# Effects of Simvastatin and Pravastatin on Gonadal Function in Male Hypercholesterolemic Patients

Adrian S. Dobs, Sam Miller, Gilberto Neri, Stuart Weiss, Ann C. Tate, Deborah R. Shapiro, and Thomas A. Musliner for the Simvastatin-Pravastatin Male Gonadal Function Study Group

**Inhibition of cholesterol biosynthesis by hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors could, in theory, adversely affect male gonadal function because cholesterol is a precursor of steroid hormones. The objective of this randomized double-blind trial was to compare the effects of simvastatin, pravastatin, and placebo on gonadal testosterone production and spermatogenesis. After a 6-week placebo and lipid-lowering diet run-in period, 159 male patients aged 21 to 55 years with type IIa or IIb hypercholesterolemia, low-density lipoprotein (LDL) cholesterol between 145 and 240 mg/dL, and normal basal levels of testosterone were randomly assigned to treatment with simvastatin 20 mg (n = 40), simvastatin 40 mg (n = 41), pravastatin 40 mg (n = 39), or placebo (n = 39) once daily. After 24 weeks of treatment, mean total cholesterol levels were decreased 24% to 27% and mean LDL cholesterol was decreased 30% to 34% in the 3 active-treatment groups ($P < .001$ for all comparisons to placebo). At 24 weeks, there were no statistically significant differences between the placebo group and any of the active-treatment groups for the change from baseline in testosterone, human chorionic gonadotropin (hCG)-stimulated testosterone, free testosterone index, follicle-stimulating hormone (FSH), luteinizing hormone (LH), or sex hormone–binding globulin (SHBG). Moreover, there were no statistically significant differences at week 12 or week 24 for the change from baseline in sperm concentration, ejaculate volume, or sperm motility for any active treatment relative to placebo. Both simvastatin and pravastatin were well tolerated. In summary, we found no evidence for clinically meaningful effects of simvastatin or pravastatin on gonadal testosterone production, testosterone reserve, or multiple parameters of semen quality.**


THE HYDROXYMETHYL GLUTARYL coenzyme A (HMG-CoA) reductase inhibitors are known to produce substantial reductions in total and low-density lipoprotein (LDL) cholesterol levels at doses commonly used to treat patients with hypercholesterolemia.[1-3] The benefits of long-term simvastatin treatment of hypercholesterolemic patients with preexisting coronary heart disease include improved survival and decreased incidence of both fatal and nonfatal major coronary heart disease events.[1] Similarly, pravastatin treatment has been shown to reduce the incidence of myocardial infarction and cardiovascular death among moderately hypercholesterolemic men without a history of prior myocardial infarction.[2]

Cholesterol is a precursor in the biosynthesis of steroid hormones. In theory, inhibition of cholesterol biosynthesis by HMG-CoA reductase inhibitors could have a potentially negative effect on male gonadal function, operating by one or more of several mechanisms: reduced plasma LDL cholesterol (an extracellular source of cholesterol for gonadal steroidogenesis), direct inhibition of cholesterol synthesis in testicular cells, inhibition of other enzymes involved in androgen biosynthesis, or alteration of the pathway for the synthesis of dolichol, which is required for the glycosylation of gonadotropins.[4] Altered function of gonadotropins could, in turn, result in impaired spermatogenesis.[5]

Many studies have examined the effect of HMG-CoA reductase inhibitors on steroidogenesis, and the preponderance of available data indicate that simvastatin, pravastatin, and lovastatin do not produce biologically or clinically significant adverse effects on adrenal or gonadal steroidogenesis or spermatogenesis.[6-13] However, some questions remain because variable small effects on testicular steroidogenesis and spermatogenesis have been reported[14-16] in addition to isolated instances of hypospermia.[17] The interpretation of the findings is hampered by the fact that most of these studies enrolled a small number of patients and were not placebo-controlled. Furthermore, both testosterone production and spermatogenesis show seasonal variation and are influenced by multiple environmental factors.[18-20]

The present study was designed to examine the effects of HMG-CoA reductase inhibitors on gonadal function in eugonadal male hypercholesterolemic patients in a multicenter setting, enrolling a larger number of patients compared with earlier studies and using a placebo control. Our objectives were to compare the effects of simvastatin, pravastatin, and placebo on gonadal testosterone production and spermatogenesis. We chose to compare these 2 agents to assess whether there might be a difference in the effect of an inactive lactone prodrug (simvastatin) compared with an active, open-acid form (pravastatin). We selected dosages at the upper end of the dosage range approved for use at the time this study was performed (40 mg for both simvastatin and pravastatin); in addition, we studied simvastatin 20 mg because this dose is approximately equivalent in lipid-lowering efficacy to pravastatin 40 mg.[3] Our primary hypothesis was that simvastatin and pravastatin, as compared with placebo, do not significantly affect basal testosterone, human chorionic gonadotropin (hCG)-stimulated increases in testosterone, or the sperm concentration.

