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Intramuscular Testosterone Undecanoate: Pharmacokinetic Aspects of a Novel Testosterone Formulation during Long-Term Treatment of Men with Hypogonadism

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In an open-label, randomized, prospective trial, we investigated pharmacokinetics and several efficacy and safety parameters of a novel, long-acting testosterone (T) undecanoate (TU) formulation in 40 hypogonadal men (serum testosterone concentrations < 5 nmol/liter). For the first 30 wk (comparative study), the patients were randomly assigned to receive either 10 × 250 mg T enanthate (TE) im every 3 wk (n = 20) or 3 × 1000 mg TU im every 6 wk (loading dose) followed by 1 × 1000 mg after an additional 9 wk (n = 20). In a follow-up study, observation continued in those patients who completed the comparative part and opted for TU treatment (8 × 1000 mg TU every 12 wk in former TU patients and 2 × 1000 mg TU every 8 wk plus 6 × 1000 mg every 12 wk in former TE patients) for an additional 20–21 months. Here we report only the pharmacokinetic aspects of the new TU formulation for the first approximately 2.5 yr of treatment. At baseline, serum T concentrations did not significantly differ between the two study groups. In the TE group, mean trough levels of serum T were always less than 10 nmol/liter before the next injection, whereas in the TU group, mean trough levels of serum T were 14.1 ± 4.5 nmol/liter after the first two doses (6-wk intervals) and 16.3 ± 5.7 nmol/liter after the 9-wk interval at wk 30. The mean serum levels of dihydrotestosterone and estradiol also increased in parallel to the serum T pattern and remained within the normal range. In the follow-up study, the former TU patients (n = 20) received eight TU injections at 12-wk intervals, and the TE patients (n = 16) switched to TU and initially received two TU injections at 8-wk intervals (loading) and continued with six TU injections at 12-wk intervals (maintenance). This regimen resulted in stable mean serum trough levels of T (ranging from 14.9 ± 5.2 to 16.5 ± 8.0 nmol/liter) and estradiol (ranging from 98.5 ± 45.2 to 80.4 ± 14.4 pmol/liter). The present study has shown that 1000 mg TU injected into male patients with hypogonadism at 12-wk intervals is well tolerated and leads to T levels within normal ranges, using four instead of 17 or more TE injections per year. An initial loading dose of either 3 × 1000 mg TU every 6 wk at the beginning of hormone substitution or 2 × 1000 mg TU every 8 wk after switching from the short-acting TE to TU were found to be a adequate dosing regimens for starting of treatment with the long-acting TU preparation. (*J Clin Endocrinol Metab* 89: 5429–5434, 2004)

ANDROGENS PLAY AN essential role in the sexual differentiation and function in men and are known to participate in the regulation of bone metabolism, body composition, and hematopoiesis (1). Therefore, androgen replacement therapy in hypogonadal men results in improvement of sexual function as well as increment in bone density, lean body mass, erythropoiesis, prostate size, and changes in lipid profiles, as described by several authors (2–4). Testosterone (T) formulations have been used for replacement therapy in male hypogonadism for over six decades. Because the number of patients with male hypogonadism is small, the effort to develop new T formulations has been modest. Subcutaneous implants were developed in the 1940s; T enanthate (TE) and T cypionate (esters for im injections) were developed in the 1950s; oral T undecanoate (TU) was developed in the 1970s; and transdermal patches were developed in the 1990s (5–7). Although frequently used, most of these formulations have unfavorable pharmacokinetics, resulting in subphysiological, supraphysiological, and/or fluctuating serum T levels. The widely used TE injections often cause discomfort not only due to fluctuating serum T levels but also because of frequent injections (5, 6). The more recently developed transdermal patches show better pharmacokinetics but frequently cause skin irritations (7). Currently, one of the most used formulations consists of injectable T esters requiring im injections every 2–3 wk. Using this regimen, patients frequently report mood swings due to high T levels shortly after the injection and relatively low T levels at the end of each cycle (5). A considerable improvement is the T gel, with daily applications resulting in stable T levels over 24 h (8, 9). Long-acting T preparations may offer a good alternative to a daily application regimen.

