A Multicenter Phase IIb Study of a Novel Combination of Intramuscular Androgen (Testosterone Decanoate) and Oral Progestogen (Etonogestrel) for Male Hormonal Contraception

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The effect of a novel combination of oral etonogestrel (ENG) and intramuscular testosterone decanoate (TD) on suppression of gonadotropins and spermatogenesis as a potential lead for male contraception was investigated. Healthy male volunteers were randomized into two groups receiving 300 μg ENG daily and 400 mg TD every 4 (n = 55) or 6 (n = 57) wk for 48 wk. At wk 48, all men except one in the 6-wk group suppressed sperm concentration to less than 1 million/ml. Faster suppression occurred in the 4-wk group. Gonadotropins were suppressed to normal levels in both groups. After treatment cessation, recovery of sperm counts and gonadotropins to normal levels occurred in both groups. Minor effects on weight and cholesterol were noted. Fourteen subjects withdrew because of an adverse event with those possibly related to the study medication reported more frequently in the 6-wk group (nine vs. one). In conclusion, the combination of 300 μg ENG with 400 mg TD every 4 wk was superior to any contraceptive (J Clin Endocrinol Metab 90: 2042–2049, 2005)

The study of male hormonal contraception has been making gradual progress over the last three decades. Suppression of gonadotropins by various pharmacological means, i.e. androgen alone (1, 2), progestogen-androgen combinations (3–6), and GnRH antagonist in combination with testosterone enanthate (7), has been shown to be both effective and reversible in suppressing spermatogenesis in healthy young men.

With most regimens using androgens alone, suppression to azoospermia occurred in 40–70% of Caucasian men, although higher efficacy has been achieved in Chinese subjects (8). The nonuniform suppression of spermatogenesis with androgen alone suggested this approach may not be optimal for Caucasian men.

Progestogen-androgen combinations have been studied with better results. Many progestogens have now been combined with androgen, including medroxyprogesterone acetate (MPA) (6), levonorgestrel (LNG) (4, 9), cyproterone acetate (5, 10), desogestrel (DSG) (11–13), and norethisterone enanthate or acetate (3, 14, 15). The additive/synergistic effect between progestogens and androgens in these combinations is important both in increasing effectiveness and allowing lower androgen doses to be used. A limitation of progestogen-androgen trials to date has been the small numbers of men studied.

Etonogestrel (ENG) is the product of DSG metabolism after oral administration via 3α-hydroxy and 3β-hydroxydesogestrel in liver microsomes (16). DSG is a potent and highly selective synthetic progestogen (17). Both DSG and ENG have been used safely and effectively in female contraceptives (e.g. Marvelon and Implanon) for some years. The application of DSG/testosterone (T) combinations in men as hormonal contraception has been studied by three groups (11–13). A 300-μg oral dose of DSG was found to be most effective in sperm suppression without significant side effects. A pharmacokinetic study in females found the optimal oral dose of ENG to be equal to DSG (18). Experience with
ENG in men has been in the study of ENG rods in combination with androgen (19, 20).

Testosterone decanoate (TD) is the major component of Sustanon 250, which has been used safely in the treatment of male hypogonadism for over 40 yr. A preliminary dosage-finding study in eight hypogonadal men using 400 mg TD found that the T concentration was restored into the physiological range for 4–6 wk (NV Organon, unpublished). An additional study in healthy men involving repeated administration confirmed that this was an appropriate dosage and interval (20). This prolonged duration of action compared with T enanthate (TE, weekly injection required) allows for less frequent injections. Supraphysiological T excursions that are well documented with TE may be minimized, therefore reducing potentially adverse androgenic effects.

The study hypothesis is that 300 µg oral ENG daily in combination with injectable 400 mg TD every 4 or 6 wk will be effective in suppression of gonadotropins and sperm concentration to less than 1 million/ml (M/ml). The aims of the study are to investigate this androgen-progestogen combination as a potential future male hormonal contraceptive and make a preliminary assessment of safety in men.