*From the Johns Hopkins University School of Medicine, Baltimore, MD; Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL; The San Diego Endocrine and Medical Center, San Diego, CA; and Clinical Research, Merck Research Laboratories, Rahway, NJ.*

*Submitted March 18, 1999; accepted June 28, 1999.*

*Supported in part by the Johns Hopkins University School of Medicine (RR00678) and a grant from Merck Research Laboratories.*

*Address reprint requests to Adrian S. Dobs, MD, Johns Hopkins University, Department of Medicine, Blalock 906, 600 N Wolfe St, Baltimore, MD 21287-4904.*



*0026-0495/00/4901-0004$10.00/0*

## SUBJECTS AND METHODS

### *Patients*

The patients were men aged 21 to 55 years with type IIa or IIb hypercholesterolemia but otherwise in good general health, with a body weight between 10% below and 30% above their ideal weight as defined in the Metropolitan Life Insurance height and weight tables. Patients on a standard lipid-lowering diet for approximately 6 weeks (American Heart Association step I diet[21] or comparable) were required to have a LDL cholesterol level of 145 to 240 mg/dL (or, in the presence of known coronary artery disease, ≤160 mg/dL) to be eligible for participation. In addition, eligible patients had normal basal levels of testosterone and prolactin and an initial sperm concentration of $20 \times 10^6$/mL or higher in conjunction with otherwise normal semen parameters.

Patients were excluded from study participation if they had fasting triglycerides greater than 350 mg/dL, homozygous familial hypercholesterolemia, hyperlipidemia types I, III, IV, or V, or secondary hypercholesterolemia. Other exclusion criteria were as follows: uncontrolled hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 95 mm Hg), diabetes mellitus, evidence of active liver disease, and either myocardial infarction, percutaneous transluminal coronary angioplasty, coronary bypass surgery, or unstable angina within 4 months of screening. A history of infertility, urinary tract infection within the prior year, documented bacterial prostatitis, orchitis, or epididymitis was also cause for exclusion. Patients could not have used another lipid-lowering agent within 6 weeks of screening (probucol within 6 months) and could not be using medications with androgenic or antiandrogenic properties or agents affecting the male reproductive system or sexual function. Hypersensitivity to HMG-CoA reductase inhibitors was also cause for exclusion from the study.

Institutional Review Board approval was obtained at each study center, and all patients signed informed-consent forms.

### *Study Design*

This randomized placebo-controlled, parallel-group study was conducted at 11 sites in the United States from September 1992 to March 1995. Clinic visits subsequent to screening were scheduled during weeks -6, -1, 6, 12, 18, and 24 relative to randomization. During weeks -1 and 24, patients returned for 3 successive visits, each 3 days apart; during week 12, they returned twice 3 days apart. The third visit during week -1 corresponded to the randomization visit and day 1 of active treatment. Patients were instructed to adhere to the same lipid-lowering diet throughout the study (ie, from week -6 to week 24), with diet reinforcement at week -1 and week 12.

After the 6-week placebo run-in period, eligible patients were randomly assigned according to a computer-generated allocation schedule to receive 24 weeks of double-blind therapy with either simvastatin 20 mg, simvastatin 40 mg, pravastatin 40 mg, or placebo once daily at bedtime. Double-blinding was achieved through the use of matching-image simvastatin (10 or 20 mg)-placebo tablets and pravastatin-placebo tablets. Patients self-administered 4 tablets every evening corresponding to 1 of the following 4 randomly assigned regimens: 2 10-mg simvastatin and 2 pravastatin-placebo tablets, 2 20-mg simvastatin and 2 pravastatin-placebo tablets, 2 20-mg pravastatin and 2 simvastatin-placebo tablets, or 2 simvastatin-placebo and 2 pravastatin-placebo tablets.

