shows that a castor oil depot produces a smaller and slightly delayed initial peak in testosterone levels and a longer half-life than tea seed oil.

Evaluations of serum gonadotropins, lipid profiles, liver function, electrolytes, prostate specific antigen (PSA) and haematology were performed in the second study. Patients with primary hypogonadism showed statistically significant suppression in gonadotropin levels. No significant changes in high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, liver function, electrolytes, haematocrit, haemoglobin, erythrocytes, leukocytes or platelet count were observed. Serum PSA values increased significantly, from a baseline of  $0.33 \pm 0.06$  to  $0.56 \pm 0.07$   $\mu$ g/l at day 28; however, by day 56, the increase was no longer statistically significant. All PSA levels remained within the normal range. This study demonstrated that, in contrast to TE and other testosterone esters, injectable TU did not result in supraphysiological testosterone levels and maintained normal serum testosterone



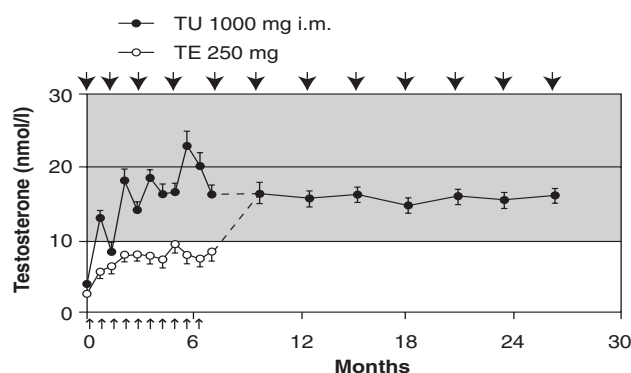
values for 6–8 weeks. The longer duration of action of TU in castor oil versus tea seed oil may be due to intrinsic properties of these vehicles, different concentrations of testosterone (125 versus 250 mg/ml) or different injection volumes (4 versus 8 ml). Injectable TU is currently available in two preparations: 1000 mg in 8 ml tea seed oil, which is a Chinese preparation and is not available outside China, 1000 mg in 4 ml castor oil (Nebido), which is a German preparation and is widely available in Europe.

The second trial was a prospective crossover clinical trial evaluating the use of two different doses of TU in eight patients with Klinefelter's syndrome [14]. Patients underwent a 6-week washout period if they had received testosterone therapy previously. Patients were divided into two groups; group 1 received a single dose of TU 500 mg in tea seed oil followed by a single dose of TU 1000 mg. Group 2 was first treated with TU 1000 mg, followed by TU 500 mg. In both groups, TU was based in tea seed oil and the two injections were separated by a washout period of 3 months. Both doses resulted in a significant increase in serum testosterone values from a baseline of  $< 10$  nmol/l to  $47.8 \pm 10.1$  and  $54.2 \pm 4.8$  nmol/l for the 500- and 1000-mg doses, respectively. Comparison of the two doses showed no differences in  $C_{max}$ , time to reach  $C_{max}$ , elimination half-life, or clearance rate at steady-state levels of testosterone. However, TU 1000 mg resulted in a significantly greater AUC of testosterone. Furthermore, substantial interindividual variability in serum testosterone concentrations was noted. Mean serum oestradiol levels increased in proportion to the increase in testosterone. Serum LH and FSH values were decreased to the same degree by both doses of TU. Levels of SHBG were near the upper limit of normal at baseline, and were reduced at 3–4 months following both doses. All subjects reported increased libido and no mood fluctuations. An improvement in secondary sexual characteristics was noted after one or two injections of TU. No major adverse events occurred, no haematological or serum chemistries were out of the normal range, and no local reaction was noted. An average weight gain of 2 kg was observed. Lower testosterone levels were achieved with TU 500 mg when it was given as the second injection compared with TU 500 mg as the first dose. Serum testosterone values were in the supra-physiological range following the administration of TU 500 mg as the first dose; however, when given as the second injection, the 500-mg dose resulted in values within the normal range. One possible explanation for this is the reduced level of SHBG developed after the initial TU injection. Reduced levels of SHBG resulted in increased levels of free testosterone that could be metabolised and eliminated more quickly; thus, patients pretreated with the 1000-mg dose developed lower SHBG levels and a faster rate of clearance of testosterone once the second dose of TU was given. The authors proposed that the pharmacokinetic profile of TU 500 mg given as a second injection provides a more accurate representation of testosterone concentration. The endogenous testosterone is suppressed by the first injection (decrease in

