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Comparison of a Gonadotropin Releasing-Hormone Antagonist plus Testosterone (T) *Versus* T Alone as Potential Male Contraceptive Regimens*

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ABSTRACT

Efforts to develop a hormonal contraceptive regimen for men have focused on administration of testosterone (T), alone or together with other agents. Previous regimens have successfully induced azoospermia in only 50–70% of subjects, however. GnRH antagonists, alone or in combination with T, have been shown to induce azoospermia in a very high percentage of nonhuman primates. We tested the hypothesis that the addition of a GnRH antagonist to a high-dose T regimen would lead to a higher percentage of men developing azoospermia than would T alone. We administered the GnRH antagonist, Nal-Glu (100 μg/kg·day sc), plus T enanthate, 200 mg im weekly or placebo sc injections daily plus T enanthate, 200 mg im weekly, to separate groups of healthy men for 16–20 weeks. Seven of 10 men who received Nal-Glu plus T and 6 of 9 men who received T alone became azoospermic; gonadotropin levels were suppressed and T levels were increased similarly in both groups. There was a trend toward higher pretreatment gonadotropin levels and lower sperm counts in men who became azoospermic. Weight gain, development of acne, and increases in hematocrit and hemoglobin were similar in the two groups. In the majority of the men, sperm counts returned to the baseline levels within 4–5 months after treatment ended.

We conclude that with the dosages of Nal-Glu and T we used in this study, the addition of GnRH antagonist to a high-dose T regimen does not increase the ability of T to suppress spermatogenesis in healthy men. Use of a higher dose of Nal-Glu, a lower dose of T, delaying the start of T replacement until several weeks after Nal-Glu injections are initiated, or prolonged hormonal administration might lead to a combination regimen that will suppress spermatogenesis more fully than does T alone. (*J Clin Endocrinol Metab* **77:** 427–432, 1993)

ALTHOUGH oral and injectable hormonal contraceptives are available for women, there is no effective hormonal contraceptive method for men. Because human spermatogenesis is dependent on gonadotropin stimulation (1, 2), efforts to develop a hormonal means of contraception for men have focused on regimens that suppress gonadotropin secretion. Administration of high-dose testosterone (T) causes profound gonadotropin suppression and results in azoospermia in 50–70% of subjects (3, 4). A recent World Health Organization trial has shown that among men who achieve azoospermia, the contraceptive efficacy of the method is nearly 100% (5). However, because it does not result in azoospermia in a higher percentage of men, T alone is unlikely to receive approval as a contraceptive method. GnRH agonists, as well as progestins, have been administered in conjunction with T (6–8), but neither regimen has been more successful than T alone.

GnRH antagonists are synthetic analogs of GnRH that compete with endogenous GnRH for pituitary binding sites, thereby causing immediate suppression of gonadotropin secretion (9). Gonadal steroid production is also severely inhibited. When GnRH antagonists are given on a daily basis, suppression of gonadotropins and gonadal products is sustained throughout the duration of treatment; when treatment is ended, hormone levels return to baseline within 1–2 weeks (10–12). GnRH antagonists and T suppress gonadotropins by different mechanisms, and we have previously shown that the short-term administration of the combination of the Nal-Glu GnRH antagonist [(AcD2Nal[1], D4ClPhe[2],D3Pal[3], Arg[5],DGlu [6](AA), DAla[10]] GnRH plus T suppresses gonadotropins and inhibin levels more completely than does either regimen alone (12). Based on these results, we hypothesized that the addition of a GnRH antagonist to a high-dose T regimen would lead to a higher percentage of men developing azoospermia. We have now tested this hypothesis in healthy men. After an initial baseline period, half of the men received GnRH antagonist plus T, whereas the other men received placebo antagonist injections plus T alone. We have thereby directly compared the two regimens under identical study conditions.

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Materials and Methods

Subjects

Twenty two healthy men, ages 19–42, enrolled in the study. All of the men had normal medical histories, physical examinations, and screening laboratory studies. All of the men had sperm counts greater than 20×10^6/mL, and all had acceptable responses to intradermal skin

testing with 10 μg Nal-Glu. An acceptable skin test is considered to be no more than the formation of a wheal with surrounding erythema, without pseudopod formation. None of the men were smokers, and none abused alcohol. All of the men signed informed consents which were approved by the Human Subjects Committee of the University of Washington.