We report here the first direct comparison of a new TU formulation for im injection *vs.* a standard treatment with short-acting TE (two-arm, active treatment-controlled study of 30 wk; main study) and the first long-term experience with

Abbreviations: DHT, Dihydrotestosterone; E2, estradiol; LOD, limit of detection; LOQ, limit of quantitation; PSA, prostate-specific antigen; T, testosterone; TE, testosterone enanthate; TU, testosterone undecanoate.

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TU given at equally extended interinjection intervals (one-arm, uncontrolled follow-up study of ~92–96 wk). Moreover, this study design provides the first clinical experience with a direct switch from a standard T therapy using TE to a new long-acting depot injection of TU according to a systematic regimen of dosing.

TU, having a midchain fatty acid bound in the 17β-position, is already approved for oral administration. The first single-dose and multidose pharmacokinetic studies of im TU in castor oil have been published, demonstrating a possible injection interval of more than 6 wk (10, 11). These prolonged intervals make the im injectable TU formulation an attractive candidate not only for replacement therapy but also for hormonal male contraception.

The active treatment-controlled study aimed to investigate the efficacy and safety of a dosage regimen of 1000 mg TU in 4 ml oily solution im at 6-wk intervals (first three doses) and 9-wk intervals (subsequent doses) *vs.* 250 mg TE in 1 ml oily solution im at 3-wk intervals during a 30-wk course of replacement therapy in men with hypogonadism. The follow-up study provided further information on efficacy and safety of the TU preparation after long-term administration over a period of approximately 19 months using a prolonged (12 wk) interval between the injections. In the main and the follow-up studies, several parameters of efficacy and safety were assessed.

Here we report the pharmacokinetic aspects of the new TU formulation and its effect on the serum levels of T, dihydrotestosterone (DHT), estradiol (E2), and SHBG. Preliminary results on efficacy (Minnemann, T., M. Schubert, D. Hübler, A. Christoph, M. Oettel, M. Ernst, U. Mellinger, W. Krone, and F. Jockenhövel, manuscript in preparation) (12, 13) and safety (14) of TU have already been presented elsewhere.

Patients and Methods

Patients

The study protocol and the protocol amendments for the main study and the follow-up studies were approved by the Ethics Committee of the University and the State Medical Board, Cologne, Germany. All 40 patients gave their written informed consent at inclusion in the main study. After completing the main study, all 20 patients of the TU group and 16 patients of the TE group gave their consent to participate in the follow-up study.

Forty men between the ages of 18 and 64 yr with serum T levels less than 5 nmol/liter due to primary or secondary hypogonadism were enrolled in the study. The men had been withdrawn from any T treatment for at least 18 wk before entering the study. At enrollment, all subjects had no evidence of a severe physical or mental illness, as deduced from medical history, physical examination, and analysis of clinical laboratory parameters. There was no evidence of alcohol or drug abuse or known contraindications for T treatment in any patient. At randomization, there were no significant differences in the baseline characteristics (Table 1) of the TU group (n = 20) and the TE group (n = 20), regarding age (41.1 ± 13.4 yr in TU group *vs.* 36.3 ± 12.3 yr in TE group), body mass index (28.1 ± 4.5 kg/m^2 in TU group *vs.* 26.6 ± 4.4 kg/m^2 in TE group), and serum T levels (3.94 ± 4.35 nmol/liter in TU group *vs.* 2.67 ± 2.31 nmol/liter in TE group). Five patients were diagnosed with primary hypogonadism (Klinefelter's syndrome, anorchism, or testicular failure) in the TU group compared with seven patients in the TE group. Secondary hypogonadism (hypothalamic or pituitary disease or pituitary tumor) was present in 15 patients in the TU group compared with 13 patients in the TE group.

TABLE 1. Descriptive statistics of age, height, weight, and BMI in the sample of 40 men with hypogonadism before start of study treatment

Variable	TU group	TE group
Age (yr)		
Mean	41.1	36.3
SD	13.4	12.3
Minimum	23.0	18.0
Maximum	64.0	62.0
Height (cm)		
Mean	177.4	183.3
SD	9.7	9.1
Minimum	158.0	166.0
Maximum	192.0	198.0
Weight (kg)		
Mean	88.8	89.7
SD	17.4	18.6
Minimum	59.0	66.0
Maximum	118.0	138.0
BMI (kg/m^2)		
Mean	28.1	26.6
SD	4.5	4.4
Minimum	22.5	21.0
Maximum	38.5	38.4
T (nmol/liter; screening 1)		
Mean	3.10	2.71
SD	2.53	1.90
Minimum	0.02	0.02
Maximum	8.11	6.07
T (nmol/liter; screening 2)		
Mean	3.94	2.67
SD	4.35	2.31
Minimum	0.02	0.02
Maximum	15.57	7.42

BMI, Body mass index.

