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AA2500 Testosterone Gel Normalizes Androgen Levels in Aging Males with Improvements in Body Composition and Sexual Function

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Testosterone replacement in hypogonadal men improves body composition, mood, and sexual functioning. In this 90-d study, we compared the pharmacokinetics and treatment effectiveness of a topical testosterone gel (AA2500) at two concentrations, 50 mg/d and 100 mg/d, to a testosterone patch and placebo gel in 406 hypogonadal men. Pharmacokinetic profiles were obtained, body composition was measured, and mood and sexual function were monitored. AA2500 treatments resulted in dose-dependent improvements in all pharmacokinetic parameters, compared with testosterone patch and placebo. Mean average concentrations at d 90 T were 13.8, 17.1, 11.9, and 7.3 nmol/liter for 50 mg/d AA2500, 100 mg/d AA2500, testosterone patch, and placebo, respectively. At d 90, the 100 mg/d AA2500 treatment improved lean body mass by 1.7 kg and percentage of body fat by 1.2% to a significantly greater degree than either control treatment. Significant improvements in spontaneous erections, sexual desire, and sexual motivation were also evidenced with the 100 mg/d AA2500 dose in comparison with placebo. Testosterone gel was well tolerated; however, the testosterone patch resulted in a high rate of application site reactions. Overall, AA2500 is an effective, well tolerated treatment for hypogonadism. (*J Clin Endocrinol Metab* 88: 2673–2681, 2003)

THE USE OF testosterone (T) replacement therapy in hypogonadal men has been well documented. Specifically, restoration of serum T concentrations to within normal limits (*i.e.* similar to that of eugonadal men) can maintain sexual characteristics, sexual behavior, energy, mood, and muscle development and improve bone density (1). Currently there are a number of different T dosage forms available for replacement therapy in hypogonadal men, but many of these formulations have limitations. Orally available T is relatively insoluble and subject to a high first-pass effect in the liver. Intramuscular depot injections are used widely for replacement therapy but are inconvenient and result in wide fluctuations in T levels. Specifically, high initial peak levels, followed by serum T levels below the lower limit of normal toward the end of the cycle, lead to a return of clinical signs and symptoms.

The skin and oral mucosa are considered favorable routes for the delivery of T. Transdermal T patches, including the scrotal patch (Testoderm), the nonscrotal permeation-enhanced patch with an alcohol-based reservoir (Androderm), and the nonscrotal patch without a reservoir (Testoderm TTS) provide a more consistent delivery of T into the systemic circulation, although serum T levels are not always maintained within normal limits over a 24-h period. Long-term use of these patches (3–10 yr) has been shown to be effective in maintaining sexual function and bone and muscle mass in both young and elderly hypogonadal males (2–5); however, skin tolerability problems or the need for shaving large areas of scrotal skin invariably affect compliance with transdermal patches. Skin reactions commonly occur at the patch application site, particularly with the permeation-enhanced T patches causing erythema or pruritus. Blister reactions also occur leading to scarring and discontinuation of treatment (6, 7).

Previously, it has been reported that a T gel (AndroGel), when applied over a larger area of skin, can achieve serum T levels in the normal range and produce less skin irritation than T patches. A new, unique topical T gel formulation (AA2500) has been designed to provide consistent transdermal absorption of T over 24 h after a single dose and is hereby reported. Before this study, the pharmacokinetic (PK) profile of this new T gel (AA2500) was compared with AndroGel. Data have demonstrated that after topical application of a single dose of AA2500 T gel or AndroGel, the time to maximum concentration (T_{max}) was comparable between the two formulations indicating no appreciable differences in the rate of absorption. However, the 0- to 24-h area under the curve (AUC_{0-24}) and maximum concentration (C_{max}) were consistently higher following application of AA2500 with approximately 30% higher serum T levels being noted. The safety profile of these two topical gel formulations was similar (8).

The study reported here involves comparisons among four parallel treatment groups in 406 patients consisting primarily of aging males with low serum T and associated signs and

Abbreviations: AUC_{0-24}, 0- to 24-h Area under the curve; BPH, benign prostatic hyperplasia; C_{avg}, mean concentration; C_{max}, maximum concentration; C_{min}, minimum concentration; DHT, dihydrotestosterone; DRE, digital rectal examination; %F, percentage fat; FM, fat mass; HDL, high-density lipoprotein; I-PSS, International Prostate Symptom Score; LBM, lean body mass; LDL, low-density lipoprotein; PK, pharmacokinetic; PSA, prostate-specific antigen; T, testosterone; TBM, total body mass; TC, total cholesterol.

symptoms of hypogonadism. Two doses of AA2500 T gel (50 mg/d and 100 mg/d) were compared with a T patch treatment (Androderm, two patches delivering 5 mg T daily), a dose that is known to give rise to clinically meaningful increases in serum T levels with amelioration of signs and symptoms (9). The fourth parallel group was a matching placebo gel to provide a blinded comparator for the two doses of AA2500 T gel, which also provided a valid overall assessment of clinical and subjective symptom improvement. In this 90-d study, periodic 24-h PK profiles of total T and dihydrotestosterone (DHT) were obtained, and the effect of normalizing serum T on body composition, sexual function, mood, and bone mineral density were assessed. Routine safety evaluations were conducted, including skin irritation assessments at the study drug application site. As such, this study design was robust and unique in the assessment of the efficacy of topical transdermal T in normalizing serum T levels, ameliorating signs and symptoms of hypogonadism, and assessing its safety.

Subjects and Methods

Subjects

Four hundred six male patients were randomized and treated at 43 clinics in the United States. Approximately 100 patients were randomized to each treatment group (Table 1). Patients were between 20 and 80 yr of age and had a morning T level of 10.4 nmol/liter or less at screening (measured at a central laboratory) and one or more symptoms of low T (*i.e.* fatigue, decreased muscle mass, reduced libido, reduced sexual functioning of a nonmechanical nature). Except for hypogonadism, the patients were in generally good health as evidenced by medical history; complete physical examination including a digital rectal examination (DRE), 12-lead electrocardiogram, vital sign assessments, clinical laboratory and urinalysis assessments, prostate assessment [International Prostate Symptom Score (I-PSS)]; and normal tests for prostate-specific antigen (PSA), hepatitis, and drugs of abuse. If the patient was receiving lipid-lowering agents, anxiolytics, lithium, antidepressants, hypnotics, antipsychotics, α_1 blockers, or herbal treatments for benign prostatic hyperplasia (BPH), the dose had to have been stable for at least 3 months before entering the study. Patients were excluded from the study if they had any generalized skin irritation or disease that might have interfered with androgen absorption; had received any estrogen therapy, an LHRH antagonist, human GH therapy; or had a history of drug abuse within 12 months. Also excluded were patients who had used either Viagra or apomorphine within 30 d or were treated with T or anabolic supplements within 6 wk before the study. The study was conducted in accordance with the Declaration of Helsinki and complied with Good Clinical Practice, and all patients signed an informed consent agreement previously approved by one of the participating institutional review boards.