Of the 22 men who enrolled in the study, 19 men completed 16–20 weeks of drug administration. One man developed a significant local reaction to Nal-Glu after 10 days and was withdrawn from the study. Two other men (one in each group) discontinued drug treatment after 8–12 weeks for personal reasons. Initially, the treatment period was designed to last 16 weeks due to limited availability of Nal-Glu. However, antagonist availability increased during the middle of the treatment period, and the study was extended for 4 additional weeks. Subjects were asked to extend their participation in the treatment phase to 20 weeks, but they were not required to do so. Three men (2 who received Nal-Glu+T and 1 man who received T alone) chose to end their participation after 16 weeks. Two of the men had made plans to leave the area for vacation; the other man chose not to continue because of local side effects from Nal-Glu.

Clinical protocol

The study consisted of a 3–4 month baseline period, a 20-week treatment period, and a posttreatment period which lasted until the subject had three sperm counts within his baseline range. The posttreatment period lasted 4–6 months for most of the men. During each phase of the study, the subjects submitted seminal fluid samples every 2 weeks. Fasting blood samples were drawn each month for analysis of hormone levels, and hematology and chemistry parameters. All blood samples were drawn before the day's injections were administered; LH, FSH, and T levels reflect the nadir values. Peak T levels were measured 2 days after injection during the fourth month of the study. Subjects attended a volunteer clinic each month. At these clinics, they were interviewed and examined by a physician.

After the baseline period, each subject was assigned randomly to receive either: 1) Nal-Glu, 100 μg/kg·day sc, plus T enanthate, 200 mg im weekly (Nal-Glu+T); or, 2) saline placebo, 0.6–1.0 mL sc daily plus T enanthate, 200 mg im weekly (T alone). The dose of Nal-Glu was chosen based on the results of our earlier single and multiple-dose studies using this antagonist (11, 12). We used the dose of T (200 mg im weekly) that has been used most often in trials of T alone as a contraceptive agent, and which has been used in the World Health Organization studies (5). Subjects were not told which regimen they were receiving.

The first 8 men who enrolled in the study began the treatment period several months before the other men. Of these men, 4 were assigned to the Nal-Glu+T group, and 4 received T alone. One man assigned to Nal-Glu+T developed a significant local reaction at the injection site beginning 10 days after starting the Nal-Glu injections. Drug treatment was discontinued in this man, and an additional subject in the cohort who began treatment later was assigned to receive Nal-Glu+T. Therefore, a total of 12 men received Nal-Glu+T, and 10 men received T alone. An additional man in each group withdrew before completing the treatment period; 19 men completed 16 or 20 weeks of treatment, and the results from these 19 men are reported below.

Three men left the area during the posttreatment period and sent only occasional seminal fluid samples by mail. Several other men became noncompliant with the protocol after the first few months of the posttreatment period. Data from the last few months of the posttreatment period are therefore incomplete.

Drug preparation

The Nal-Glu GnRH antagonist was provided by the NICHD Contraceptive Development Branch. The antagonist was dissolved in bacteriostatic water containing 4% mannitol, diluted to a concentration of 10 mg/mL, and then, under sterile conditions, passed through a 0.2-μm filter into sterile vials and stored at −20°C until used. All of the subjects were taught to self-administer their injections. Subjects received a new vial of antagonist each month and refrigerated each vial between injections. To ensure compliance, subjects returned their empty vials of drug each month.

T enanthate (ER Squibb and Sons, Princeton, NJ) was administered in a dosage of 1 mL weekly by nursing staff at the Clinical Research Center at the University of Washington or Pacific Medical Center.

Hormone assays

Serum levels of T were measured by RIA using reagents from the WHO matched Reagent Program by methods previously described (13). T was separated from serum by ether extraction; bound and free hormone were separated by dextran-coated charcoal. The assay sensitivity was 0.35 nmol/L; the inter- and intraassay variabilities were 4.1% and 8.1%, respectively. Serum levels of LH and FSH were measured by an immunoradiometric method (MAIA clone, Serono Laboratories, Geneva, Switzerland). The limits of detectability of each assay was 0.5 IU/L. The inter-assay variabilities for LH and FSH were 10% and 11%, respectively. The intraassay variabilities were 4.8% and 7.0% for LH and FSH, respectively.