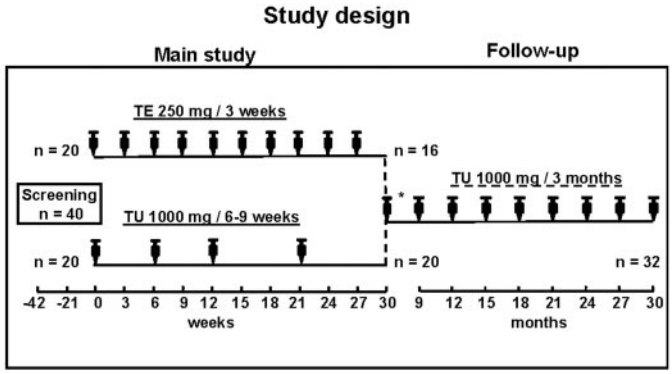

FIG. 1. Flow diagram of the study protocol. For the first 30 wk of the study, patients were randomized to receive im injections of either a commercially available TE formulation (250 mg every 3 wk; n = 20) or a long-acting TU formulation (1000 mg every 6 wk during the first 12 wk and, thereafter, 1000 mg every 9 wk; n = 20). After 30 wk of therapy, all patients received 1000 mg TU im every 12 wk. *, In the patients of the TE group, the interval between the first and second TU injections was 8 wk.

Study design

The main study was designed as an open-label, active treatment-controlled, randomized, and prospective clinical trial. To ensure that the patients met the inclusion criteria, screening visits were performed 42 and 21 d before randomization (for study design, see Fig. 1). In addition to thorough physical, clinical, and andrological examinations, the following endocrine parameters were evaluated: serum levels of T, DHT, E2, and SHBG, and parameters of liver function and bone metabolism,

prostate-specific antigen (PSA), serum lipid profile, and hematological indices.

For the 30 wk of the main study, patients were randomized to one of the following treatments: TU patients (n = 20), 3 × 1000 mg TU in 4 ml oily solution im at 6-wk intervals followed after 9 wk by 1 × 1000 mg in 4 ml oily solution im for an additional 9 wk; and TE patients (n = 20), 10 × 250 mg TE in 1 ml oily solution im at 3-wk intervals.

Both the TE and TU formulations were manufactured by Jenapharm GmbH & Co. KG (Jena, Germany). All im injections were injected into the gluteus medius muscle, starting at d 0. Patients returned to the study center every 3 wk during the main study for a clinical examination, assessment of serum levels of T, DHT, E2, and SHBG, and assessment of other study variables.

Patients who had already received TU injections (4 × 1000 mg at 6- and 9-wk intervals, see first paragraph on this page) during the main study were offered to continue their participation in the follow-up study receiving the same dose at 12-wk intervals. Patients who had been on TE treatment (10 × 250 mg TE at 3-wk intervals) were given the opportunity to switch over from the previous treatment to TU (1000 mg TU). On initiation of TU therapy, a dosage interval of 8 wk between the first two injections was observed to achieve loading. The further injections were given at intervals of 12 wk.

The following treatment regimens were established during the follow-up study: former TU patients, 8 × 1000 mg TU in 4 ml oily solution at 12-wk intervals; and former TE patients, 2 × 1000 mg TU in 4 ml oily solution at an 8-wk interval plus 6 × 1000 mg TU in 4 ml oily solution at 12-wk intervals.

Baseline data for the individual study variables of interest during the follow-up study were obtained at wk 30 of the main study (Table 2). In the follow-up study, routine examinations and assessment of T, E2, and SHBG were performed every 3 months.