Study drugs

AA2500 T gel (Testim) was supplied by Auxilium Pharmaceuticals, Inc. (Norristown, PA). The four daily treatments under study were 50 mg/d AA2500 or 100 mg/d AA2500, matching placebo gel, and a transdermal T patch (Androderm, two patches × 2.5 mg T), each containing 12.2 mg T. The AA2500 and placebo gel were identical and applied as two tubes of 50 mg T (100 mg/d), one tube of 50 mg T and one tube of placebo (50 mg/d), or two tubes of placebo. Neither the patients nor the investigators were aware of the contents of the tubes.

All study drug treatments were applied in the morning; repeat applications occurred at the same time of day for the duration of the study. Each day in the gel-treated group, patients applied the contents of two tubes. The content of one tube was applied to one shoulder and the content of the remaining tube was applied to the other shoulder. Patients allocated to receive the T patch applied two adhesive patches daily. Application sites included the back, abdomen, upper arms, and thighs. Patches were to be worn for 24 h and then replaced each morning at approximately the same time.

Study design

The study was designed as a randomized, multidose, multicenter, active, and placebo-controlled study. Patients were randomized to 50 mg AA2500 T gel (99 patients) or 100 mg AA2500 T gel (106 patients), matching placebo gel (99 patients), or T patch (102 patients). Randomization was performed to ensure an equal distribution of treatments across study centers. The study was double blinded for the AA2500 and placebo groups and open label for the T patch group. Patients randomized to one of the two AA2500 arms could be titrated at d 60 based on their d 30 T PK profile. Patients were titrated from 50 mg/d to 100 mg/d at d 60 if their d 30 mean serum T concentration (C_{avg}) was less than 10.4 nmol/liter (300 ng/dl). Patients were titrated from 100 mg/d to 50 mg/d at d 60 if their d 30 T C_{avg} was more than 34.7 nmol/liter (1000 ng/dl). These titration decisions were undertaken by a third-party physician who was unaware of any clinical aspects of the individual patients and not otherwise involved in the study.

On d −1, patients had a baseline 24-h profile for serum T and DHT consisting of serum samples taken at 0800, 1000, and 1200 h, and 1600

TABLE 1. Subject characteristics

	AA2500		T patch	Placebo	Total
	50 mg/d	100 mg/d			
Demographics					
n	99	106	102	99	406
Age (yr)	58.1 ± 9.7	56.8 ± 10.6	60.5 ± 9.7	56.8 ± 10.8	58.0 ± 10.3
Height (cm)	178 ± 6	178 ± 8	178 ± 6	180 ± 7	179 ± 7
Weight (kg)	95.7 ± 13.4	95.7 ± 14.4	95.1 ± 13.5	98.5 ± 15.6	96.2 ± 14.2
BMI	30.0 ± 3.7	29.9 ± 3.3	29.9 ± 3.8	30.3 ± 3.8	30.0 ± 3.6
T (nmol/liter)[a]	8.1 ± 2.0	8.1 ± 2.2	8.3 ± 2.4	7.9 ± 2.8	8.1 ± 2.3
I-PSS score	6.5 ± 6.0	4.8 ± 5.0	6.2 ± 5.5	5.0 ± 5.3	5.6 ± 5.5
PSA (ng/ml)	1.17 ± 0.89	1.29 ± 0.96	1.45 ± 1.18	1.13 ± 1.00	1.26 ± 1.02
Cause of hypogonadism[b]					
Primary (n)	8	7	4	3	22
Secondary (n)	91	98	98	95	382
Aging (%)[c]	70.7	58.1	66.7	61.2	64.1
Normogonadotrophic (%)[c]	19.2	30.5	26.5	31.6	27.0

Demographic values are expressed as means ± 1 SD. BMI, Body mass index.

[a] 0800 h serum concentration at screening examination.

[b] Two subjects had a missing cause of hypogonadism.

[c] Percentage of total by treatment group. Some subjects had more than one symptom, but all were required to have at least one. Distribution by cause is shown only if it occurred in ≥4% of subjects.

and 0800 h on d 1, immediately before the first dose of study drug. On d 30 and 90, patients had a 24-h profile for T and DHT consisting of serum samples at predose and 2, 4, 8, 12, and 24 h after study drug administration. On d 60, a single 0800-h serum sample was taken for T and DHT. Blood samples for clinical laboratory assessment were collected at screening and on d −1, 30, 60, and 90. The prostate was evaluated at screening (PSA levels only) and d −1 and 90 with PSA levels, I-PSS, and DRE. Body composition [total body mass (TBM), lean body mass (LBM), and fat mass (FM)] and bone mineral density of the L1-L4 section of the lumbar spine were measured by dual energy x-ray absorptiometry on d −1 and d 90. Percentage fat (%F) was derived from FM and TBM. All body composition and bone mineral density measurements were centrally monitored and analyzed by Synarc, Inc. (Maynard, MA). Sexual function and mood questionnaires were recorded daily for 14 d before d 1 and daily for 7 d before d 30, 60, and 90. Data were collected centrally in real time via an interactive voice response system using the telephone. Skin irritation examination using a standardized, discrete scoring system was performed at d 1 (before dosing), 30, 60, and 90. Medical history and physical exams were completed, and all adverse events were recorded.

Methods

The skin irritation scoring was based on the following schema: 0, no erythema; 1, minimal erythema; 2, moderate erythema with sharply defined borders; 3, intense erythema with or without edema; 4, intense erythema with edema and blistering.

Sexual functioning and mood assessments were based on a questionnaire, one that had been validated for assessment of sexual function and mood and used previously in the evaluation of the effects of T gel on sexual function and mood (2). The questionnaire elicited information on sexual functions: performance, motivation, spontaneous erections, desire, enjoyment (with and without a partner), and satisfaction with erection duration and size. The sexual performance assessment was based on the following activities: orgasm, ejaculation, intercourse, masturbation, and erection in response to a sexual activity. The sexual performance score was the average number of days per 7-d week of these five activities. The sexual motivation assessment was based on the following activities: sexual daydreams, anticipation of sex, sexual interaction with partner, flirting by subject, and flirting by others toward subject. The sexual motivation score was the average number of days per 7-d week that these five activities occurred. The evaluation of spontaneous erections was the average number of days in a 7-d week that either spontaneous nighttime or daytime erections occurred. Sexual desire, sexual enjoyment, and satisfaction with erection were assessed on a Likert-type scale (score 0 to 7) and were calculated as average scores. Percentage of full erection was scored from 0% to 100%. Patients also rated positive mood (alert, full of energy, friendly, well or good) and negative mood (angry, irritable, sad or blue, tired, nervous) on a 0 to 7 categorical scale (0 = not at all true to 7 = very true). Average daily scores were computed.