**Subjects and Methods**

**Subjects**

One hundred twelve healthy male volunteers were recruited from six centers (19 Helsinki, 31 Turku, 22 Münster, 20 Edinburgh, 20 Manchester, and 18 Brussels). The inclusion criteria included age at least 18 yr and no more than 45 yr; normal mental and physical health; body mass index (BMI) from 18–30 kg/m²; normal semen analysis on two occasions at least 2 wk apart [examination within 60 min, based on World Health Organization (WHO) criteria for sperm density and WHO criteria or local reference ranges for sperm motility and morphology (21)]; normal hormone (FSH, LH, and T) levels based on local reference ranges; and willingness to provide written informed consent. Men in a heterosexual relationship at study inclusion had to be willing to use a reliable form of contraception. The exclusion criteria included use of investigational drugs within six months before screening and any use of lipid-lowering drugs or prolonged use of hepatic microsomal enzyme-inducing anti-convulsant medication or other drugs known to interfere with the pharmacokinetics of steroids.

**Study design**

This was a phase IIb, open-label, randomized multicenter trial. The six participating centers obtained approval from the relevant local research ethics committees. After initial screening, subjects were randomized into two treatment groups receiving 1) 300 µg oral ENG daily and 400 mg TD every 4 wk (4-wk group) or 2) 300 µg oral ENG daily and 400 mg TD every 6 wk (6-wk group). Subjects were randomized centrally into the two treatment groups via an interactive voice response system. This was based on a minimization method that should result in a difference of fewer than three subjects between the two treatment groups. No stratification was applied.

Treatment phase duration was 48 wk and was followed by a 24-wk recovery phase. The primary endpoint was suppression of sperm to less than 1 M/ml, and the secondary endpoint was gonadotropin suppression. Physical examination and monitoring of routine hematological/biochemical analyses were made at wk 8, 24, 36, and 48 during the treatment phase and wk 4 and 24 of the recovery phase in both groups. All subjects provided written informed consent at entry to the study. The local institutional review boards reviewed and approved the study protocol and consent forms at each center. The subjects were required to use reliable, additional contraception at study commencement.

**Medications**

The daily dose of ENG for all subjects was 300 µg, administered as two 150-µg tablets. NV Organon supplied both ENG (150-µg) tablets and TD (400 mg in 2 ml of castor oil). Diary cards were supplied to be completed daily by the subject. The investigator cross-checked and collected the diary cards and blister packs at each visit to evaluate compliance during the study. Each visit corresponded with a blood test and/or semen analysis and/or TD injection. Compliance was calculated as the actual number of tablets taken or injections received, divided by the total number of tablets or injections scheduled. In subjects who discontinued the trial, the total number of tablets and injections scheduled would be calculated to the day before the discontinuation date. TD was administered as a single deep im injection every 4 or 6 wk.

**Clinical monitoring**

Subjects provided regular blood and semen samples, and any adverse events or concomitant medications were recorded. Physical examination included general assessment, weight, blood pressure, testicular size, and prostate assessment. Testicular size was assessed by orchidometer. Prostate assessment was by digital rectal examination and, where possible, transrectal ultrasonography to assess total prostate volume. Both were performed after blood sampling for prostate-specific antigen (PSA). Sexual function was assessed by the Derogatis questionnaire (22). Questions concerning tolerability of the TD injections were completed. The questions were in relation to any swelling, redness, induration, or tenderness occurring after the injection. All these assessments were made at screening and treatment wk 8, 24, 36, and 48 and recovery wk 4 and 24. A brief satisfaction questionnaire was completed at the end of the recovery phase.

**Semen analysis**

Semen collection and analysis of semen volume, sperm density, motility, and morphology were carried out according to the WHO Laboratory Manual for the Examination of Human Semen Sperm-Cervical Mucus Interaction (21). Where reference ranges for motility and morphology had been established locally in a fertile male population, these were used if different from WHO criteria. Two normal semen samples were required during the screening period. Throughout the treatment and recovery phases, semen samples were provided every 4–6 wk. Azoospermia was verified by centrifugation (15 min at 3000 × g) of the entire semen sample. The resulting pellet was then thoroughly examined to exclude the presence of any sperm. Subjects completed follow-up when at least one sperm concentration had reached more than 20 M/ml.