In the main and the follow-up studies, the following efficacy and safety parameters were assessed: efficacy of erythropoiesis (hemoglobin and hematocrit); grip strength; well-being, mood, and sexual function; serum levels of hormones (T, E2, and DHT; only during the main study) and SHBG; bone mineral density; bone metabolism (calcium and osteocalcin in serum, calcium, pyridinoline, and deoxypyridinoline in urine); body composition (weight, body mass index, waist-to-hip ratio, skin-fold thickness, lean body mass, fat weight, and fat and lean proportion); lipid parameters (total cholesterol, low- and high-density lipoprotein cholesterols, very low-density lipoproteins, triglycerides, apolipoprotein A1 and B, lipoprotein (a); safety and adverse events; serum levels of PSA; prostate size by transrectal ultrasonography; hematology (erythrocytes, leukocytes, thrombocytes, and partial thromboplastin time); liver function (alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, abd total bilirubin); ferritin and iron; and vital signs (blood pressure and heart rate). Additionally, the injection side was monitored regularly. For safety reasons, serum levels of T and PSA were closely monitored during the whole study.

Statistical analysis

Data were analyzed by descriptive statistical methods using SAS version 6.12 (SAS Institute, Inc., Cary, NC). To compare the two groups at baseline, the Wilcoxon rank sum test was used. Treatment-induced changes in the parameters of interest were analyzed for each group using the Wilcoxon signed rank test. All results are presented as mean ± SD unless stated otherwise.

Hormone assays

Serum T levels were measured by a coat-a-count total T solid-phase ^{125}I RIA (DPC Biermann, Bad Nauheim, Germany). The assay sensitivity was limit of quantitation (LOQ) of 0.69 nmol/liter and limit of detection (LOD) of 0.14 nmol/liter; the intraassay and interassay variability corresponded to 7.3 and 7.9%, respectively. Serum DHT concentrations were measured by a coated-tube RIA, ACTIVE DHT (DSL, Sinsheim, Germany). The assay sensitivity was LOQ of 0.086 nmol/liter and LOD of 0.014 nmol/liter; the intraassay and interassay variability corresponded to 4.6 and 6.4%, respectively. Serum E2 was measured by IMMULITE Estradiol, a solid-phase chemiluminescent enzyme immunoassay (DPC Biermann). The assay sensitivity was LOQ of 20 pg/ml and LOD of 12 pg/ml; the intraassay and interassay variability corresponded to 9.3 and 10.6%, respectively. Serum levels of SHBG were measured by IMMULITE SHBG, an immunometric assay (DPC Biermann). The assay sensitivity was LOD of 0.2 nmol/liter; the intraassay and interassay variability corresponded to 6.5 and 8.7%, respectively.

All samples from each individual were measured in the same session at the end of the main study and the follow-up study to avoid interassay variability.

Results

Forty hypogonadal men were initially randomized to one of the two treatment regimens (either TE, 250 mg every 3 wk; or TU, 1000 mg every 6–9 wk). There were four dropouts during the main study (all from the TE group; three patients left the study for personal reasons and one patient was excluded because inclusion criteria had been violated). All 20 patients on TU and the remaining 16 patients on TE decided (and were considered by the investigator as suitable) to enter the follow-up study and to receive TU injections at extended intervals of 12 wk. During the follow-up study, four patients dropped out (two patients left the study for family-related reasons, one patient died in a car accident, and one patient moved abroad). No patients discontinued treatment due to adverse events. No serious side effects were recorded during

TABLE 2. Serum levels of hormones (T, DHT, E2) and SHBG in patients with hypogonadism at baseline and after 30 wk of treatment with TU (four doses of 1000 mg) or TE (10 doses of 250 mg) followed by eight TU injections in 12 weekly intervals (to convert estradiol to picomoles per liter, multiply by 3.671)

Parameter [unit] (reference range)	Main study TU		Main study TE		Follow-up study with eight TU doses	
	Baseline	wk 30	Baseline	wk 30	2nd TU injection	8th TU injection
Patients [n]	20	20	20	16	36	32
T [nmol/liter] (10–30)						
Mean	3.94	16.31	2.67	8.29	16.46	16.17
SD	4.35	5.66	2.31	3.99	7.99	4.99
DHT [nmol/liter] (0.32–2.5)						
Mean	0.316	0.984	0.414	0.513		
SD	0.264	0.498	0.455	0.396		
Estradiol [pg/ml] (20.4–44.9)						
Mean	21.55	29.63	23.07	27.46	26.82	22.85
SD	6.91	8.02	4.96	9.33	12.30	4.94
SHBG [nmol/liter] (15–70)						
Mean	30.01	25.14	29.80	25.96	25.34	25.81
SD	20.57	12.43	14.17	11.05	11.37	11.23

the entire period of the two studies. One serious adverse event (convulsion at the time after the fourth TU injection during the follow-up study in a patient with a 5-yr history of similar symptoms) was assessed as not related to the study drug, and the study treatment was continued in this patient. Intramuscular injections were well tolerated by all patients.