Blood was collected 3 times at 20-minute intervals for hormone evaluations on the first clinic visit of weeks -1, 12, and 24. Equal volumes from each of the 3 samples were pooled for measurement of testosterone, sex hormone–binding globulin (SHBG), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels. On the second visit during weeks -1 and 24, patients received an intramuscular injection of 5,000 IU hCG (Profasi, Serono, Italy); stimulated testosterone was measured 72 hours later.

Semen samples were obtained twice (3 days apart) during weeks -1, 12, and 24. Samples were obtained by masturbation at the clinic after a 72-hour period of abstinence. Men were asked to abstain from ejaculation for 3 days prior to each specimen collection.

Fasting lipids, including total and high-density lipoprotein (HDL) cholesterol and triglycerides, were measured at weeks -1, 6, and 24. In addition, serum chemistry and hematology were analyzed at weeks -1 and 24. Aspartate transaminase, alanine transaminase, and creatine kinase levels were measured at weeks 6, 12, and 18. An electrocardiogram was performed at week -1, and a physical examination was performed at weeks -1 and 24. Vital signs (weight, pulse, and blood pressure) were determined at screening and during weeks -1, 12, and 24.

### *Laboratory Methods*

Hematology and urinalysis were performed at the study sites. Blood samples for plasma lipid, hormone, and serum chemistry determinations were separated by centrifugation at the study sites and stored at −20°C until shipment to the central laboratory. Samples for hormone measurements (other than those at screening) were stored at the central laboratory at −70°C until the end of the study, at which time they were analyzed simultaneously (for any individual patient) to eliminate interassay variability. Testosterone measurements were performed at Endocrine Sciences, Calabasas Hills, CA. All other hormone, lipid, and serum chemistry measurements were performed at Corning/Nichols Institute, San Juan Capistrano, CA.

The total serum testosterone level was measured by radioimmunoassay after extraction (sensitivity 30 ng/dL). SHBG was assayed by measuring binding capacity in a radioimmunoassay (sensitivity 5 nmol/L),[22] FSH by immunochemiluminometric assay (sensitivity 0.05 mIU/mL), and LH by immunochemiluminometric assay (sensitivity 0.05 mIU/mL). The interassay and intraassay coefficients of variation were 2% to 14%. The free testosterone index was calculated as the ratio of testosterone to SHBG.

Sperm morphology slides were evaluated by a single technician at MedLab International Central Clinical Trials Laboratory, San Antonio, TX. The rest of the semen analysis was performed from 0.5 to 2 hours after ejaculation at the study sites by technicians who used a standard protocol (developed and provided for this purpose by Dr James Overstreet, Department of Reproductive Biology and Medicine, University of California, Davis) and who underwent training and subsequent quality-assurance testing for the purposes of this study. The following parameters were measured: ejaculate volume, sperm concentration, percentage of motile sperm, sperm progression, viscosity, agglutination, and percentage of morphologically normal sperm. Analyses were performed at room temperature with the exception of sperm progression, which was assessed on slides warmed to 37°C.

Total cholesterol, HDL cholesterol, and triglyceride levels were measured using colorimetric enzymatic methods (sensitivity 2 mg/dL) on a Hitachi 704 chemistry analyzer (Hitachi, Tokyo, Japan). HDL cholesterol analysis used dextran sulfate–magnesium chloride precipitation. LDL cholesterol was calculated using the Friedewald approximation.[23]

### *Statistical Methods*

Continuous variables (hormone, semen, and lipid parameters) were analyzed using an ANOVA with terms for treatment and investigator. The percent change from baseline was examined for basal testosterone and lipid variables; the change from baseline was examined for other hormones and for semen variables. For the analysis of hCG-stimulated testosterone, baseline and treatment values constituted the percent change from basal testosterone (ie, the level just before administration of hCG). The assumptions of the ANOVA model were tested using Hartley's F-Max test for the homogeneity-of-variance assumption. The Shapiro-Wilk test and an examination of the plot of residuals were used to test the normality assumption. Within-group changes from baseline

were analyzed using the paired *t* test. Fisher's exact test was used to compare treatment groups for the incidence of adverse events. All statistical tests were 2-tailed at an $\alpha$ level of .05.