Serum T and DHT levels were all measured at ICON Laboratories (Farmingdale, NY), using validated RIA kits. Kits (Diagnostic Products, Los Angeles, CA) were used for the T assays and kits obtained from Diagnostic Systems Laboratories, Inc. (Webster, TX) were used for DHT assays. The lower limits of detection for the T and DHT pharmacokinetic assays were 0.1 nmol/liter (4 ng/ml) and 0.01 nmol/liter (4 pg/ml), respectively. The DHT assay had a 0.02% or less cross-reactivity (after solvent extraction) with T and T had a 3.3% or less cross-reactivity with DHT up to 173.6 nmol/liter (5000 ng/dl). The mean accuracy (recovery) of T determined by spiking steroid-free serum with varying amounts of T [1.5–1.3 nmol/liter (44–36 ng/dl)] was 98% (range, 93–103). The intra- and interassay coefficients of the T assay were 6.7% and 7.9% for a control group adult male range of 8.5–63.8 nmol/liter (245–1836 ng/dl). The mean accuracy (recovery) of DHT determined by spiking steroid-free serum with various amounts of DHT [0.2–1.4 nmol/liter (59–418 pg/ml)] was 94% (range, 85–130). The intra- and interassay coefficients of the DHT assay were 4.6% and 6.4%, respectively, for a control group adult male range of 0.3–2.4 nmol/liter (97–711 pg/ml).

Statistical analyses

The 24-h PK profiles for T and DHT were summarized by C_{avg} (AUC_{0-24} divided by the 24-h sampling period, where AUC is calculated using the trapezoidal rule), the minimum postdose concentration (C_{min}), and the postdose C_{max}. The changes from baseline to d 30 and d 90 in $C_{min,}$ C_{avg}, and C_{max} were analyzed using an analysis of covariance with baseline value as the covariate and treatment group as the factor. Patients randomized to AA2500 (50 mg/d or 100 mg/d) may have had their dose changed at the d 60 visit. Those patients with a dose change will be analyzed at d 90 using the dose they received at the d 60 visit. Similar analyses were used for the change from baseline in sexual function, mood, and body composition as well as for the clinical laboratory parameters at d 30, 60, and 90. Treatment-emergent adverse events were compared using a Fisher's exact test. Skin irritation at d 30, 60, and 90 was analyzed using a Wilcoxon rank sum test. At d 30 and 90, the 50 mg/d and 100 mg/d AA2500 treatment groups were compared with T patch (PK parameters, sexual function, body composition, and mood) and placebo (sexual function, body composition, and mood). For each comparison, including safety parameters, an α-value of 0.05 was considered significant. The changes from baseline in sexual function, body composition, and mood were also analyzed for nonzero differences within each treatment group based on the adjusted least squares means from the analysis of covariance model. SAS version 6.12 (SAS Institute, Inc., Cary, NC) was used for all analyses. All data in tables are presented as means (±SD).

Results

Subjects

A total of 406 patients were randomized with 99, 106, 102, and 99 being randomized to the 50 mg/d AA2500, 100 mg/d AA2500, T patch, and placebo treatment groups, respectively (Table 1). Baseline patient characteristics (age, height, weight, body mass index, serum T at screening, I-PSS scores, and PSA levels) were comparable. Of the patients who had a valid PK profile, 70 of 399 (17.5%, 21 patients in 50 mg/d AA2500, 20 patients in 100 mg/d AA2500, 16 patients in T patch, and 13 patients in placebo groups) had a C_{avg} above 10.4 nmol/liter at baseline. Of these patients, 71% had at least one or more serum T measurement less than 10.4 nmol/liter during the course of d −1. Baseline mean C_{avg} serum T concentrations were 12.6, 12.1, 12.8, and 12.4 nmol/liter in the 50 mg/d AA2500, 100 mg/d AA2500, T patch, and placebo groups, respectively. Fifty percent of the patients were aged 58 yr or older and approximately 26% were aged 65 yr and older with a mean age of 58 yr. Patient hypogonadism was primarily attributed to the secondary cause of aging and normogonadotrophic hypogonadism; these cases accounted for 91% of all causes in the overall population (Table 1). A significant proportion of enrolled patients completed the 90-d study (90% and 92% in the AA2500 and placebo groups, respectively, and 75% in the T patch group). The primary reason for the higher rate of discontinuations in the T patch group was adverse events (17%) with the majority of events being related to skin irritations at the patch site. Titrations made at d 60 in the AA2500 T gel groups were: 52 patients started on 50 mg/d dose and remained on 50 mg/d dose for the entire study, 43 patients who started on 50 mg/d dose were titrated up to the 100 mg/d dose, 93 patients who started on 100 mg/d dose remained at the 100 mg/d dose for the entire study, and 4 patients who started on 100 mg/d dose were titrated down to 50 mg/d dose. Patients who remained at 50 mg were more likely to have secondary hypogonadism, excluding aging, than patients who titrated to 100 mg. Dosing compliance ranged from 94.9% (placebo) to

97.1% (50 mg/d AA2500 and 100 mg/d AA2500 combined analysis).

T pharmacokinetics (Fig. 1 and Table 2)

At baseline, mean C_{avg} serum T concentrations were below the normal adult range (10.4–34.7 nmol/liter) and similar across treatment groups. By d 30, the mean C_{avg} for the 50 mg/d AA2500 treatment had increased 50% over baseline with a similar increase being evidenced in the T patch treatment group. The 100 mg/d AA2500 dose resulted in a 173% increase with a significant difference ($P < 0.001$) in comparison with the T patch treatment group. The C_{avg} was increased above 10.4 nmol/liter in 55% of 50 mg/d AA2500 patients, 95% of the 100 mg/d AA2500 patients, 68% of the T patch patients, and 8% of the placebo patients. In the 100 mg/d AA2500 group, 30 patients had a C_{max} higher than the upper limit of normal (34.7 nmol/liter), but 26 of these patients had a C_{avg} still between 10.4–34.7 nmol/liter. The degree of fluctuation during a day in serum values [$(C_{max} - C_{min})/C_{avg}$] was significantly smaller in the two AA2500 dose groups in comparison with the T patch group. By d 90, similar results were seen across the treatment groups. Approximately 75% of 50 mg/d AA2500 and 80% of 100 mg/d AA2500 treated patients had C_{avg} values above 10.4 nmol/liter, in comparison with 57% of the T patch-treated patients and 10% of placebo-treated patients.