**Blood tests**

During the screening phase, routine hematology (hemoglobin, hematocrit, white cell count, and platelets), biochemistry [renal and liver function; albumin; total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C); triglycerides; glucose; and glycosylated hemoglobin], PSA, and hormone analyses were carried out. The routine hematological, biochemical, and PSA measurements were arranged locally by each participating center throughout the duration of the trial. Hormone assays were undertaken at a central laboratory and included FSH, LH, total and bioavailable T (T and bio-T), 5α-dihydrotestosterone (DHT), estradiol (E2), and SHBG. During the treatment phase, samples for hormone assay were taken at wk 1, 2, 4, 8, 16, 17, 18, 20, 24, 36, and 48 in the 4-wk group (trough samples at wk 4, 8, 16, 20, 24, 36, and 48 and peak samples at wk 1, 2, 4, 6, 8, 12, 18, 19, 20, 24, 36, and 48 in the 6-wk group (trough samples at wk 6, 12, 18, 24, 36, and 48 and peak samples at wk 1, 2, 4, 6, 8, 12, 18, 19, 20, 24, 36, and 48 in the respective groups. Blood sampling was to occur before ingestion of ENG or administration of injectable TD where possible. Fasting samples were taken when the lipid profiles and glucose were measured at screening and wk 8, 24, 36, and 48 of the treatment phase.

During the recovery phase, fasting samples were taken for all parameters except ENG at wk 4 and 24 in both groups.
Hormone assays

All serum samples were stored at -20°C at the individual centers. Samples were shipped on dry ice to a central laboratory of Organon for assay. Serum gonadotropins, E2, and SHBG were determined by the Delfia fluoroimmunoassay (Delfia, PerkinElmer Wallac, Turku, Finland). Assay sensitivities were 0.25 U/liter, 0.52 U/liter, and 49.93 pmol/liter, and intra- and interassay coefficients of variation were 1.9–7.6, 2.6–4.9, and 17.3–34.1% for FSH, LH, and E2, respectively. The lower limit of quantification for SHBG was 6.25 nmol/liter with intra- and interassay coefficients of variation of 3.2–5.0%. T and DHT were determined by capillary gas chromatography-mass spectrophotometry. The assay sensitivities were 0.35 nmol/liter for T and 0.34 nmol/liter for DHT with intra- and interassay coefficients of variation of 4.5–21.9 and 8.3–11.7%, respectively. Bio-T was determined after precipitation of the SHBG-bound T fraction by ammonium sulfate, and therefore no lower limit of detectability is available. The intra- and interassay coefficients of variation for bio-T were 2.3–7.7%. ENG was measured by in-house RIA (NV Organon), and the lower limit of quantification was 30.0 pg/ml.

Statistical analysis

NV Organon performed all statistical analyses using the statistical package SAS version 8.2. The intention-to-treat analysis is presented. Frequencies of subjects with suppression of sperm concentration to a specified level and a certain time point were compared by means of a Fisher exact test. A cube root scale for sperm concentration is used (Fig. 1). The faster suppression in the 4-wk compared with the 6-wk group was also reflected in the Kaplan Meier curves (P = 0.019; Fig. 2). The median time to attain the sperm density suppression target of less than 1 M/ml was approximately 8 wk in the 4-wk and 12 wk in the 6-wk group.

Three subjects only demonstrated sperm concentration less than 1 M/ml at wk 48 (33 of 53) of men in the 4-wk group were suppressed to less than 1 M/ml compared with 33.3% (18 of 54) in the 6-wk group (P = 0.004). At treatment wk 16, sperm concentrations in all except three men in the 4-wk group (94.3%, 50 of 53) were suppressed to less than 1 M/ml compared with 83.0% (39 of 47) in the 6-wk group (P = 0.108). The percentage of men responding continued to increase to 98.0% (49 of 50) and 87.5% (42 of 48) at wk 24 (P = 0.057), and at the end of treatment (48 wk), all men were less than 1 M/ml, except one in the 6-wk group who had a sperm concentration of 1.3 M/ml. The pattern of suppression to azoospermia followed a very similar pattern (Table 1). Seventy percent (35 of 50) and 54.2% (26 of 48) of subjects at treatment wk 24, and 95.3% (41 of 43) and 82.5% (33 of 40) at wk 48 achieved azoospermia in the 4- and 6-wk groups, respectively.

The faster suppression in the 4-wk compared with the 6-wk group was also reflected in the Kaplan Meier curves (P = 0.019; Fig. 2). The median time to attain the sperm density suppression target of less than 1 M/ml was approximately 8 wk in the 4-wk and 12 wk in the 6-wk group.