A per-protocol approach (prespecified prior to unblinding) was used for the main analysis because the key study endpoints constituted safety outcomes. Specifically, patients with major protocol violations were excluded from the analysis. Reasons for exclusion from the per-protocol analysis were receipt of treatment for less than 75% of the active-treatment period and a basal testosterone value at baseline less than 280 ng/dL (the latter excluded the patient from analysis of testosterone only). If a patient was off the study medication for 8 or more days before a clinic visit, data from that visit were not included. The value for hCG-stimulated testosterone was included only if the sample was drawn between 2 and 4 days of hCG administration. The intention-to-treat approach was used as a supplementary analysis for the safety outcomes; the results are not described here but were similar to those of the per-protocol analysis.

With the planned sample size of 30 completing patients per treatment group, the study had 80% power to detect a difference of 17% (assuming a standard deviation [SD] of 23%) in the percent change from baseline to week 24 in testosterone; a difference of 78% (SD 100%) in the change from baseline in hCG-stimulated testosterone; and a difference of 40.1 $\times$ $10^6$/mL (SD 54.6 $\times$ $10^6$/mL) in the change from baseline in sperm concentration.

## RESULTS

### *Patients*

A total of 159 patients were randomly assigned to treatment with the study medication. The demographic characteristics of the 4 treatment groups were similar and are summarized in Table 1. No clinically important differences between treatment groups were evident in the distribution of secondary diagnoses and use of concomitant therapies. One hundred thirty-eight patients completed the study (Table 1). Ten, 3, 7, and 2 patients in the placebo, simvastatin 20 mg, simvastatin 40 mg, and pravastatin 40 mg groups, respectively, discontinued prematurely, including 1 patient who withdrew from the placebo group and subsequently re-enrolled and was re-randomized to pravastatin 40 mg. The latter patient was also missing critical data and was therefore excluded from both the per-protocol and intention-to-treat analyses. Of 22 total dropouts, 5 (1 from each treatment group plus 1 from the simvastatin 40 mg group for an adverse event that occurred during placebo run-in) were due to clinical or laboratory adverse events and the remainder were for personal/administrative reasons.

**Table 1. Baseline Characteristics of the Male Patients**

| Characteristic | Placebo | Simvastatin 20 mg | Simvastatin 40 mg | Pravastatin 40 mg |
|---|---|---|---|---|
| Total no. of patients enrolled* | 40 | 40 | 41 | 39 |
| No. of patients completing the study | 30 (75%) | 37 (93%) | 34 (83%) | 37 (95%) |
| Mean age (yr) | 40.2 | 41.0 | 41.2 | 38.4 |
| SD | 7.5 | 7.3 | 6.4 | 8.7 |
| Range | 26-55 | 23-52 | 28-54 | 22-52 |
| Race | | | | |
| Caucasian | 32 (80%) | 31 (78%) | 38 (93%) | 31 (80%) |
| Hispanic | 4 (10%) | 4 (10%) | 1 (2%) | 4 (10%) |
| Black | 3 (8%) | 3 (8%) | 2 (5%) | 1 (3%) |
| Oriental | 1 (3%) | 2 (5%) | 0 | 3 (8%) |
| Mean lipid values (mg/dL) | | | | |
| Total cholesterol | 262.1 | 261.2 | 257.7 | 251.4 |
| LDL-C | 186.3 | 186.0 | 182.6 | 182.0 |
| HDL-C | 41.0 | 43.9 | 38.8 | 41.7 |
| TG | 213.9 | 190.5 | 210.9 | 155.6 |

*One patient received placebo for 18 days, dropped out of the study, and then was reallocated to receive pravastatin 40 mg; thus, he appears twice in the patient counts (a total of 159 individual patients were enrolled in the study).

