

CLINICAL STUDY

Safety aspects of 36 months of administration of long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals

J W Jacobeit, L J Gooren¹ and H M Schulte

Endokrinologikum Hamburg, Center for Hormonal and Metabolic Diseases, Reproductive Endocrinology, Lornsenstraße 4–6, Hamburg 22767, Germany and ¹Andrology Section, Department of Endocrinology, Vrije Universiteit Medical Center, Amsterdam, The Netherlands

(Correspondence should be addressed to J W Jacobeit; Email: jens.jacobeit@endokrinologikum.com)

Abstract

Design: Testosterone treatment is essential for the induction and maintenance of virilization of female-to-male (FTM) transsexuals.

Aim: To test the safety of a novel testosterone preparation for this purpose.

Methods: Parenteral long-acting testosterone undecanoate (TU) was administered to 17 FTM transsexuals over 36 months. Observations were made while subjects received treatment.

Results: Serum testosterone rose from 0.50 ± 0.25 to 6.2 ± 1.3 ng/ml at 6 months and remained stable thereafter. The testosterone profiles were largely identical with those in hypogonadal receiving TU. There were no side effects. Over the 36 months of the study, there was a small but significant decrease in plasma cholesterol (from 218 ± 47 to 188 ± 42 mg/dl) and low-density lipoprotein-cholesterol (from 139 ± 48 to 139 ± 48 mg/dl), while plasma levels of high-density lipoprotein-cholesterol and triglycerides did not change significantly. Liver enzymes did not change during treatment. There was an increase of both levels in hemoglobin (from 13.6 ± 1.2 to 16.0 ± 1.5 g/dl) and hematocrit (from 41 ± 4 to 46 ± 4) upon administration but they remained almost without exception within the physiological range. No special measures were needed. Breast and gonads/internal genitalia did not show pathological changes over the observation period.

Conclusion: This study reports that TU is suited for induction of virilization in FTM transsexuals without significant side effects over a longer term.

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Introduction

Transsexualism, the condition in which a person with an apparently normal somatic sexual differentiation has the conviction that she/he is actually a member of the opposite sex, is becoming more and more a mainstream subject in medicine. Transsexuals have the irresistible urge to be hormonally and surgically adapted to the sex they regard themselves to belong to. Endocrine profiles of basal serum levels of sex steroids and responses in endocrine function tests are not different between transsexuals and nontranssexuals of the same genetic sex (1).

Androgen administration is usually the first step in somatic sex reassignment treatment of female-to-male transsexuals (FTM), and commonly parenteral testosterone preparations are used (2, 3). The resulting endocrine profiles (2, 3) and effects on cardiovascular risk factors (2, 3) have been reported. With exception of the effects on genitalia, the physical changes and their timetable following androgen administration are rather

similar to those occurring in androgen-naïve hypogonadal men receiving testosterone treatment (3).

Intramuscular testosterone undecanoate (TU) has become available (Nebido 1000 mg TU, Bayer Schering Pharma) in November 2004 in Europe for the treatment of male hypogonadism (4, 5). For induction and maintenance of virilization of FTM transsexuals, continuous androgen administration is necessary, both prior to sex reassignment surgery and thereafter for the remainder of the individual's lifetime to maintain virilization and, equally important, to prevent the sequelae of sex steroid deprivation (such as osteoporosis) following ovariectomy, which is part of sex reassignment surgery (2). Several reports document the use of parenteral TU in FTM (6–8). These reports indicate the feasibility and safety of the use of parenteral TU for the purpose of inducing virilization in FTM. These studies were limited to observations over 12 months. This report investigated the merits and side effects of administration of long-acting TU in FTM for a minimum period of 36 months.

Subjects and methods

Seventeen FTM, aged 23–47 years, were eligible for testosterone administration. They had been diagnosed following the guidelines of 'German Standards of Care', derived from the guidelines of the International Harry Benjamin Gender Dysphoria Association and according to Endocrine Society Guidelines (9). All the subjects were healthy and eugonadal as assessed by medical history, physical examination, and biochemical criteria.

There was a single physician observer. Virilization was assessed according to Tanner stages of male pubertal development in as far as applicable to a female body. At each visit, we checked hair loss, development of facial hair, beard growth (shaving frequency), degree of virilization (Ferriman & Gallwey scoring system), and clitoral length.

Ethical guidelines as formulated by the German 'Ärztekammer' (the German Medical Association) for observational studies in patients receiving standard treatment were followed. After receiving an explanation regarding the nature and the purpose of the study, all subjects consented to be included in the research of their treatment protocol.