Serum T concentrations

At baseline, serum T concentrations did not significantly differ between the two study groups, with endogenous levels (mean ± SD) of 2.67 ± 2.31 nmol/liter in the TE group and 3.94 ± 4.35 nmol/liter in the TU group (Table 1). These serum T levels were markedly below the normal adult range of 10–30 nmol/liter. Trough levels of serum T (Fig. 2) were significantly higher in men receiving TU than in men receiving TE (14.14 ± 4.48 *vs.* 8.02 ± 3.66 nmol/liter, $P < 0.0001$, and 16.31 ± 5.66 *vs.* 8.29 ± 3.99 nmol/liter, $P < 0.0001$, after 12 and 30 wk of therapy, respectively). Trough levels of serum T were less than 10 nmol/liter in the TE group compared with trough levels between 10 and 20 nmol/liter in the TU group and still rose (accumulating) when TU injections were applied at intervals of 6 wk.

It must be pointed out that, due to the selected measurement time points, the graph for serum T levels in the TE group in Fig. 2 only reflects T concentrations at the end of each cycle, giving no information about T concentrations between two TE injections. However, as known from previous studies of TE (1, 15), high supraphysiological serum T concentrations are rapidly achieved and are maintained for a few days. Subsequently, serum T levels decline and reach subnormal levels within 3 wk, as confirmed at the measurement time points in the present study.

Slow accumulation of serum T after TU administration, as detected at the end of the 6-wk intervals, was prevented by extending the interval between the last two TU injections of the main study to 9 wk.

During the follow-up study, injections of 1000 mg TU im every 12 wk yielded stable mean T levels within the normal range (value at the time of the eighth TU injection: 16.17 ± 4.99 nmol/liter; Fig. 2). The maximal trough T levels ranged between 26.00 and 34.81 nmol/liter. Slightly elevated trough values of T were found in few patients only.

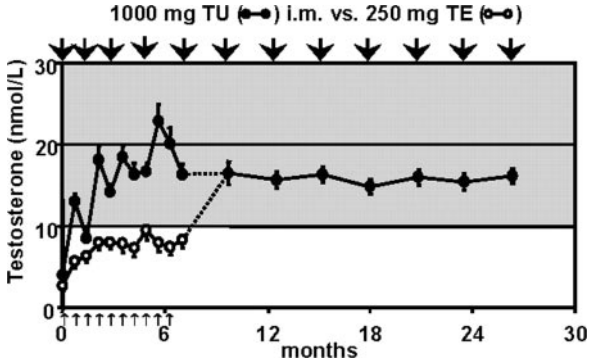

FIG. 2. Serum T levels (mean ± SEM) during the whole study period (up to 30 months of therapy). After 30 wk of therapy, all patients switched to TU injected every 12 wk.

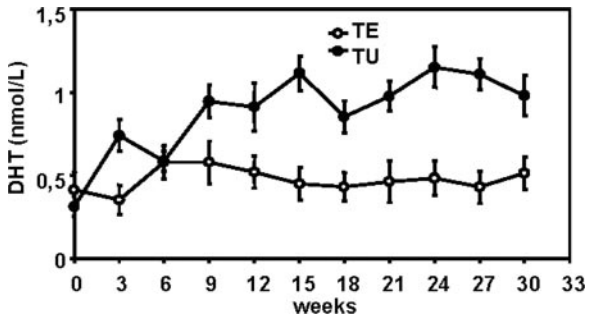

FIG. 3. Serum DHT levels (mean ± SEM) during the first 30 wk of therapy. Blood samples were collected every 3 wk.