Three subjects only demonstrated sperm concentration rebound to more than 1 M/ml after wk 24 of treatment. Two subjects saw minor increases to 1.5 M/ml (wk 42, returned to <1 M/ml again at wk 48) and 1.3 M/ml (wk 48). One subject who had achieved less than 1 M/ml at wk 20 subsequendy rebounded to 2.1 and 4.6 M/ml at wk 24 and 28. The likely cause for rebound in this case was noncompliance. Six consecutive doses (300 μg daily) had been missed between wk 20 and 23 of the treatment period. Suppression to less than 1 M/ml was again achieved by wk 32.

After cessation of treatment, sperm densities recovered to normal levels in all men (Figs. 1 and 3). The median time to completed 48 wk of treatment (46 and 43 in the respective groups).

Compliance

Subjects in both groups were highly compliant with treatment. The percentage compliance with tablet ingestion and injection was 98–100% in both groups.

Sperm concentration

Mean sperm densities suppressed rapidly into the oligozoospermic range in both groups (Fig. 1 and Table 1). The extent and rate of fall in sperm density were greater in the group receiving 300 μg of ENG with 4 weekly injections of TD. Thus, at treatment wk 8, 62.3% (33 of 53) of men in the 4-wk group were suppressed to less than 1 M/ml compared with 33.3% (18 of 54) in the 6-wk group (P = 0.004). At treatment wk 16, sperm concentrations in all except three men in the 4-wk group (94.3%, 50 of 53) were suppressed to less than 1 M/ml compared with 83.0% (39 of 47) in the 6-wk group (P = 0.108). The percentage of men responding continued to increase to 98.0% (49 of 50) and 87.5% (42 of 48) at wk 24 (P = 0.057), and at the end of treatment (48 wk), all men were less than 1 M/ml, except one in the 6-wk group who had a sperm concentration of 1.3 M/ml. The pattern of suppression to azoospermia followed a very similar pattern (Table 1). Seventy percent (35 of 50) and 54.2% (26 of 48) of subjects at treatment wk 24, and 95.3% (41 of 43) and 82.5% (33 of 40) at wk 48 achieved azoospermia in the 4- and 6-wk groups, respectively.

FIG. 1. Sperm density (cube root scale) during the screening (wk -4 and 0), treatment (wk 4–48), and recovery (wk 4–24) phases in two groups of healthy men receiving 300 μg oral ENG daily in combination with im TD 400 mg at 4- or 6-weekly intervals.

TABLE 1. Percentage of subjects suppressed to several sperm density targets who received oral ENG 300 μg daily in combination with im TD 400 mg at 4- or 6-weekly intervals.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Duration of treatment</th>
<th>n</th>
<th>% of subjects reaching the suppression targets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 M/ml</td>
</tr>
<tr>
<td>4-wk</td>
<td>wk 8</td>
<td>53</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td>wk 16</td>
<td>53</td>
<td>50.9</td>
</tr>
<tr>
<td></td>
<td>wk 24</td>
<td>50</td>
<td>70.0</td>
</tr>
<tr>
<td></td>
<td>wk 48</td>
<td>43</td>
<td>95.3</td>
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<tr>
<td>6-wk</td>
<td>wk 8</td>
<td>54</td>
<td>9.3</td>
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<tr>
<td></td>
<td>wk 16</td>
<td>47</td>
<td>44.7</td>
</tr>
<tr>
<td></td>
<td>wk 24</td>
<td>48</td>
<td>54.2</td>
</tr>
<tr>
<td></td>
<td>wk 48</td>
<td>40</td>
<td>82.5</td>
</tr>
</tbody>
</table>

Results

Among the 112 men recruited into the study, 55 were randomized to the 4-wk group and 57 to the 6-wk group. The age (mean ± SEM) of subjects was 30.2 ± 0.85 and 31.8 ± 0.82 yr in the 4- and 6-wk groups, respectively. In total, 99 (88%) men completed 24 wk of treatment, and 89 (79%) men com-
recovery (>20 M/ml) was 16 wk in both groups. Overall, a faster rate of recovery was evident in the 6-wk compared with the 4-wk group (P = 0.009; Fig. 3). Eighty-six men recovered normal sperm density within 24 wk and 22 men beyond 24 wk after the end of treatment.

**LH and FSH**

Both dose regimens were highly effective in suppressing circulating LH and FSH into the hypogonadotropic range (<1 IU/liter; Fig. 4). In the 4-wk group, mean LH and FSH levels declined to the lower assay detection limit after 4–8 wk of treatment; this was maintained until the end of the treatment period. In the 6-wk group, mean LH levels were less consistently suppressed during the first 24 wk of treatment but subsequently reached the lower detection limit in the second 24 wk of treatment. FSH was not totally suppressed in all men of the 6-wk group with mean levels remaining slightly above the lower limit of assay detection (Fig. 4).