Seminal fluid analysis

Seminal fluid samples were collected by masturbation after a minimum of 48 h of abstinence. All samples were analyzed by the same technician throughout the course of the study. Sperm concentrations in seminal fluid samples were determined by Coulter counter (Coulter Electronics, Hialeah, FL) (14). Concentrations less than 15 million/mL were confirmed by hemocytometer using the method of the World Health Organization (15).

Statistical analysis

For each parameter, each man's pretreatment data were meaned; these values were then meaned to give the group mean value. Similarly, the data from the fourth and fifth treatment months and the last 2 months of the recovery period were meaned for each man. In the three men who did not complete 20 weeks of treatment, the value from the fourth treatment month was used in computing group means. Where appropriate, data were log-transformed before analysis. Differences within each treatment group (across time) and between the two groups were determined using two-way analysis of variance with repeated measures, with time and treatment as the dependent variables. Differences in hormone levels or sperm counts between men who did or did not become azoospermic were determined in the same manner. Within each group, the presence of differences among the monthly gonadotropin values were determined by one way analysis of variance with repeated measures, followed by Dunnett's multiple range test.

Results

Sperm counts (Fig. 1)

During the baseline period, the mean sperm count in men who later received Nal-Glu+T was 110.0 ± 16.3 × 10^6/mL (range, 25.8 to 201 × 10^6/mL). In men who later received T, the mean baseline sperm count was 108.2 ± 21.5 × 10^6/mL (range, 26.1 to 227 × 10^6/mL). Sperm counts in both groups decreased within the first month after treatment began. One man in the Nal-Glu+T group became azoospermic after 1 month; after 2 months, one additional man in the Nal-Glu+T group and two men in the T alone group became azoospermic. After 5 months, 6 of the 10 men who received Nal-Glu+T and 6 of the 9 men who received T had reached azoospermia. One additional man in the Nal-Glu+T group became azoospermic during the first month after treatment had ended. Of the men who did not become azoospermic at any time, 2 men (1 in each group) had nadir sperm counts

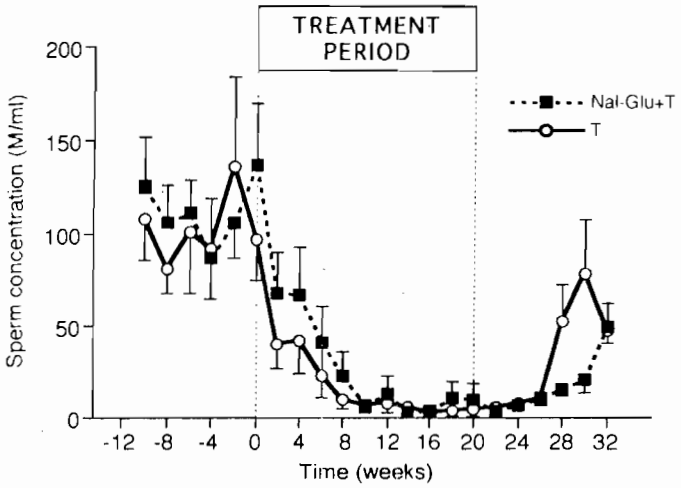

FIG. 1. Mean sperm concentrations (in millions per mL) before, during treatment, and during the first 3 months after treatment in men who received Nal-Glu+T (n = 10, *closed squares*) and men who received T alone (n = 9, *open circles*).

less than 1 × 10^6/mL, 1 man in the Nal-Glu+T had nadir counts between 1 and 5 × 10^6/mL, and 3 men (2 who received T, one who received Nal-Glu+T) maintained counts greater than 10 × 10^6/mL. There was a trend toward a lower mean pretreatment sperm count in men who became azoospermic by the end of the treatment period (Table 2), but the difference was not statistically significant ($P = 0.56$). In both treatment groups, sperm counts returned to the baseline ranges within 4–5 months; two men took more than 7 months to recover.

Serum hormone levels

Mean serum T levels before treatment were similar in men who received Nal-Glu+T or T alone (Table 1). At the end of the treatment period, the respective values in the two groups were significantly higher than the control values and were not different from each other. There were no differences in serum T levels between men who did or did not become azoospermic, either before or during drug treatment (Table 2). Peak T levels were measured in all of the men who received Nal-Glu+T and in six of the men who received T alone. Mean peak T values were not different in the two treatment groups, nor was there a difference in mean peak T levels between the men who became azoospermic and those who did not (Tables 1 and 2).