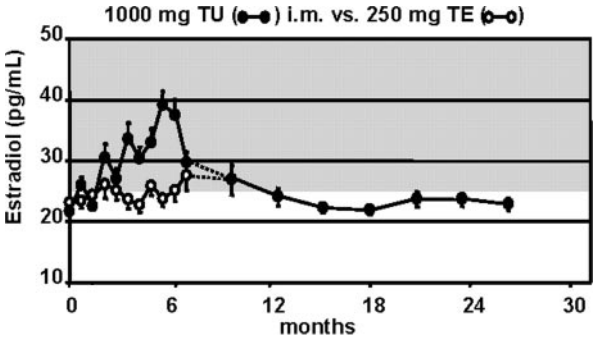

FIG. 4. Serum E2 levels (mean ± SEM) during the whole study period (up to 30 months of therapy). After 30 wk of therapy, all patients switched to TU injected every 12 wk. Blood samples were collected every 3 wk in the first phase of the study and every 12 wk during the follow-up period (to convert E2 to picomoles per liter, multiply by 3.671).

Serum DHT levels

In both treatment groups, serum levels of DHT (Fig. 3) increased in parallel to the serum T pattern (Fig. 2). During the main study, mean DHT levels were significantly higher in the TU group at wk 3, 9, 12, 15, 18, 24, 27, and 30 ($P \leq 0.01$) and remained always within normal range of 0.32–2.5 nmol/liter (Fig. 3). During the follow-up study, DHT was no longer measured.

Serum E2 and SHBG levels

As expected, at the beginning of treatment, mean serum levels of E2 in both treatment groups (Fig. 4) rose in parallel to the serum T levels (Fig. 2). During the comparative part of the study, E2 values ranged from 82.7 ± 13.7 to 143.6 ± 36.2 pmol/liter in the TU group and from 83.4 ± 17.4 to 100.8 ± 34.3 pmol/liter in the TE group. In the TU group, E2 was slightly higher, reaching statistical significance compared with the TE group at wk 24 ($P \leq 0.01$). During the follow-up study, mean serum E2 levels remained between 80.4 ± 14.4 and 98.5 ± 45.2 pmol/liter (Fig. 4). Slight trends toward decrease of serum E2 levels in individual patients led to normalization of initially elevated values in five patients. Slight decrease of E2 concentrations within the reference ranges became apparent in 14 patients.

SHBG levels decreased slightly during the study period. However, these changes were not significant because of large interindividual variations (Fig. 5).

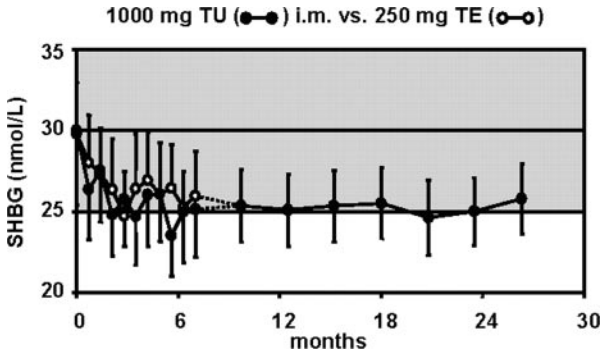

FIG. 5. Serum SHBG levels (mean ± SEM) during the whole study period (up to 30 months of therapy). After 30 wk of therapy, all patients switched to TU injected every 12 wk. Blood sampling was performed every 3 wk in the first phase of the study and every 12 wk during the follow-up period.

Discussion

Currently, injectable TE is the most frequently used T formulation for T replacement in male hypogonadism (1, 5) as well as in trials for male contraception (16). However, injectable TE has pharmacokinetic disadvantages. It produces supraphysiological serum T levels during the first days after injection with a steep decrease to the lower limit of normal range within 10–14 d (1, 5), causing discomfort to the patients, which they experience as ups and downs in vigor, mood, and sexual activity. Other T formulations, such as T cypionate, with nearly identical pharmacokinetics (17) do not offer substantial advantages (5). In the present study, doses of 1000 mg TU for im injection were used. Single-dose pharmacokinetic studies have proven that a dose of 1000 mg TU in 4 ml castor oil does not result in supraphysiological serum T levels but in prolonged action with a half-life (mean ± SEM) of 33.9 ± 4.9 d calculated from the T net values (11). Based on the results of these studies, a computer simulation with the T half-life of 34 d was performed, resulting in an optimal injection interval of 6 wk. Consequently, the first multiple-dose pharmacokinetic phase II study of 1000 mg TU im was planned with 6-wk injection intervals (10). The T measurement after the first injection confirmed the results of the previously reported phase I study. However, beginning with the second injection, T levels rose above normal in five patients in the TU group in the first 3 wk. After each following TU injection, more patients displayed supraphysiological T levels. These results suggest that an injection interval of 6 wk and longer might be sufficient to restore normal T levels in hypogonadal men. Therefore, the injection interval in the main study was extended to 9 wk after the third injection and to 12 wk after the fifth injection in the follow-up study. This interval was also confirmed in preliminary studies by Von Eckardstein and Nieschlag (18). Compared with TE, TU has a prolonged half-life due to the longer aliphatic and thus more hydrophobic side chain comprising 11 instead of seven carbon atoms.