LH and FSH), and after the second injection, only exogenous testosterone is measured in the serum.

### 5.3 Phase II trials

Several Phase II trials have evaluated the efficacy and safety of TU (in the formulation of Nebido) administration in hypogonadal men. The first study was an open-label, nonrandomised, clinical trial of 13 hypogonadal men, age 19–57 years, with serum testosterone levels  $< 10$  nmol/l [9]. Previous androgen replacement therapy was discontinued for 4 weeks preceding the study. The study involved TU 1000 mg in castor oil (250 mg/ml) administered intramuscularly at 6-week intervals for 24 weeks. Hormonal levels were evaluated weekly. Biochemical parameters were measured 1 week before each injection and prostate size was assessed with transrectal ultrasound at each injection. No patient reported any pain or swelling at injection site despite the large volume of injection (4 ml). Testosterone levels increased from a baseline value of  $5.3 \pm 0.9$  to  $24.3 \pm 2.9$  nmol/l on day 7. Levels decreased linearly from day 7 to a value of  $12.4 \pm 1.2$  nmol/l directly before the second injection. Maximal serum testosterone levels after the third and fourth injection were  $37.2 \pm 3.9$  and  $40.8 \pm 3.9$  nmol/l, respectively. There was, however, a trend toward increased testosterone levels with continued treatment. DHT and oestradiol both increased significantly, remaining within the normal range. Patients with primary hypogonadism ( $n = 7$ ) showed significant suppression of LH and FSH secretion. Routine serum chemistries did not change during the course of treatment. Levels of HDL and total cholesterol decreased significantly; LDL cholesterol and triglycerides were unchanged. Haemoglobin increased significantly from a baseline value of  $142 \pm 3$  to  $154 \pm 4$  g/l. Haematocrit also showed an increase from  $42.5 \pm 1.1\%$  to  $45.7 \pm 1.0\%$ . There was a significant increase in erythrocytes from  $4.8 \pm 0.1 \times 10^{12}/l$  to  $5.1 \pm 0.1 \times 10^{12}/l$ . These haematological parameters remained within the normal range. Patients showed a significant increase in weight, from a baseline value of  $82.3 \pm 3.8$  to  $85.8 \pm 3.7$  kg at the completion of the study. This increase in body weight is most likely due to the anabolic effects of testosterone on LBM. Patients also reported an improvement in emotional stability, improved sense of wellbeing and improved sexual function. Transrectal ultrasound showed a slight but significant increase in prostate volume from  $13.6 \pm 2.4$  ml at baseline to  $15.7 \pm 2.0$  ml at the end of the study. PSA levels also increased significantly from  $0.6 \pm 0.3$   $\mu\text{g}/l$  to maximal levels of  $1.2 \pm 0.7$   $\mu\text{g}/l$  at week 19. However, both the prostate size and PSA levels did not exceed the normal range. This study showed the efficacy of TU 1000 mg in maintaining physiologically normal serum testosterone levels when given at 6-week intervals. Furthermore, based on the tendency towards increased testosterone levels with multiple injections, this study also suggested that the dose intervals of TU could be increased to 10–12 weeks. Patients did not report mood-swings or emotional instability, a common complaint with TE. This observation suggested



**Figure 4. Serum testosterone levels (mean  $\pm$  SEM) during the whole study period (30 months of therapy).** After 30 weeks of therapy all patients switched to TU injected every 12 weeks. Reproduced with permission from SCHUBERT M, MINNEMANN T, HBLER D *et al.*: Intramuscular testosterone undecanoate: pharmacokinetic aspects of a novel testosterone formulation during long-term treatment of men with hypogonadism. *J. Clin. Endocrinol. Metab.* (2004) **89**(11):5429-5434.