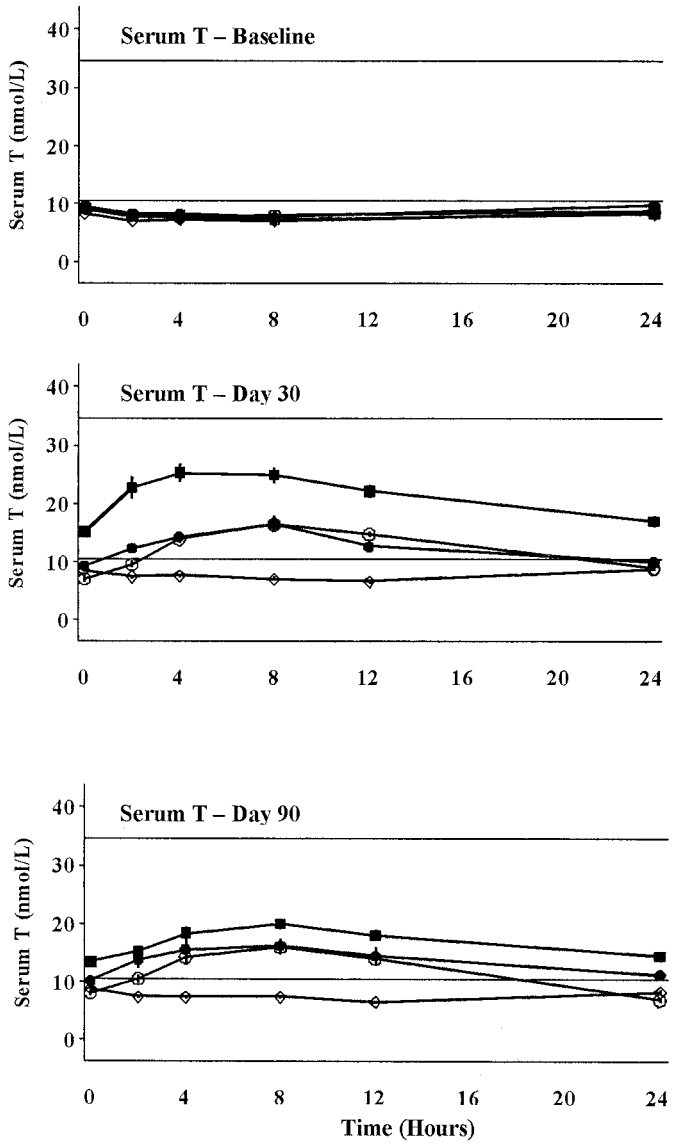

FIG. 1. Serum T concentrations before (baseline) and after study drug treatment on d 30 and 90. Time 0 was approximately 0800 h. *Solid horizontal lines* denote the adult male range (10.4–34.7 nmol/liter). ●, 50 mg/d AA2500; ■, 100 mg/d AA2500; ○, T patch; ◇, placebo.

DHT pharmacokinetics (Fig. 2 and Table 3)

At baseline, mean C_{avg} serum DHT concentrations were below the normal adult male range (0.9–2.6 nmol/liter) and similar across treatment groups. Mean changes in DHT C_{avg} from baseline to d 30 for the 50 mg/d AA2500 and 100 mg/d AA2500 dose groups were more than 4- and 7-fold greater, respectively, than changes observed in the T patch treatment group ($P < 0.001$ for each comparison). Similar to C_{avg}, C_{min} results further demonstrated the effectiveness of both AA2500 doses in increasing the d 30 C_{min} to a significantly greater degree than the T patch treatment ($P < 0.001$ for each comparison). The 100 mg/d AA2500 dose achieved a mean d 30 C_{min} that was within the normal range. For C_{max}, the d 30 effects reported were similar to that observed with C_{avg}. The C_{max} mean changes in serum DHT from baseline to d 30 for both AA2500 dose groups were approximately 4- and 7-fold greater than that evidenced in the T patch group ($P < 0.001$ for each comparison) with 15 (16%), 39 (42%), 1 (1%), and no patients in the 50 mg/d AA2500, 100 mg/d AA2500, T patch, and placebo groups, respectively, exceeding the normal range. At d 30, examination of the DHT to T C_{avg} ratio demonstrated that this ratio was not altered by either the T patch or placebo treatment, whereas a near doubling of the ratio was, respectively, evidenced with both AA2500 doses. By d 90, similar results were seen across the treatment groups. Additionally, the higher serum levels of DHT obtained with the AA2500 treatments correlated with the serum T levels obtained.

Body composition (Fig. 3)

At baseline, there were no significant differences in LBM, FM, %F, and TBM among the four treatment groups. At d 90, the 100 mg/d AA2500 treatment increased LBM to a significantly greater degree than the T patch or placebo treatment ($P < 0.05$ for each comparison) with mean changes from baseline of 1.5 ± 4.5, 1.7 ± 2.6, 0.9 ± 1.8, and 0.6 ± 1.8 kg for the 50 mg/d AA2500, 100 mg/d AA2500, T patch, and placebo treatment groups, respectively. With the exception of placebo treatment, all treatments resulted in a decrease in FM, which were significant, compared with placebo ($P < 0.01$). Reductions of 0.8 ± 2.4, 0.8 ± 2.0, 0.4 ± 1.8, and 0.1 ± 1.5 kg were noted in the 50 mg/d AA2500, 100 mg/d AA2500, T patch, and placebo treatment groups, respectively. Reductions in %F were evidenced in all treatment groups, with the AA2500 treatments yielding the most notable decreases. Specifically, at d 90, the 50 mg/d AA2500 dose resulted in a reduction of 1.1 ± 3.2% which was sig-

TABLE 2. T (nmol/liter): mean d 30 and 90

		AA2500		T patch	Placebo
		50 mg/d	100 mg/d		
Day 30					
C_{avg}	Baseline	8.6 ± 2.8	7.8 ± 2.8	8.2 ± 2.8	7.5 ± 2.8
	Actual	12.7 ± 6.5	21.3 ± 9.9[b]	12.7 ± 4.2	7.5 ± 2.8
C_{min}	Baseline	6.8 ± 2.4	6.2 ± 2.6	6.7 ± 2.3	5.9 ± 2.3
	Actual	7.7 ± 4.4[a]	13.6 ± 6.5[b]	6.2 ± 2.9	5.7 ± 2.2
C_{max}	Baseline	10.7 ± 3.6	9.9 ± 3.2	10.2 ± 3.7	9.5 ± 3.6
	Actual	18.8 ± 12.9[a]	31.2 ± 19.8[b]	18.8 ± 6.9	9.4 ± 3.8
Day 90					
C_{avg}	Baseline	9.2 ± 3.4	7.7 ± 2.4	8.3 ± 2.8	7.6 ± 2.8
	Actual	13.8 ± 8.1	17.1 ± 8.2[b]	11.9 ± 4.6	7.3 ± 2.7
C_{min}	Baseline	7.4 ± 2.8	6.1 ± 2.3	6.7 ± 2.1	6.0 ± 2.4
	Actual	8.7 ± 3.9[b]	10.9 ± 6.0[b]	5.7 ± 2.8	5.9 ± 2.4
C_{max}	Baseline	11.3 ± 4.1	9.8 ± 2.9	10.3 ± 3.7	9.5 ± 3.6
	Actual	19.5 ± 12.2	24.4 ± 13.8[b]	18.5 ± 8.2	9.1 ± 3.5