Scrutiny of data reveals that, at all measurement points, the mean serum T trough levels in the TE group were lower compared with the TU group. The measurements in patients receiving TE were always obtained at the end of the scheduled treatment interval, whereas in patients receiving TU, the measurements were performed once in the middle and once at the end of the required interval, thus explaining the markedly higher T levels measured in the TU group in wk 3 and 9. These results can be explained also by the higher total exposure to TU compared with TE and the prolonged release of T from the new formulation. After the third TU injection (wk 12), a 9-wk interval was chosen before the fourth injection, which was further prolonged to 12 wk after the fifth injection.

The trends in the changes in mean serum DHT and E2 levels were similar during the two treatments. As expected, DHT and E2 increased more markedly after TU administration.

The present results show that injecting 1000 mg TU im every 12 wk is sufficient to maintain normal T levels in hypogonadal men without causing major oscillations in serum T levels. We also demonstrate for the first time the pharmacokinetics of a direct transition from a standard regimen with TE every 3 wk to the new TU preparation without interruption. An initial load in the TE patients switching to TU, assured by an interval of 8 wk between the first two TU injections of 1000 mg, and followed by 12-wk intervals between the subsequent injections proved to be a suitable regimen to replace a short-acting formulation by the new TU formulation.

There might be some concerns about the TU injection volume of 4 ml. However, during the study period of approximately 2 yr, we did not observe any local adverse side effects in injection site, and none of the patients expressed any complaints. The TU preparation with a 4-ml volume was tolerated as well as the TE injection with a smaller volume. None of the patients opted to switch back to TE during the follow-up period. Further prolongation of the study, which is still ongoing, was welcomed by the patients.

Recently, a new transdermal preparation (gel) to deliver T, which is a very convenient system with a good local tolerability, has been approved in the United States and Europe. Daily application leads to stable T levels and confirmed clinical efficacy (8, 9). The present study shows that im TU given at 12-wk intervals is an attractive formulation for T supplementation in hypogonadism. Only four im injections per year without any further drug application in between might be very appealing to active men requiring permanent substitution of T instead of daily gel administration. The first multiple-dose pharmacokinetic studies using 1000 mg per injection of this new TU formulation proposed an injection interval of 6 wk. Here we demonstrate that injecting 1000 mg TU every 12 wk is sufficient to maintain normal T and estrogen levels in hypogonadal men, without causing local or systemic adverse side effects using this new formulation (19, 20). The only prerequisite consists of either two to three initial loading doses at 6- and 9-wk intervals at the start of T substitution or two doses at 8-wk intervals when switching from short-acting preparations to TU.