After cessation of treatment, there was rapid recovery of LH and FSH in both groups. The 6-wk group showed a faster rate of recovery as indicated by LH levels (IU/liter, mean ± SEM) at wk 4 of the recovery phase: 1.24 ± 0.15 and 2.92 ± 0.23 in the 4- and 6-wk groups, respectively (P < 0.0001). This was also the case for FSH: 1.82 ± 0.22 and 3.69 ± 0.25 in the 4- and 6-wk groups, respectively (P < 0.0001). At wk 24 of recovery, LH and FSH were back to baseline levels in both treatment groups.

**Other hormones**

Mean T concentrations declined to below the normal range in both treatment groups at 4 or 6 wk after the first TD injection (Fig. 5). The trough T levels (nmol/liter, mean ± SEM), immediately before the second TD injection, were 7.4 ± 0.38 in the 4-wk group and 5.3 ± 0.32 in the 6-wk group. Subsequently, trough T concentrations gradually increased in both groups with the 4-wk group rising to the normal range after the third injection (wk 8), but trough T levels in
the 6-wk group remained just below the normal range for the entire treatment period. Peak T concentrations were assessed after the first and fifth (4-wk group) or fourth (6-wk group) TD injection and were within the normal range in both treatment groups. SHBG decreased by approximately 35–40% in both treatment groups (Table 2). Bio-T, DHT, and E2 showed a comparable pattern to total T (Fig. 5). All hormones returned to the normal range (group means and individual values) after cessation of treatment.

ENG concentrations were highly variable throughout the treatment phase. Mean ENG concentrations (pg/ml, mean ± SEM) were the highest at wk 0, with values of 3.06 (1.36) in the 4-wk group and 3.02 (1.31) in the 6-wk group. However, during the treatment phase (wk 4–48), ENG concentrations were highly variable, with values ranging from 0.35 (0.22) to 10.38 (1.12) in the 4-wk group and from 0.34 (0.21) to 10.29 (1.11) in the 6-wk group. ENG concentrations were similar in both treatment groups during the recovery phase (wk 4 and 24).

**TABLE 2.** Clinical and biochemical parameters at wk 0 and 48 of the treatment phase and at the last assessment of the recovery phase

<table>
<thead>
<tr>
<th>Parameter</th>
<th>4-wk group</th>
<th>6-wk group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>wk 0</td>
<td>wk 48</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>Last assessment</td>
</tr>
<tr>
<td>n</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>Left testicular volume (ml)</td>
<td>23.56 (0.78)</td>
<td>16.45 (0.70)*</td>
</tr>
<tr>
<td>Right testicular volume (ml)</td>
<td>23.86 (0.86)</td>
<td>17.02 (0.81)*</td>
</tr>
<tr>
<td>Prostate volume (ml)</td>
<td>17.58 (0.86)</td>
<td>18.14 (1.04)</td>
</tr>
<tr>
<td>PSA (µg/liter)</td>
<td>0.79 (0.05)</td>
<td>0.84 (0.05)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.40 (1.26)</td>
<td>82.73 (1.72)</td>
</tr>
<tr>
<td>SHBG (nmol/liter)</td>
<td>37.2 (1.94)</td>
<td>24.4 (1.69)*</td>
</tr>
<tr>
<td>Hb (g/liter)</td>
<td>152.1 (0.85)</td>
<td>157.8 (1.39)</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.45 (0.003)</td>
<td>0.46 (0.004)</td>
</tr>
<tr>
<td>TC (mmol/liter)</td>
<td>5.07 (0.14)</td>
<td>4.64 (0.14)</td>
</tr>
<tr>
<td>HDL-C (mmol/liter)</td>
<td>1.41 (0.04)</td>
<td>1.10 (0.03)</td>
</tr>
<tr>
<td>LDL-C (mmol/liter)</td>
<td>3.15 (0.13)</td>
<td>3.84 (0.85)</td>
</tr>
<tr>
<td>Triglyceride (mmol/liter)</td>
<td>1.10 (0.06)</td>
<td>1.14 (0.10)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>4.93 (0.07)</td>
<td>5.05 (0.07)</td>
</tr>
<tr>
<td>Glucose fasting (mmol/liter)</td>
<td>4.82 (0.06)</td>
<td>4.99 (0.10)</td>
</tr>
<tr>
<td>ALAT (U/liter)</td>
<td>25.5 (2.09)</td>
<td>27.0 (2.15)</td>
</tr>
<tr>
<td>ASAT (U/liter)</td>
<td>24.8 (1.50)</td>
<td>21.6 (0.98)</td>
</tr>
<tr>
<td>ALP (U/liter)</td>
<td>121.5 (9.07)</td>
<td>107.8 (9.05)</td>
</tr>
<tr>
<td>γ-GT (U/liter)</td>
<td>20.7 (1.44)</td>
<td>23.5 (1.89)</td>
</tr>
<tr>
<td>Bilirubin (µmol/liter)</td>
<td>12.98 (0.87)</td>
<td>15.26 (1.07)</td>
</tr>
<tr>
<td>LDH (U/liter)</td>
<td>331.4 (14.0)</td>
<td>335.4 (14.8)</td>
</tr>
</tbody>
</table>