Values are expressed as means ± 1 SD. Change from baseline significant *vs.* T patch: [a] $P < 0.05$, [b] $P < 0.001$.

nificant in comparison to the reduction evidenced with placebo treatment (0.2 ± 1.4%, $P < 0.05$). Furthermore, the 100 mg/d AA2500 treatment resulted in a 1.2 ± 1.9% reduction at d 90, which was not only significant in comparison with placebo ($P < 0.01$) but also significant in comparison with the T patch treatment (0.5 ± 1.6%, $P < 0.05$). Although all treatments resulted in minimal increases in TBM, no significant differences were noted among the treatment groups.

Mood and sexual function (Table 4)

Although all treatments resulted in mean improvements from baseline in both positive and negative mood scores, no significant differences among the treatment groups were observed.

At baseline, sexual function scores were similar across the four treatment groups. Evaluation of the mean data demonstrated that the 100 mg/d AA2500 dose showed a significant improvement at d 90 over placebo treatment for spontaneous erections ($P < 0.001$), sexual motivation ($P < 0.05$), sexual desire ($P < 0.01$), and sexual performance ($P < 0.05$). Furthermore, the improvement from baseline was also significant for these parameters.

All other measures of sexual function (*e.g.* sexual enjoyment with a partner, sexual enjoyment without a partner, satisfaction with erection duration, and percentage of full erection) showed no significant difference in improvement between treatment groups.

Safety

Adverse events. The incidence of treatment-related adverse events was 29.1%, 36.9%, 62.7%, and 40.4% in the 50 mg/d AA2500, 100 mg/d AA2500, T patch, and placebo groups, respectively. Although treatment in the AA2500 and placebo groups was relatively well tolerated over the 90-d study period, the T patch-treated patients experienced a substantially higher rate of adverse events. Those most commonly seen were application site erythema, application site rash, application site pruritus, application site reactions, and application site irritation.

Specific events that were possibly or probably related to study drug and reported by 1% or more of the AA2500 patients and greater than placebo included application site reactions, BPH, increases in blood pressure and hematocrit/hemoglobin, gynecomastia, headache, hot flushes, insomnia, increased lacrimation, mood swings, smell and taste disorders, and spontaneous penile erections.

Only six patients in AA2500 treatment groups experienced adverse events that led to discontinuation. Specific events in the 100 mg/d AA2500 treatment group included vertigo, coronary artery disease, depression with suicidal ideation, urinary tract infection/pneumonia, and hypertension. All events with the exception of hypertension were considered unrelated to treatment. Mood swings, considered related to treatment, was the only event in the 50 mg/d AA2500 treatment group that led to discontinuation. Lastly, no patients in the 50 mg/d or 100 mg/d AA2500 treatment groups discontinued because of skin reaction, whereas the majority of patients that discontinued in the T patch group did so as a result of local dermal site reactions (n = 15).

With regard to prostate-related events, mild BPH was reported in two patients in the 100 mg/d AA2500 treatment group and one patient in the placebo treatment group. Additionally, two T patch-treated patients were diagnosed with prostatic cancer.

Laboratory analyses

Statistically significant differences between the 50 mg/d and/or 100 mg/d AA2500 groups and placebo groups in serum blood urea nitrogen (−2.0 ± 4.0, −1.7 ± 4.3, and −0.6 ± 3.9 mg/dl, respectively), creatinine (0.04 ± 0.12, 0.07 ± 0.14, and −0.02 ± 0.12 mg/dl, respectively), and fasting glucose levels (−2.2 ± 18.1, −5.6 ± 25.1, and 4.0 ± 25.3 mg/dl, respectively) were observed; however, these differences were minor and not clinically meaningful.

At d 90, clinically notable decreases from baseline in average total cholesterol (TC), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) were evidenced with the 100 mg/d AA2500 group (−7%, −7%, and −8%, respectively). Mean d 90 LDL/HDL ratios (2.73, 2.56, 2.52, and 2.41 for the 50 mg/d AA2500, 100 mg/d AA2500, T patch, and placebo groups, respectively) remained essentially unchanged from baseline. Additionally, mean d 90 HDL/TC

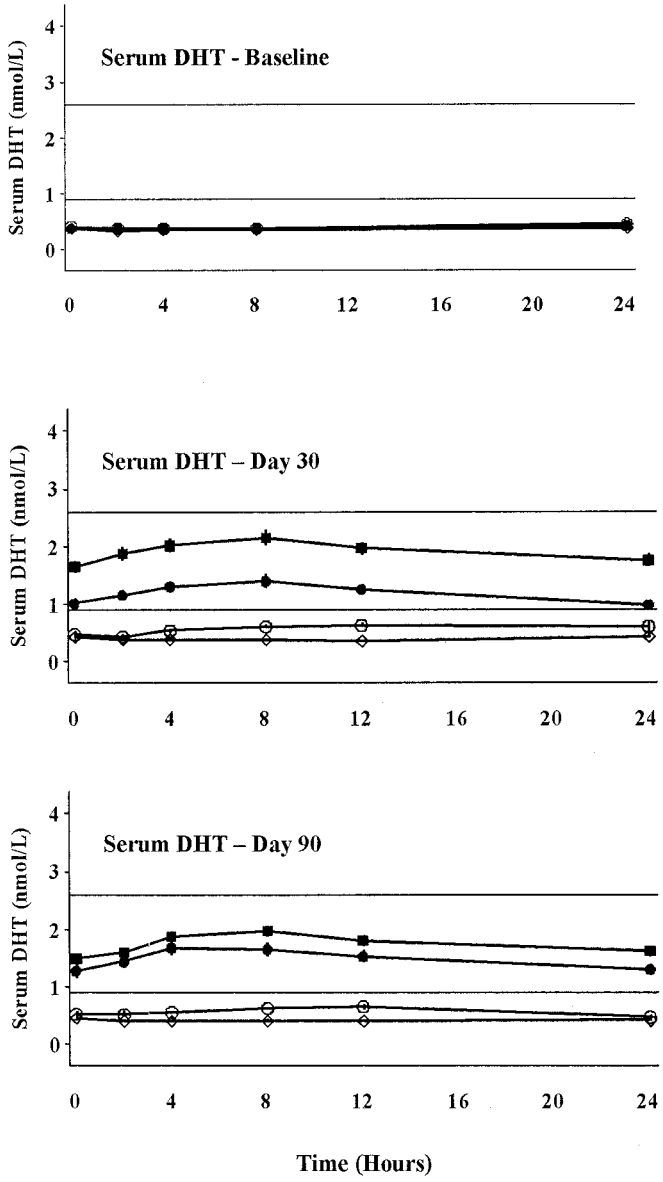

FIG. 2. Serum DHT concentrations before (baseline) and after study drug treatment on d 30 and 90. Time 0 was approximately 0800 h. *Solid horizontal lines* denote the adult male range (0.8–2.6 nmol/liter). ●, 50 mg/d AA2500; ■, 100 mg/d AA2500; ○, T patch; ◇, placebo.

ratios (0.23, 0.24, 0.24, and 0.24 for the 50 mg/d AA2500, 100 mg/d AA2500, T patch, and placebo groups, respectively) also remained unchanged.