Mean serum LH and FSH levels in the two treatment groups were not different during the baseline period. At the end of the treatment period, mean LH and FSH levels were suppressed to near the limit of detectability of the assay in both treatment groups (Table 3). Baseline gonadotropin levels were reestablished in 1 to 2 months after treatment ended. Analysis of the FSH levels showed a significant interaction between time and treatment due to higher recovery values in the men in the T alone group. There were no differences in serum gonadotropin levels before or at the end of treatment in men who did or did not become azoospermic, although there was a trend toward higher pretreatment LH and FSH levels in the men who did become azoospermic (Table 4).

Blood counts and blood chemistries

There were no changes in routine blood chemistries (including glucose and aspartate aminotransferase (SGOT) levels) during the course of the study. Mean hematocrit increased from 44.9 ± 0.5% to 46.8 ± 0.4% ($P < 0.001$) in men who received Nal-Glu+T and from 44 ± 0.5% to 46.3 ± 0.8% ($P < 0.001$) in men who received T alone. Mean hemoglobin increased from 15.4 ± 0.2 to 16.0 ± 0.1 g/L ($P < 0.01$) in men who received Nal-Glu+T and from 15.3 ± 0.2 to 15.8 ± 0.2 g/L ($P < 0.01$) in men who received T alone.

Side effects

Weight gain due to T treatment was similar in both groups; the mean weight gain in men who received Nal-Glu+T was 4.2 ± 0.8 kg and in men who received T alone was 3.8 ± 0.6 kg. Most of the weight gain was reversed within 2–3 months after treatment ended. There was a wide range of weight responses to the experimental regimens; the amount of weight gained ranged from 0.1–8.6 kg in men who received Nal-Glu+T and from 0.1 to 5.9 kg in men who received T alone. Approximately half the men in each group had increased acne. All of the men who received Nal-Glu+T developed induration at the sc injection sites. The degree and extent of induration varied considerably among the individual men, as did the discomfort caused by injection of the antagonist. Four of the men took antihistamines to prevent or reduce the symptoms caused by Nal-Glu. None of the men who received T alone developed local symptoms at the sc injection sites, although occasional bruising did occur.

Discussion

We administered T enanthate, 200 mg im weekly, alone or in combination with the Nal-Glu GnRH antagonist, to healthy men for 16–20 weeks. At the end of the treatment

TABLE 1. Serum hormone levels and sperm counts in men who received Nal-Glu+T (n = 10) or T alone (n = 9)

	Nal-Glu+T			T Alone		
	Pretreatment	Treatment	Recovery	Pretreatment	Treatment	Recovery
T (nmol/L)	17.2 ± 1.3	26.8 ± 1.8[a]	16.0 ± 1.1	16.4 ± 1.4	25.5 ± 1.3[a]	17.9 ± 2.0
Peak T (nmol/L)		32.9 ± 3.3			34.5 ± 4.0	
Sperm count (×10^6/mL)	110.0 ± 16.3	9.7 ± 8.9[a]	68.5 ± 8.7	108.2 ± 21.5	4.5 ± 2.7[a]	71.9 ± 13.1

[a] Significantly different from pretreatment and recovery values ($P < 0.05$).

TABLE 2. Serum hormone levels and sperm counts in men who became azoospermic (n = 12) or failed to reach azoospermia (n = 7)

	Azoospermic			Not azoospermic		
	Pretreatment	Treatment	Recovery	Pretreatment	Treatment	Recovery
T (nmol/L)	16.8 ± 1.2	24.8 ± 1.4[a]	15.9 ± 1.0	16.8 ± 1.7	28.7 ± 1.6[a]	18.0 ± 2.1
Peak T (nmol/L)		32.2 ± 3.0			35.1 ± 4.3	
Sperm count ($\times 10^6$/mL)	98.8 ± 1.5	0[a]	65.4 ± 7.1	121.0 ± 24.5	13.5 ± 5.4[a]	78.2 ± 16.8

[a] Significantly different from pretreatment and recovery values ($P < 0.05$).