All values shown represent the mean (SEM). Testicular volumes were assessed by orchidometer. Prostate volume was via ultrasonography and was not measured at all centres (n = 23–31). Last assessment could be at wk 16, 20, and 24 of the recovery phase. Hb, Hemoglobin; HbA1c, glycated hemoglobin; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; ALP, alkaline phosphatase; γ-GT, γ-glutaryl transferase; LDH, lactate dehydrogenase.

*Significant difference to baseline value with P < 0.0001. There were no significant differences (P < 0.0001) between the treatment groups in any parameter.
at wk 24 were 1329 ± 203.7 and 1590 ± 164.6 and at wk 48 were 676 ± 176.0 and 1071 ± 254.1 in the 4- and 6-wk group, respectively. It is likely that many samples were not taken before tablet ingestion as instructed, and consequently these were not trough levels. Mean trough levels could be estimated from these data and were approximately 500 pg/ml.

Physical

Testicular volumes, measured clinically by orchidometry, decreased to a comparable extent (~30%) in both treatment groups and recovered to baseline values after cessation of treatment (Table 2).

Prostate volumes were measured in 29 and 31 men in the 4- and 6-wk groups, respectively, with variation during treatment around the baseline values without any significant change in either group (Table 2).

Weight gain was observed in both treatment groups but was more pronounced in the 4-wk group with a mean increase body weight of 5% compared with 2% in the 6-wk group at the end of the treatment period (see also Table 2). At the last assessment of the recovery phase, the mean weight had returned to near baseline values.

Over 48 wk of treatment, acne or worsening of acne was reported in 16 (29.1%) and eight (14.0%) subjects in the 4- and 6-wk group, respectively. One subject in the 6-wk group reported gynecomastia.

Hematology, biochemistry, and lipids

The laboratory results for the two treatment groups are presented in Table 2. Mean hemoglobin increased in the 4-wk group from 152.1 g/liter at baseline to 157.8 g/liter at wk 48 (P = 0.0005) and from 150.5 to 153.5 g/liter between baseline and wk 48 in the 6-wk group (P = 0.05). No significant changes were seen in mean hematocrit values. TC and HDL-C decreased by 10% (P < 0.0001) in both groups and 22 and 17% (P < 0.0001) in the 4- and 6-wk groups, respectively. These values had returned to baseline levels at the end of the recovery phase (Table 2). No significant change occurred in either LDL-C or triglycerides. A reduction in alkaline phosphatase within the normal range was observed in both groups. There were no clinically significant changes in liver transaminases, bilirubin, PSA, or glycosylated hemoglobin (Table 2).

Discontinuations and side effects

A total of 23 subjects (21%) withdrew from the study, nine in the 4-wk group and 14 in the 6-wk group. The reasons for withdrawal were occurrence of an adverse event (14 subjects), personal (eight subjects), and failure to achieve azoospermia at wk 24 (one subject). More men withdrew from the study because an adverse event in the 6-wk group compared with the 4-wk group: 10 vs. four. Moreover, adverse events in the 6-wk group were more likely to be related to the study medication, e.g. depression (3), emotional lability (2), nervousness (1), gynecomastia (1), increased sweating (1), and decreased libido (1), whereas in the 4-wk group, one subject discontinued because of nervousness. Other adverse events that were considered unlikely to be related to the trial medication but led to discontinuation were atrial fibrillation (1), constipation (1), umbilical hernia (1) (all in the 4-wk group) and accidental injury (1) (in the 6-wk group).