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References

1. **Nieschlag E, Behre HM** 1998 Pharmacology and clinical uses of testosterone. In: Nieschlag E, Behre HM, eds. Testosterone–action, deficiency, substitution. 2nd ed. Berlin: Springer-Verlag; 293–328
2. **Atkinson LE, Chang Y-L, Snyder JP** 1998 Long-term experience with testosterone replacement through scrotal skin. In: Nieschlag E, Behre HM, eds. Testosterone–action, deficiency, substitution. 2nd ed. Berlin: Springer-Verlag; 364–388
3. **Wang C, Swerdloff RS** 1997 Androgen replacement therapy. Ann Med 29: 365–370
4. **Wang C, Swerdloff RS** 1999 Androgen replacement therapy, risks and benefits In: Wang C, ed. Male reproductive function. Boston: Kluwer; 157–172
5. **Nieschlag E** 1998 If testosterone, which testosterone? Which androgen regimen should be used for supplementation in older men? Formulation, dosing, and monitoring issues. Therapeutic controversy VII. J Clin Endocrinol Metab 83: 3443–3445
6. **Behre HM, Nieschlag E** 1998 Comparative pharmacokinetics of testosterone esters. In: Nieschlag E, Behre HM, eds. Testosterone–action, deficiency, substitution. 2nd ed. Berlin: Springer-Verlag; 329–348
7. **Meikle AW, Mazer NA, Moellmer JF, Stringham JD, Tolman KG, Sanders SW, Odell WD** 1992 Enhanced transdermal delivery of testosterone across nonscrotal skin produces physiological concentrations of testosterone and its metabolites in hypogonadal men. J Clin Endocrinol Metab 74:623–628
8. **Swerdloff RS, Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, Weber T, Longstreth J, Berman N** 2000 Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. J Clin Endocrinol Metab 85:4500–4510
9. **Wang C, Berman N, Longstreth JA, Chuapoco B, Hull L, Steiner B, Faulkner S, Dudley RE, Swerdloff RS** 2000 Pharmacokinetics of transdermal testosterone gel in hypogonadal men: application of gel at one site versus four sites: a General Clinical Research Center Study. J Clin Endocrinol Metab 85:964–969
10. **Nieschlag E, Buechter D, Von Eckardstein S, Abshagen K, Simoni M, Behre HM** 1999 Repeated intramuscular injections of testosterone undecanoate for substitution therapy in hypogonadal men. Clin Endocrinol (Oxf) 51:757–763
11. **Behre HM, Abshagen K, Oettel M, Hübler D, Nieschlag E** 1999 Intramuscular injection of testosterone undecanoate for the treatment of male hypogonadism: phase I studies. Eur J Endocrinol 140:414–419
12. **Hübler D, Christoph A, Schubert M, Minnemann T, Oettel M, Ernst M, Mellinger U, Krone W, Jockenhövel F** 2002 Effect of a new long-term treatment with a new sustained-action testosterone undecanoate (TU) formulation for intramuscular androgen replacement therapy on sexual function and mood in hypogonadal men. Int J Impot Res 14(Suppl 4):S51
13. **Hübler D, Christoph A, Schubert M, Oettel M, Ernst M, Mellinger U, Krone W, Jockenhövel F** 2001 Effect of a new long-acting testosterone undecanoate (TU) formulation vs. testosterone enanthate (TE) for intramuscular androgen replacement therapy on sexual function and mood in hypogonadal men. Int J Impot Res 13(Suppl 1):S31
14. **Sommer F, Schwarzer U, Christoph A, Hübler D, Engelmann U, Jockenhövel F** 2002 The effect of long-term testosterone replacement therapy on prostate specific antigen and prostate volume in hypogonadal men–results of a prospective study. Eur Urol 1(Suppl 1):61
15. **Nieschlag E, Cüppers HJ, Wiegelmann W, Wickings EJ** 1976 Bioavailability and LH-suppressing effect of different testosterone preparations in normal and hypogonadal men. Horm Res 7:138–145
16. **World Health Organization Task Force on Methods for the Regulation of Male Fertility** 1996 Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men. Fertil Steril 65:821–829
17. **Schulte-Beerbuhl M, Nieschlag E** 1980 Comparison of testosterone, dihydrotestosterone, luteinizing hormone, and follicle-stimulating hormone in serum after injection of testosterone enanthate or testosterone cypionate. Fertil Steril 33:201–203
18. **Von Eckardstein S, Nieschlag E** 2002 Treatment of male hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks: a phase II study. J Androl 23:419–425
19. **Kamischke A, Heuermann T, Kruger K, von Eckardstein S, Schellschmidt I, Rübig A, Nieschlag E** 2002 An effective hormonal male contraceptive using testosterone undecanoate with oral or injectable norethisterone preparations. J Clin Endocrinol Metab 87:530–539
20. **Kamischke A, Venherm S, Ploger D, von Eckardstein S, Nieschlag E** 2001 Intramuscular testosterone undecanoate and norethisterone enanthate in a clinical trial for male contraception. J Clin Endocrinol Metab 86:303–309

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