Clinical and laboratory investigation provided no evidence of contraindications for testosterone administration (i.e. hormone-dependent tumors, sleep apnea, and polycythemia).

Administration of 1000 mg TU by i.m. injection followed the protocol developed for hypogonadal men. Six weeks after the first injection, the second injection was administered, and subsequent injections of 1000 mg were given at 12-week intervals (10, 11).

Plasma total testosterone was determined using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH), and the kit works at Modular Analytics E170 Module. The lower detection limit is 0.02 ng/ml (0.069 nmol/l). Intra-assay coefficient of variation (CV) is 2.0% and inter-assay CV (2.5%) in female reference ranges from 0.06 to 0.82 ng/ml (0.22–2.9 nmol/l). Intra-assay CV is 2.7% and inter-assay CV (5.6%) in male reference ranges from 2.8 to 8.0 ng/ml (9.9–27.8 nmol/l).

Plasma testosterone levels were measured before the first injection, and then after consecutive periods of 3 months before a following injection was given. Levels of hemoglobin and hematocrit, total cholesterol, triglycerides, high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)-cholesterol, and liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined every 6 months during administration of TU. Routine laboratory methods were used to determine their values.

Routinely, all FTM receive (breast ablation, extirpation of ovaries, and internal genitalia) an annual checkup by a gynecologist with special attention to pathological changes of breast and internal genitalia/gonads, if indicated, comprising ultrasound assessment until sex reassignment surgery (12).

Owing to aromatization of testosterone to estradiol (E_2), serum E_2 levels were sometimes elevated and 'spotting' or minor bleeding occurred. These subjects received for initiation of hormone-withdrawal bleeding norethisterone acetate (NETA) 10 mg/day for 14 days. NETA treatment leads to complete termination of bleeding.

For statistical analysis of the data, Wilcoxon's signed rank test was used.

Results

All patients were satisfied with their virilization. Undesirable side effects have not been observed; the use of TU did not lead to significant degrees of acne or seborrhea. No standardized checklist was used to assess progression of virilization, but development of sexual hair was measured by Tanner scales and Ferriman & Gallwey scoring system and their development was satisfactory to the subject.

The progress of virilization as measured by Tanner scales and Ferriman & Gallwey scoring system was satisfactory to the subject. Over the study period, body weight increased 1.5 ± 1.3 kg.

Laboratory results are presented in Table 1.

Plasma testosterone levels rose considerably over the first 6 months of administration of TU and were stable at that level thereafter. Testosterone levels achieved indicated sufficient testosterone substitution applying eugonadal male reference values to this population. The time period between TU applications was prolonged in three subjects from 12 to 14 weeks based on laboratory measurements and clinical evaluation 6–9 months after initiation of TU therapy. Over the observation period, there was a modest but significant change in body weight and body mass index.

Both hemoglobin ($P=0.02$) and hematocrit ($P=0.010$) rose upon administration and reached a plateau after 18–24 months. In one subject, hematocrit values were above normal on two occasions returning to normal upon dose adjustment. In three other subjects, an elevated hematocrit was measured on one occasion in each of them returning to normal without intervention.

There was a small but significant decrease in plasma cholesterol ($P=0.03$) and LDL-cholesterol ($P=0.004$), becoming significant after 18 months of TU administration, while plasma HDL-cholesterol and triglycerides did not change significantly ($P=0.34$) over time. Levels of the liver enzymes ALT and AST did not change over the study period.

Upon annual checkups of breasts and ovaries/internal genitalia, there were no pathological changes. At the end of the 36 months observation period, 13 out of 17 MTF had received sex reassignment surgery.

Table 1 Weight, body mass index (BMI), and laboratory data during 36 months of testosterone administration.