Increases in hemoglobin and hematocrit are known pharmacological class effects of T. Consistent with this, patients in the 50 mg/d and 100 mg/d AA2500 group experienced statistically significant mean d 90 increases in hematocrit and hemoglobin of 2.3 ± 3.4% and 0.96 ± 0.96 g/dl, respectively, in the 50 mg/d AA2500 group and 2.8 ± 3.5% and 0.94 ± 1.06 g/dl in the 100 mg/d AA2500 group, compared with the placebo treatment group (−0.1 ± 2.8% and 0.12 ± 0.71 g/dl) and T patch treatment group (1.1 ± 2.6% and 0.48 ± 0.74 g/dl). The effects observed with T patch treatment were consistently greater than observed with placebo treatment but less than those observed with the AA2500 treatments, reflecting the lower average serum T levels associated with the T patch treatment. At d 30 and 60, similar effects were reported for the AA2500 treatment group. Overall, approximately 3%, 6%, 1%, and 1% of patients in the 50 mg/d AA2500, 100 mg/d AA2500, T patch, and placebo groups, respectively, experienced a hematocrit value more than 55% at least once during the study. Statistically significant mean changes were also reported for lymphocytes and monocytes, but the changes were small and not of apparent clinical significance.

PSA values (Table 5) more than 4.0 ng/ml were noted at least once during treatment in 1.8%, 2.9%, 6.6%, and 3.2% of patients in the 50 mg/d AA2500, 100 mg/d AA2500, T patch, and placebo treatment groups, respectively. PSA elevations were noted in all groups with the T patch group evidencing the greatest number of transient and persistent elevations. Mean changes from baseline to d 90 of 0.3 ± 1.8, 0.1 ± 0.4, 0.2 ± 0.6, and-0.1 ± 0.4 ng/ml for the 50 mg/d AA2500, 100 mg/d AA2500, T patch, and placebo treatment groups, respectively. Of note, one patient in the 50 mg/d AA2500 treatment group experienced a transient elevation of 17.6 ng/ml (without clinically valid explanation) that upon repeat evaluation returned to normal (3.6 ng/ml).

The changes from baseline for I-PSS were small, and the incidence of patients experiencing a general worsening of their DRE was low (3.4%, 1.4%, 0%, and 4.2% in the 50 mg/d AA2500, 100 mg/d AA2500, T patch, and placebo groups, respectively). Both parameters provided no evidence of clinically relevant treatment-related effects or differences.

Skin irritation (Fig. 4)

Figure 4 provides a graphic illustration of the frequency distribution of patients having positive skin irritation scores. It can be seen that the events occurred predominantly in the T patch treatment group and only a few mild reactions occurred in the combined AA2500 and placebo treatment groups. Additionally, the figure illustrates that the T patch acted as an irritant in some patients who experienced classic signs of contact dermatitis and that the AA2500 treatments were no more irritating than the placebo gel vehicle from d 60 through the completion of the study.

Discussion

This study demonstrated that this new, unique T gel (AA2500), when titrated to clinical effectiveness, was superior to the T patch in normalizing serum T in patients with hypogonadism. Specifically, the 100 mg/d dose was not only effective in significantly improving sexual performance, sexual motivation, and sexual desire and increasing spontaneous erections but also increasing LBM and decreasing FM and %F. There were associated increases in hemoglobin and hematocrit, which are known pharmacological class effects of T administration. The small mean increases in PSA observed with AA2500 doses and the T patch treatment groups, but not the placebo group, were not associated with an increase in I-PSS. Small decreases in TC, LDL, and HDL were observed in the AA2500 treatment groups with no changes in HDL/TC or LDL/HDL ratios. Erythema, rash, pruritus,

TABLE 3. DHT (nmol/liter): mean d 30 and 90

		AA2500		T patch	Placebo
		50 mg/d	100 mg/d		
Day 30					
C_{avg}	Baseline	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.3 ± 0.2
	Actual	1.2 ± 0.7[a]	1.9 ± 1.0[a]	0.6 ± 0.3	0.4 ± 0.2
C_{min}	Baseline	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.2 ± 0.1
	Actual	0.8 ± 0.6[a]	1.4 ± 0.9[a]	0.4 ± 0.2	0.3 ± 0.2
C_{max}	Baseline	0.5 ± 0.2	0.5 ± 0.3	0.5 ± 0.3	0.5 ± 0.2
	Actual	1.7 ± 1.0[a]	2.6 ± 1.4[a]	0.8 ± 0.7	0.5 ± 0.3
DHT/T†	Baseline	0.05 ± 0.02	0.05 ± 0.03	0.05 ± 0.02	0.06 ± 0.04
C_{avg}	Actual	0.09 ± 0.04[a]	0.09 ± 0.04[a]	0.05 ± 0.02	0.06 ± 0.04
Day 90					
C_{avg}	Baseline	0.5 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.2
	Actual	1.5 ± 0.7[a]	1.8 ± 0.9[a]	0.6 ± 0.3	0.4 ± 0.2
C_{min}	Baseline	0.3 ± 0.1	0.2 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
	Actual	1.0 ± 0.6[a]	1.2 ± 0.7[a]	0.3 ± 0.2	0.3 ± 0.2
C_{max}	Baseline	0.6 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2
	Actual	2.0 ± 0.9[a]	2.3 ± 1.2[a]	0.8 ± 0.4	0.5 ± 0.3
DHT/T†	Baseline	0.05 ± 0.03	0.05 ± 0.02	0.05 ± 0.02	0.06 ± 0.04
C_{avg}	Actual	0.11 ± 0.04[a]	0.10 ± 0.04[a]	0.05 ± 0.03	0.06 ± 0.05

Values are expressed as means ± 1 SD. †DHT/T = ratio of C_{avg} of DHT and T (nmol/liter units do not apply).
[a] $P < 0.001$. Change from baseline significant *vs.* T patch.