TABLE 3. Mean serum LH and FSH levels before treatment, during each month of treatment, and after treatment in men who received Nal-Glu+T (n = 10) or T alone (n = 9)

	Pre-tx	Month 1	Month 2	Month 3	Month 4	Month 5	Recovery
Nal-Glu+T							
LH (IU/L)	3.8 ± 0.4	0.6 ± 0.1[a]	0.6 ± 0.1[a]	0.7 ± 0.1[a]	0.6 ± 0.1[a]	0.7 ± 0.1[a] (n = 8)	3.3 ± 0.6
FSH (IU/L)	3.8 ± 0.3	0.7 ± 0.1[a]	0.9 ± 0.1[a]	0.9 ± 0.2[a]	1.0 ± 0.2[a]	0.7 ± 0.2[a] (n = 8)	3.4 ± 0.2
T alone							
LH (IU/L)	3.2 ± 0.2	1.1 ± 0.2[a]	0.8 ± 0.1[a]	0.7 ± 0.1[a]	0.6 ± 0.1[a]	0.6 ± 0.1[a] (n = 8)	3.6 ± 0.6 (n = 8)
FSH (IU/L)	3.9 ± 0.3	1.0 ± 0.2[a]	0.6 ± 0.1[a]	0.7 ± 0.1[a]	0.7 ± 0.1[a]	0.9 ± 0.2[a] (n = 8)	4.7 ± 0.4 (n = 8)

[a] Significantly different from pretreatment and recovery values ($P < 0.05$).

TABLE 4. Mean serum LH and FSH levels before treatment, during each month of treatment, and after treatment in men who became azoospermic (n = 12) or failed to reach azoospermia (n = 7)

Azoospermic	Pre-tx	Month 1	Month 2	Month 3	Month 4	Month 5	Recovery
Azoospermic							
LH (IU/L)	3.9 ± 0.3	0.9 ± 0.1[a]	0.7 ± 0.6[a]	0.6 ± 0.1[a]	0.6 ± 0.1[a]	0.7 ± 0.1[a] (n = 10)	3.4 ± 0.5 (n = 10)
FSH (IU/L)	4.0 ± 0.3	0.7 ± 0.1[a]	0.8 ± 0.1[a]	0.9 ± 0.2[a]	0.8 ± 0.1[a]	0.9 ± 0.2[a] (n = 10)	4.0 ± 0.9 (n = 10)
Not azoospermic							
LH (IU/L)	3.0 ± 0.4	0.9 ± 0.3[a]	0.8 ± 0.1[a]	0.7 ± 0.1[a]	0.9 ± 0.2[a]	0.7 ± 0.1[a] (n = 6)	3.1 ± 0.6
FSH (IU/L)	3.6 ± 0.3	1.1 ± 0.3[a]	0.7 ± 0.2[a]	0.9 ± 0.3[a]	0.9 ± 0.3[a]	0.8 ± 0.2[a] (n = 6)	3.9 ± 0.4

[a] Significantly different from pretreatment and recovery values ($P < 0.05$).

period, 6 of 10 men who received Nal-Glu+T and 6 of 9 men who received T alone achieved azoospermia. Gonadotropin levels in the two groups were similar before and at the end of treatment. These findings suggest that in the paradigm of hormone administration we used, the combination of antagonist plus T does not result in a more effective hormonal contraception than does T alone.

We have previously shown that in monkeys, high-dose GnRH antagonist plus T can induce azoospermia (16). Recently, using different dosing regimens of antagonist and T, two groups of investigators have shown the combination of Nal-Glu+T can induce azoospermia in a high percentage of healthy men (17, 18). Although the number of subjects in each of the studies was small, there are several possible reasons for the difference between our present results and those of others. First, it is possible that we did not use an adequate dose of Nal-Glu. We administered Nal-Glu at a dosage of 100 μg/kg·day (7.5–8.5 mg/day), whereas doses of 10–20 mg/day have been used by others (17). A higher dose of antagonist might result in more complete gonadotropin suppression, which in turn might lead to further suppression of spermatogenesis.