SEM: Standard error of measurement; TE: Testosterone enanthate; TU: Testosterone undecanoate.

that patients may be more sensitive to rapid fluctuations in testosterone levels after administration of TE compared with slower extended fluctuation with TU. No serious adverse events occurred. Two patients reported mild acne, one patient experienced gynecomastia and a further two complained of breast tenderness.

In a second open-label, nonrandomised clinical trial, seven hypogonadal men were treated with TU in castor oil at increasing intervals over a 3.2-year period [10]. Patients first received four injections of TU 1000 mg at 6-week intervals. Thereafter, intervals were gradually increased between the fifth and the tenth injection. Intervals were extended if serum testosterone values were  $> 12$  nmol/l and if patients reported no impairment in wellbeing. After the tenth injection, TU was administered at 12-week intervals. Results showed that testosterone levels increased from a baseline of  $5.2 \pm 3.1$  to  $23.8 \pm 7.8$  nmol/l after four injections at 6-week intervals. With extended treatment intervals, serum testosterone values measured just before the next injection were at the lower limit of normal, at  $12.6 \pm 3.7$  nmol/l. After 102 weeks of treatment, steady-state kinetics were observed, with a testosterone half-life of  $70.2 \pm 21.2$  days. The mean  $C_{max}$  of testosterone was 32 nmol/l with a range of 15.6 – 44.3 nmol/l. This mean  $C_{max}$  of 32 nmol/l seen during steady-state with TU administration was lower than that achieved by AndroGel 100 mg/day (37.5 nmol/l), however, it was higher than AndroGel 50 mg/day (28.8 nmol/l) and Androderm patch 5 mg/day (26.5 nmol/l). DHT and oestradiol increased comparably to testosterone. DHT occasionally exceeded the upper limit of normal during the 6-week injection period but

returned to physiological levels with extended treatment periods. Gonadotropin levels decreased significantly with TU treatment. A small increase in haemoglobin, haematocrit and erythrocytes occurred from the baseline values; only one patient developed levels above the upper limit of normal. This is in contrast to TE, which is almost three times as likely to cause polycythemia compared with transdermal testosterone replacement. No changes were observed in serum electrolytes, liver function or prothrombin time. Changes in lipid parameters did not reach statistical significance; however, a slight decrease in HDL cholesterol ( $-13.8\%$ ) and LDL cholesterol ( $-10.4\%$ ) was noted. There was a slight and insignificant increase in prostate volume from a baseline of  $13.6 \pm 6$  to  $23.1 \pm 6.1$  ml at study completion. PSA levels remained within the normal range but did show a small increase during the 6-week injection period. Body weight increased slightly but the increase was not statistically significant. Patients reported a general sense of wellbeing and normal sexual function during treatment. These parameters were not different when evaluated at the half point of injection intervals versus the end of the interval period. This suggests that physiologically normal testosterone values were maintained throughout the 12-week period with no major fluctuations. No serious adverse events occurred. One patient experienced mild acne but this resolved with longer interval periods (12 week intervals). This same patient also developed gynecomastia. Hence, this study confirms that treatment intervals can be extended up to 12 weeks with TU once physiologically normal serum testosterone levels have been reached. Because all patients in this trial were enrolled in the previous trial of TU administration at 6-week intervals, it is difficult to predict the testosterone profile of patients treated at 12-week intervals from the initiation of treatment.