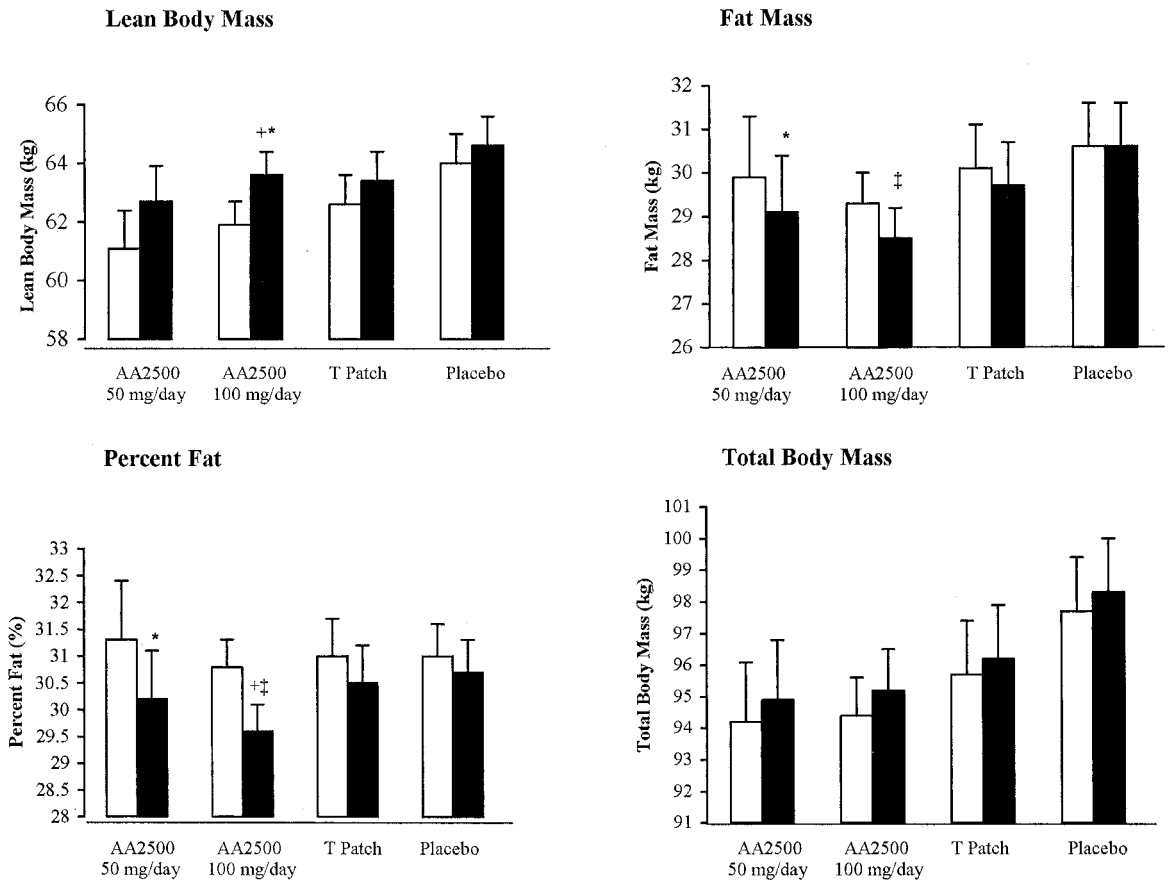

FIG. 3. Values are expressed as means ± 1 SE in LBM, FM, %F, and TBM after treatment with 50 mg/d AA2500, 100 mg/d AA2500, T patch, and placebo. □, Baseline; ■, d 90; *, Significant *vs.* placebo: $P < 0.05$; +, significant *vs.* T patch: $P < 0.05$; ‡, significant *vs.* placebo: $P < 0.01$.

application site reactions, and irritation were observed much more frequently in the T patch group, compared with both AA2500 treatment groups and the placebo treatment group. Additionally, the T patches acted as an irritant in some patients who experienced classic signs of contact dermatitis, whereas the AA2500 gel treatments resulted in minimal skin erythema in only a few patients with the incidence being similar to that observed in the placebo treatment group.

The 100 mg/d AA2500 treatment increased LBM to a greater degree than either the T patch or placebo, and both

TABLE 4. Sexual function scores: mean change from baseline to d 90

		AA2500		T patch	Placebo
		50 mg/d	100 mg/d		
Spontaneous erections	Baseline	0.7 ± 0.9	0.8 ± 1.1	1.0 ± 1.3	1.0 ± 1.2
(average weekly)	Change	0.3 ± 1.3	0.7 ± 1.4[c,f]	0.3 ± 1.1	0.0 ± 1.0
Motivation	Baseline	1.6 ± 1.5	1.8 ± 1.4	1.6 ± 1.2	1.5 ± 1.2
(average weekly)	Change	0.2 ± 1.5	0.6 ± 1.4[a,f]	0.4 ± 1.1[d]	0.1 ± 1.2
Desire	Baseline	2.3 ± 1.4	2.4 ± 1.4	2.2 ± 1.4	2.1 ± 1.4
(average daily)	Change	0.5 ± 1.2[e]	1.0 ± 1.4[b,f]	0.6 ± 1.2[f]	0.5 ± 1.0[f]
Performance	Baseline	0.8 ± 0.9	0.8 ± 0.9	0.7 ± 0.8	0.8 ± 0.8
(average weekly)	Change	0.3 ± 1.1	0.5 ± 1.2[a,f]	0.3 ± 0.7[d]	0.2 ± 0.9[d]

Values are expressed as means ± 1 SD. Significant *vs.* placebo: [a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$. Significant within treatment group change from baseline: [d] $P < 0.05$, [e] $P < 0.01$, [f] $P < 0.001$.

TABLE 5. PSA: summary of changes to d 90 and classification of overall elevations

	AA2500		T patch	Placebo
	50 mg/d	100 mg/d		
Baseline (ng/ml)	1.2 ± 1.0	1.2 ± 0.9	1.4 ± 1.1	1.1 ± 1.0
Change (ng/ml)	0.3 ± 1.8[a]	0.1 ± 0.4	0.2 ± 0.6	−0.1 ± 0.4
PSA elevations[b]				
>4.0 ng/dl	1	4	6	3
Transient	1	2	2	1
Persistent	0	2	4	2

Baseline and change values are expressed as means ± 1 SD.
[a] $P < 0.01$, significant *vs.* placebo.
[b] Number of subjects experiencing at least one PSA value >4.