A second possible explanation of our results is that the dosage of T was too high. In rats, supplemental T with antagonist will increase FSH levels and cause a lesser decrease in sperm production compared to antagonist alone (19–22). Nearly all monkeys treated with antagonist alone become azoospermic; we have shown that the combination of antagonist and T can be highly successful in inducing azoospermia in monkeys (16), but other investigators have reported that fewer monkeys become azoospermic on a combination regimen than on antagonist alone (23, 24). In men, a supplemental T dose of 100 mg/week is required to maximally suppress gonadotropins and sperm production; however, suppression of gonadotropins and sperm production in men receiving 300 mg/week is similar to men receiving 100 mg weekly (3). A dose of exogenous T of more than 100 mg/week may also cause stimulation of spermatogenesis by a testicular effect in humans. A combination antagonist plus T regimen may therefore be more effective if the T dosage used is not sufficient to stimulate the seminiferous tubules.

Third, it is possible that a few of the men receiving antagonist plus T did not become azoospermic because we began T replacement concurrently with antagonist administration. In monkeys, a 2–4 week delay in initiating T replacement was reported to induce azoospermia move reliably than beginning the antogonist and the T at the same time (25). In both previous studies of Nal-Glu plus T administration in humans, T replacement was delayed by 2 weeks. An initial period during which antagonist alone is administered might therefore also enhance the effectiveness of the regimen in humans.

Fourth and perhaps most likely, a longer duration of drug exposure may have enabled additional men in both groups to reach azoospermia. Although most men who become azoospermic in response to hormonal contraceptive regimens do so within the first 20 weeks, a few men require 30 weeks or more (4). Finally, because the number of subjects in each of the studies of Nal-Glu plus T was small, it is possible that the lower percentage of men becoming azoospermic in our study compared to the others was due to chance.

The percentage of men in this study who became azoospermic on either regimen is similar to the results of other studies using T alone (3, 5). The reasons for differing sensitivities to T among men are not well-understood. Enhanced testicular sensitivity to low levels of gonadotropins may account for the failure of some individuals to become azoospermic. Another possible explanation is that men who do become azoospermic have a subtle, underlying testicular defect manifested by a slight elevation of gonadotropin levels, although these levels are well within the normal range. The men in this study who did become azoospermic had slightly (although not significantly) lower mean pretreatment sperm counts and slightly higher pretreatment levels of LH and FSH than did the men who did not achieve azoospermia. However, since all of the men had normal baseline data, it would be impossible to predict whether an individual would become azoospermic based on his pretreatment data. In our earlier study (12), gonadotropin levels were suppressed more completely by Nal-Glu+T than by T alone, while in the current study, suppression at the end of treatment was similar in both treatment groups. It is possible that the effect we observed earlier is not maintained over a longer duration of drug exposure. Gonadotropins in the Nal-Glu+T group were lower than in the T alone group after 1 month of treatment, but during the last 3 months mean gonadotropin levels were similar in both groups. Based on inspection of drug vials and verbal questioning, we have no reason to believe that compliance decreased in the Nal-Glu+T groups.

Nal-Glu causes predictable erythema and induration at the injection sites; it also requires daily administration. These characteristics make it unlikely that this GnRH antagonist would be acceptable to large numbers of men. However, new antagonists with fewer local effects are under development (26, 27). If one of these new compounds proves to be effective, reversible, safe, and relatively devoid of local effects, it is likely that a depot preparation of antagonist will be formulated. Such a formulation would allow for longer dosing intervals and would make a hormonal contraceptive method for men more attractive to potential users. Despite the paucity of contraceptive choices for men now available, over 30% of all contraception in the United States at the present time makes use of a male method (28), and over 40 million men worldwide use condoms (29). These data suggest that an effective, hormonal method for men would be widely used. It is therefore important to determine whether there exists a combination of GnRH antagonist plus T that will cause azoospermia in a higher proportion of men than does T alone.

In summary, we administered T enanthate, 200 mg im weekly, alone or in combination with the Nal-Glu GnRH antagonist, to healthy men. Seven of 10 men who received Nal-Glu+T and 6 of 9 men who received T alone achieved azoospermia. The hormonal characteristics of the men in each treatment group were indistinguishable both before and at the end of treatment. It appears that addition of antagonist to high-dose T administration using this paradigm did not enhance the effectiveness of the regimen. However, studies in humans and in monkeys in which different doses of antagonist and T were tested have shown that a combination regimen can be highly effective. Additional studies which systematically address the questions of drug dose the timing of T replacement and duration of drug exposure will help determine whether combination regimens containing GnRH antagonist and T have potential for use in large numbers of men.

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