The final trial was an open-label, randomised, prospective trial comparing TU and TE [4]. A total of 40 hypogonadal men with serum testosterone values  $< 5$  nmol/l were enrolled; those being treated with androgen replacement therapy underwent an 8-week withdrawal period. Patients in the TU group received three doses of TU 1000 mg at 6-week intervals followed by an extended 9-week interval period before the last injection. TE-treated patients received TE 250 mg at 3-week intervals for 30 weeks. After the 30-week treatment period, all patients were given TU 1000 mg at 12-week intervals for 20 months. Trough serum testosterone values were 16.31 and 8.29 nmol/l for TU and TE, respectively, demonstrating a more stable elevation of testosterone levels with TU compared with TE. Several patients developed supraphysiological testosterone levels with 6-week intervals of TU injection; extending the injection interval prevented this effect (Figure 4). Mean serum DHT values were significantly higher in the TU group, and were always within the normal range. Similarly, oestradiol was elevated in both groups, and was statistically higher in TU-treated patients by week 24. Patients initially treated with TE who switched to TU for the follow-up study were treated initially with two doses of TU at 8-week intervals

followed by an increase to 12-weeks between injections. These patients showed normal testosterone values, demonstrating the safety and efficacy of a change in treatment regimen from TE to TU at 12-week intervals.

## 6. Safety and tolerability

No major adverse effects were seen in the clinical trials of TU. Common side effects of testosterone administration, such as gynecomastia, breast tenderness and acne were reported in only a minority of patients. These adverse effects were mitigated when the dosing frequency was increased from 9 – 12 weeks, which is the current recommended regimen. Very few patients reported irritation or pain at the sight of injection despite the large volume of injection. Significant increase 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. Furthermore, PSA levels and prostate size remained within the normal range. Similarly, increases in haematological parameters were seen, but there was no occurrence of polycythemia. One study showed a decline in serum HDL cholesterol; however, it remained within the normal range.

## 7. Expert opinion

As most hypogonadal men will require lifelong treatment, it is important to find a therapeutic option that is effective, safe and convenient to use. A variety of testosterone replacement modalities are available in the market; however, each modality has its shortcomings (as discussed in Section 1). This is especially true in the case of intramuscular testosterone esters. Currently available esters do not provide physiological testosterone levels and have to be administered frequently. Hence, there was a need to develop a more patient-friendly ester that provides physiological testosterone levels and has a long half-life.

After a recommended loading dose in the form of an initial 6-week interval, TU is the first intramuscular agent that can be taken every 3 months. These properties of the ester may be of significant convenience to the patients. TU also produces a modest maximal testosterone concentration that has a gradual decline, hence, reducing the untoward side effects often seen with other esters. Clinical trials of TU have shown that testosterone levels are maintained within the normal range for 12 weeks with one injection. Patients report fewer mood swings and more stable levels of energy and libido with TU compared with TE. Furthermore, TU only requires 4 injections/year compared with 26 injections/year of TE (if taken at a dose of 200 or 250 mg every 2 weeks). In addition to the favourable kinetic profile, TU is efficacious in improving LBM, haematological parameters and mood. No serious side effects have been noted with the use of TU.

Although clinical trials have shown that TU has a good safety profile, its current use should be limited to young hypogonadal men. As polycythemia and prostate-related adverse effects are more common in the elderly population, short-acting transdermal agents (which allow immediate interruption) should be used in older hypogonadal men. However, after the safety of testosterone treatment in an elderly hypogonadal patient has been established, after a period of 3 – 6 months, switching to long-acting preparation may be considered based on patient preference.

TU is both a desirable and safe option for the treatment of young hypogonadal men. Patients will benefit from the stable testosterone levels and fewer required injections, while achieving the desired benefits of androgen replacement. However, head-to-head trials between TU and transdermal preparations should be conducted to determine its efficacy and patient-acceptance over topical preparations. Furthermore, there is a need to evaluate safety and efficacy of TU in elderly hypogonadal men.

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