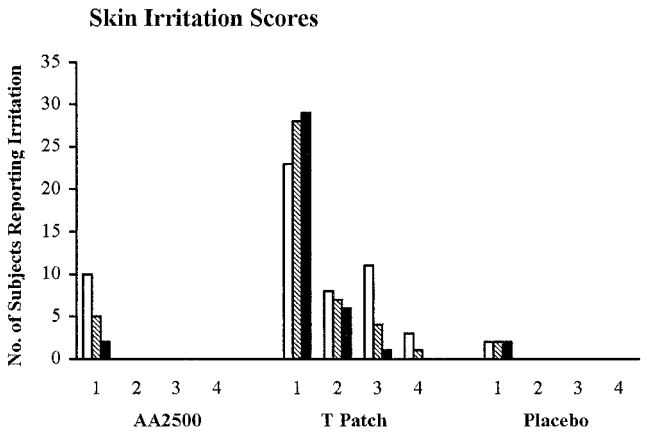

FIG. 4. Distribution of subjects with positive application site/skin irritation scores on d 30, 60, and 90. 1, Minimal erythema; 2, moderate erythema with sharply defined borders; 3, intense erythema with or without edema; 4, intense erythema with edema and blistering/erosion. The 50 mg/d and 100 mg/d AA2500 treatment groups combined. □, d 30; ▨, d 60; ■, d 90.

doses of AA2500 also resulted in a significantly greater decrease in FM and %F, compared with placebo. Normalization of serum T levels were achieved with both doses of AA2500 for average T levels and minimum T levels over a 24-h dosing period. In contrast, the T patch group was able to restore only average T levels. Previously reported data suggest that increases in LBM and decreases in FM are correlated with serum T levels (1). This difference in normalization may explain the greater increase in LBM and greater decrease in FM and %F observed with the AA2500 treatments. In previous studies in hypogonadal men, T replacement therapy has resulted in decreases in FM in some studies using injectable or transdermal T but not in other studies in which either injectable or sublingual T has been administered. The difference in results observed in these previous reports might be due to lower serum T levels achieved by different T preparations.

Regarding DHT, although it is true that the AA2500 treatments produced higher serum levels at d 30 and 90, the DHT/T ratio remained stable and similar to that reported in normal men, demonstrating concordance with the naturally occurring 5α-reductase conversion of T to DHT. The effect of serum DHT levels on the intraprostatic levels of DHT is not known. As with serum T levels, a prospective relationship between DHT serum levels and the incidence of prostate cancer has not been demonstrated (10, 11). Further long-term studies are needed to clarify the effect of increased DHT on the prostate.

There were no unexpectedly abnormal laboratory values and the incidence of clinically relevant abnormal findings was low. By d 90, patients in the AA2500 group who were administered 50 mg/d or 100 mg/d experienced statistically significant increases in hematocrit and hemoglobin, compared with patients receiving T patch or placebo. The increases observed in the T patch group were consistently greater than those observed in the placebo group but less than those observed in the AA2500 groups. This is likely a result of the lower serum T levels achieved with T patch. A previous study demonstrated similar increases in hematocrit and hemoglobin with T replacement therapy, with these increases being more marked with higher doses of T (1). These small increases in hematocrit and hemoglobin, which can occur with T replacement therapy, may even be beneficial in hypogonadal patients in whom anemia, lethargy, and fatigue are commonly found; however, a small percentage of treated individuals may increase their hematocrit levels to more than 55% and in turn be prone to the problems

associated with polycythemia. To this end, periodic monitoring of hematocrit is recommended to determine whether T therapy dose adjustments or termination (*i.e.* in the event hematocrit values do not fall below 55%) may be required.

Small increases in PSA similar to those seen in previous studies with T replacement therapy were observed in both AA2500 groups and in the T patch group. However, the magnitude of the increase in PSA, changes in I-PSS, and findings from DRE following treatment with either dose of AA2500 or T patch in this study were not of clinical concern. Although T has not been shown to induce cancer of the prostate, two patients on the T patch were diagnosed with prostate cancer during the study. This is not surprising because elderly men are at an increased risk of developing prostate cancer and the diagnosis can be made as a result of an elevated PSA subsequently leading to prostatic biopsy.

Very few adverse effects were reported following topical application of AA2500, and those that were reported were similar in type to the known class effects of T. Of particular note was the very low incidence of skin irritation reported with AA2500, which was comparable to placebo and significantly lower than T patch. Furthermore, no patient in the gel groups discontinued because of skin intolerability.

This study clearly shows that 100 mg/d AA2500 dose is superior to T patch in normalizing serum T and DHT in hypogonadal men. The AA2500 treatments resulted in increasing LBM (100 mg/d dose) and decreasing FM and %F to a greater degree than either the T patch or placebo. Furthermore, significant improvements from baseline and in comparison to placebo were observed for spontaneous erections, sexual motivation, sexual desire, and sexual performance with 100 mg/d AA2500 dose. Overall, this new, unique T gel (AA2500) can offer benefit over other transdermal preparations because of improved 24-h serum T levels and improved compliance as a result of a lower incidence of local dermal irritation.

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References

1. **Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, Matsumoto M, Weber T, Berman N, Testosterone Gel Study Group** 2000 Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. J Clin Endocrinol Metab 85:2839–2853
2. **Arver S, Dobs AS, Meikle AW, Caramelli KE, Rajaram L, Sanders SW, Mazer NA** 1997 Long-term efficacy, and safety of a permeation-enhanced testosterone transdermal system in hypogonadal men. Clin Endocrinol (Oxf) 47:727–737
3. **Behre HM, von Eckardstein S, Kliesch S, Nieschlag E** 1999 Long-term substitution therapy of hypogonadal men with transscrotal testosterone over 7–10 years. Clin Endocinol (Oxf) 50:629–635
4. **Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, Dlewati A, Staley J, Santanna J, Kapoor SC, Attie MF, Haddad Jr JG, Strom BL** 1999 Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab 84:1966–1972
5. **Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, Holmes JH, Dlewati A, Santanna J, Rosen CJ, Strom BL** 1999 Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab 84:2647–2653
6. **Jordan Jr WP, Atkinson LE, Lai C** 1998 Comparison of the skin irritation potential of two testosterone transdermal systems: an investigational system and a marketed product. Clin Ther 20:80–87
7. **Jordan Jr WP** 1997 Allergy and topical irritation associated with transdermal testosterone administration: a comparison of scrotal and nonscrotal transdermal systems. Am J Contact Dermatitis 8:108–113
8. **Marbury T, Hamill E, Bachand R, Sebree T, Smith T** 2003 Evaluation of the pharmacokinetic profiles of the new testosterone topical gel formulation, Testim compared to AndroGel. Biopharm Drug Dispos 24:115–120
9. **Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA** 1999 Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with biweekly injections of testosterone enanthate for the treatment of hypogonadal men. J Clin Endocrinol Metab 84:3469–3478
10. **Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ** 1996 Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst 88:1118–1126
11. **Mohr BA, Feldman HA, Kalish LA, Longcope C, McKinlay JB** 2001 Are serum hormones associated with the risk of prostate cancer? Prospective results from the Massachusetts Male Aging Study. Urology 57:930–935