Among possible side effects that did not lead to discontinuation, acne, increased sweating, mood changes, and libido changes were most frequently reported.

Questionnaires

The Derogatis questionnaire on sexual function did not show any changes in mean subscores and total scores throughout treatment, nor were there any differences between the treatment groups (data not shown).

At the last assessment, all subjects (including dropouts) were asked whether they were satisfied with the treatment, and 77% in the 4-wk and 60% in the 6-wk group answered yes. Similarly, 85 and 72% would recommend it to others, and 77 and 50% in the two respective treatment groups would definitely or probably use it if it were on the market. The injections were well tolerated.

Discussion

This is the first study in men using oral ENG in combination with injectable TD. Oral ENG 300 μg daily in combination with 400 mg TD every 4 wk results in efficient, safe, and reversible spermatogenesis suppression. Unlike most previous progestogen-androgen combination studies we have included group sizes exceeding 15 men per treatment group and continued treatment beyond 24 wk. In the 4-wk group, severe oligozoospermia of less than 1 M/ml (the primary end point) was achieved in 98 and 100% and azoospermia in 70 and 95.3% after 24 and 48 wk of treatment, respectively. These results are comparable with previous smaller studies of oral DSG and T combinations with 67–100% of subjects achieving the target of less than 1 M/ml and 57–100% azoospermia (11–13). These results are also comparable to other progestin-testosterone combinations, e.g. depot MPA plus T implant (23) and norethisterone enanthate plus T undecanoate (14, 15). Furthermore, the present results support that spermatogenesis suppression can be maintained in the majority of subjects for up to 48 wk without escape above 1 M/ml by this oral/injectable combination. The degree and maintenance of sperm suppression attests to the overall high level of compliance with this regimen.

Previous studies have demonstrated that suppression to severe oligozoospermia (<1 M/ml) provides high contraceptive efficacy (1, 2, 8, 23). The WHO studies on 670 men showed that contraceptive failure rate was proportional to residual sperm output (1, 2). The reported pregnancy rates were 0.8 per 100 person-years [95% confidence interval (CI), 0.02–4.5] for azoospermia and 8.1 per 100 person-years (95% CI, 2.2–20.7) for oligozoospermia (<3 M/ml). A combined pregnancy rate of 1.4 per 100 person-years (95% CI, 0.4–3.7) for sperm density 0–3 M/ml is comparable to the failure rate for female oral contraceptives. In a recent efficacy study in Chinese men using testosterone undecanoate alone (8), no pregnancies resulted during the efficacy phase of the study in men suppressed to 3 M/ml. Sperm rebound occurred in six men, and one pregnancy occurred. These studies pro-
vided the evidence for the consensus that less than 1 M/ml is an appropriate target for suppression of spermatogenesis (24). The first efficacy study using a progestogen-androgen regimen recently reported no pregnancies in 426 person-months of treatment (23) using less than 1 M/ml as entry criterion for the efficacy phase. The degree of spermatogenic suppression found in the present study is therefore likely to confer a similar degree of contraceptive efficacy.

There was a clear difference in the rate of suppression between the groups (Figs. 1 and 2), highlighting the importance of the androgen component of any progestogen-androgen combination. This is because of the less consistent suppression of LH and FSH in the 6-wk compared with the 4-wk group. LH and FSH were above the assay lower detection limit in all subjects who failed to suppress to less than 3 M/ml at wk 24. The degree of gonadotropin suppression has been shown to relate to residual sperm production in several previous studies of male hormonal contraception (25). Therefore, in the first 24 wk of treatment the lower percentage of men reaching the sperm suppression targets in the 6-wk group was most likely a consequence of inadequate gonadotropin suppression (Fig. 4).

With continued treatment, the difference in percentage responding between the groups narrowed, such that by wk 48 there was no longer any difference in achieving the target of less than 1 M/ml. The continued suppression beyond 24 wk is an important new finding because most previous studies did not extend treatment after this time. Although 400 mg TD every 6 wk was clearly suboptimal, the progressive suppression occurring after 24 wk could potentially be explained by the increasing trough T levels toward the normal range. This would support the necessity for an adequate androgen dose in any progestogen-androgen regimen. Another possible explanation for the continued spermatogenic suppression could be a gonadotropin-independent action of progesterin on the testis.