	Reference	Months of use						
		0	6	12	18	24	30	36
Age (years)		34 ± 7		35 ± 7		36 ± 7		37 ± 7
Weight (kg)		74.4 ± 8.2		76.3 ± 8.9		75.1 ± 7.9		75.9 ± 8.1
BMI	25–30	28.3 ± 2.8		29.5 ± 2.9		28.7 ± 3.0		29.2 ± 2.9
Testosterone	2.8–8.0 ng/ml	0.50 ± 0.25	6.2 ± 1.3*	5.9 ± 1.2	6.3 ± 1.4	5.8 ± 1.5	6.2 ± 1.6	6.1 ± 1.5
Hemoglobin	13.3–17.7 g/dl	13.6 ± 1.2	14.9 ± 1.3*	15.0 ± 1.2	15.1 ± 1.3	16.2 ± 1.5†	15.1 ± 1.5	16.0 ± 1.5
Hematocrit	40–52%	41 ± 4	44 ± 3*	46 ± 4	47 ± 4†	46 ± 5	47 ± 5	46 ± 4
AST	< 35 U/l	24 ± 9	25 ± 11	23 ± 9	24 ± 8	25 ± 9	22 ± 7	23 ± 9
ALT	< 43 U/l	22 ± 7	23 ± 8	21 ± 7	24 ± 9	22 ± 8	24 ± 8	22 ± 7
Cholesterol	< 220 mg/dl	218 ± 47	216 ± 44	202 ± 46	190 ± 47*	190 ± 42	189 ± 43	188 ± 42
Triglycerides	< 180 mg/dl	88 ± 14	92 ± 13	89 ± 14	90 ± 13	91 ± 13	88 ± 16	87 ± 15
LDL-Chol	< 150 mg/dl	139 ± 48	140 ± 47	132 ± 46	125 ± 47*	120 ± 50	118 ± 44	119 ± 46
HDL-Chol	< 55 mg/dl	50 ± 11	47 ± 12	46 ± 11	48 ± 10	49 ± 10	51 ± 11	51 ± 10

* $P < 0.05$ versus baseline. † $P < 0.05$ versus *.

Discussion

This is an observational study on safety aspects of hormonal treatment of FTM transsexuals with the long-acting TU. Traditionally, FTM transsexuals have been treated with the conventional parenteral testosterone esters. With this treatment modality, serum testosterone levels, measured cross-sectionally, were 10.3 ± 4.1 ng/ml (mean $\pm$ s.d.), which is largely supra-physiological (13, 14). The wide range of plasma testosterone in these subjects is the result of the pharmacokinetic profile of the conventional testosterone esters, with serum testosterone levels varying from subnormal to supranormal (15).

As can be expected, administration of TU led to an increase in hemoglobin levels and hematocrit. In one subject, supranormal hematocrit levels were measured on two occasions. When the dose of TU was adjusted, the hematocrit returned to normal. In three other subjects, there was a single measurement of a supranormal hematocrit returning to normal without intervention. Androgens stimulate erythropoiesis, and in most studies, a 2–5% increase in the hematocrit over baseline has been observed, with 6–25% of subjects developing erythrocytosis with hematocrits over 50% (16) (for review (17)). To our knowledge, the effect of testosterone administration on hemoglobin levels and hematocrit in FTM transsexuals has not been systematically studied, but polycythemia has been observed with traditional parenteral testosterone injections (personal observation J J and L G).

Erythrocytosis may increase the risk of stroke and requires corrective measures such as temporary interruption or dose adaptation of testosterone administration and/or phlebotomy. There is evidence that the risk of erythrocytosis is related to the achieved levels of testosterone with the mode of testosterone administration (17, 18). This observation included relatively few subjects, but larger scale studies with TU have neither shown development of erythrocytosis (11, 19–21). This is in all likelihood due to the fact

that plasma testosterone levels remain largely in the physiological range with TU as opposed to treatment with the more traditional testosterone esters. There is a clear dose–response relationship between plasma testosterone and hematopoiesis (22, 23).

Furthermore, the effects of TU administration on lipid profiles were investigated. Plasma levels of cholesterol and LDLs decreased somewhat, while triglycerides and HDL were not significantly affected. Subjects were encouraged to adopt a healthy lifestyle, and weight gain, as has been observed often in this population receiving testosterone, was observed in this population but quantitatively modest. Results are rather similar as in hypogonadal men receiving TU in whom a slight decrease in cholesterol and LDL has been observed (21), while plasma HDL decreased but remained well within a range considered not to constitute a cardiovascular risk. The effects of TU on HDL compare favorably with the results reported in FTM transsexuals receiving traditional testosterone esters in whom a decline of 20% in HDL was found (24–26). This may be, again, related to the on-average higher plasma testosterone levels following administration of testosterone enanthate compared with TU.

In this observation under routine conditions of 17 FTM transsexuals receiving treatment with TU over 36 months, plasma testosterone was in the range of eugonadal men as has been recommended for this group (27). There were no signs of deleterious effects on hematological or cardiovascular risk parameters.

In conclusion, TU is a safe and effective therapy for FTM transgender individuals, maintaining testosterone levels within physiological limits. The 12-week intervals render TU a convenient treatment mode. Individual adjustments by prolongation/shortening of the injection intervals for FTM transgender individuals are possible.

Declaration of interest

There is no financial or other potential conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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