The median time to recovery of 16 wk in the present study is comparable to previous studies (range 16–20 wk) (1, 8, 23). Recovery was faster in the 6-wk compared with the 4-wk group. The difference in the rate of spermatogenesis recovery was reflected in the rise in gonadotropin after treatment cessation. The faster recovery rate seen in the 6-wk group may indicate that the rate of recovery is related to the duration and degree of spermatogenesis suppression during treatment. Furthermore, the shorter injection interval in the 4-wk group (last injection wk 44 vs. wk 42 in the 4- and 6-wk groups) would potentially result in a continued suppressive effect from exogenous T in the initial weeks of the recovery phase (starting at wk 48). In Fig. 1, mean sperm densities at the end of the recovery phase appear lower than at baseline. At and beyond wk 16 recovery, subjects who had achieved a sperm concentration of at least 20 M/ml completed the trial. Because they did not provide any additional semen samples, this results in artificially low mean sperm densities after wk 16 because all recovered men with normal sperm concentration are no longer represented.

In this study, LH and FSH recovered to the normal range by wk 24 in the recovery phase in all subjects. However, in 20% of men, recovery of spermatogenesis occurred after wk 24 recovery phase. In this group, all except three subjects were recovered before or by wk 52 recovery. The final three subjects subsequently recovered at wk 56, 69 (no assessment after wk 46 until then), and 124 (subject had relatively low baseline counts). These findings of apparent late recovery may not be different from previous studies because there is often incomplete data collection with increased duration of the recovery phase, and those slow to recover are more likely to be lost to follow-up. Although it is not possible to say that slow recovery is specific to the present treatment or to any other hormonal treatment, the possibility of direct action on the testis needs to be considered because gonadotropins had normalized. Plasma membrane progesterone receptors are detectable in the testis (26, 27), and various progestins can compete for androgen receptor binding with T (28), down-regulate Leydig cell LH receptors (29), and inhibit Leydig cell steroidogenic enzyme (30) and 5α-reductase activity (31). More research on progestins in men is needed.

The ENG-TD regimen resulted in decreases in both TC and HDL-C. The changes observed were similar to those reported in previous studies of DSG-TE (11, 12). TC and HDL-C decreased by 10 and 17–22%, respectively, compared with the 9–11 and 20–23% reported in the DSG studies (11–13). There was no difference in any lipid parameter between the groups. The changes in TC and HDL-C were apparent at wk 8 (data not shown) and returned to baseline during the recovery phase. T alone has been reported to lower HDL-C in healthy men receiving 200 mg TE by 13–18% with no observed change in TC, LDL-C, or triglycerides (2, 32, 33). The effect of different progestogen/androgen combinations in male hormonal contraception has been variable because of the compounds and doses used. Although studies of DSG and LNG have consistently found lowering of both TC and HDL-C (9, 11, 12), the recent efficacy study using depot MPA (23) found no significant lipid changes. The clinical significance of TC and HDL-C changes (within the normal range) in response to exogenous sex steroids in terms of cardiovascular risk is unknown (34).

Weight gain proportional to increasing DSG dose (150 or 300 μg DSG plus 100 mg TE) has previously been demonstrated (11, 12). Here, we found a small difference in weight gain between the 4- and 6-wk TD groups (+5 and +2% in the 4- and 6-wk group, respectively; not significant). However, whether the weight gain represents lean or fat mass increase or both is currently unclear. LNG alone had no effect on lean mass and increased abdominal fat mass, but LNG and TE increased total and regional lean body mass but had no effect on abdominal fat mass (35). The effect of LNG upon fat mass appeared to be opposite to that of T. Further study of body composition in hormonal male contraception is currently in progress.

Mood-related events leading to discontinuation appeared to be more prevalent in the 6-wk group. This may indicate that 400 mg TD at 6-weekly intervals is an inadequate dose; the trough T levels in this group corroborate this. A study currently underway is including a placebo group to allow further objective assessment of adverse events associated with an ENG-T combination.

In conclusion, the novel combination of oral ENG and im TD suppressed gonadotropin and spermatogenesis with high efficacy over a 1-yr treatment period. A dose of 300 μg
ENG combined with 400 mg TD every 4 wk is superior to 300 µg ENG combined with 400 mg every 6 wk in terms of efficacy, hormone profiles, and safety. This represents a promising approach to male hormonal contraception.

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