**Table 2. Mean Percent Change From Baseline in Lipid Levels**

| Parameter (mg/dL) | Treatment | Week 24 No. | Week 24 % Change (SD) |
|---|---|---|---|
| Total cholesterol | Placebo | 29 | −1.0 (10.4) |
| | Simvastatin 20 mg | 34 | −25.8 (8.5)† |
| | Simvastatin 40 mg | 30 | −26.8 (12.3)† |
| | Pravastatin 40 mg | 34 | −23.6 (10.3)† |
| LDL-C | Placebo | 29 | 0.6 (12.1) |
| | Simvastatin 20 mg | 34 | −33.1 (10.5)† |
| | Simvastatin 40 mg | 30 | −34.3 (15.4)† |
| | Pravastatin 40 mg | 34 | −30.1 (12.6)† |
| HDL-C | Placebo | 29 | −5.4 (11.1) |
| | Simvastatin 20 mg | 34 | 7.9 (12.2)† |
| | Simvastatin 40 mg | 30 | 5.0 (13.9)† |
| | Pravastatin 40 mg | 34 | 2.5 (12.3)* |
| TG | Placebo | 25 | 5.7 (46.6) |
| | Simvastatin 20 mg | 30 | −24.6 (23.1)† |
| | Simvastatin 40 mg | 23 | −14.5 (27.4)* |
| | Pravastatin 40 mg | 30 | −15.7 (46.6)* |

*$P \leq .05$, †$P \leq .001$ *v* placebo.

### *Lipid Parameters*

Lipid parameters were comparable in the 4 treatment groups at baseline (Table 1). After 24 weeks of treatment, significant ($P < .001$) mean percent decreases in both total and LDL cholesterol were observed for patients receiving active treatments; these decreases were significantly greater ($P < .001$) than those for patients receiving placebo (Table 2). At week 24, the mean percent decreases in total cholesterol were 26%, 27%, and 24% in the simvastatin 20 mg, simvastatin 40 mg, and pravastatin 40 mg groups, respectively; the mean percent decreases in LDL cholesterol were 33%, 34%, and 30%, respectively. Triglycerides decreased significantly ($P < .05$) from baseline at week 24 in all 3 active-treatment groups (by 25%, 15%, and 16%, respectively). Total and LDL cholesterol and triglycerides remained essentially unchanged in the placebo group. Mean HDL cholesterol levels increased in the 3 active-treatment groups and decreased by 5% in the placebo group at week 24 (Table 2).

### *Hormonal Parameters*

The 4 treatment groups were generally similar with regard to values for hormonal parameters at baseline. Changes from baseline at 24 weeks in testosterone and the free testosterone index are summarized in Table 3. The change in hCG-stimulated testosterone, which represents the difference between the percent increase in testosterone at baseline and the percent increase in testosterone after 24 weeks of treatment, is shown in Fig 1. There were no statistically significant differ-

**Table 3. Testosterone and Free Testosterone Index at Baseline and Changes After 24 Weeks of Treatment**

| Parameter | No. | Baseline (mean ± SD) | Week 24 (mean ± SD) | Change From Baseline | 95% CI for Change | *P* Relative to Placebo |
|---|---|---|---|---|---|---|
| Testosterone (ng/dL) | | | | | | |
| Placebo | 28 | 538 ± 146 | 542 ± 171 | 1.5% | −5.7-8.6 | — |
| Simvastatin 20 mg | 29 | 493 ± 122 | 496 ± 123 | 3.1% | −6.2-12.3 | .906 |
| Simvastatin 40 mg | 27 | 511 ± 138 | 479 ± 102 | −3.0% | −11.0-5.1 | .499 |
| Pravastatin 40 mg | 29 | 555 ± 149 | 528 ± 154 | −2.7% | −10.9-5.5 | .503 |
| Free testosterone index* | | | | | | |
| Placebo | 28 | 1.18 ± 0.52 | 1.19 ± 0.58 | 0.01 | −0.10-0.12 | — |
| Simvastatin 20 mg | 29 | 1.14 ± 0.45 | 1.26 ± 0.52 | 0.12 | −0.03-0.28 | .316 |
| Simvastatin 40 mg | 27 | 1.15 ± 0.40 | 1.19 ± 0.48 | 0.04 | −0.11-0.19 | .812 |
| Pravastatin 40 mg | 29 | 1.17 ± 0.51 | 1.15 ± 0.51 | −0.02 | −0.16-0.12 | .786 |

*Free testosterone index was calculated as testosterone/SHBG.

ences between the placebo group and any of the active-treatment groups nor any statistically significant within-group changes from basal levels. The observed mean changes in testosterone after hCG stimulation at 24 weeks for the simvastatin 20 mg, simvastatin 40 mg, pravastatin 40 mg, and placebo groups were −30.9% (95% confidence interval [CI], −70.9% to 9.2%), −6.5% (95% CI, −30.9% to 17.9%), 30% (95% CI, −21.7% to 81.8%), and −3.2% (95% CI, −32.3% to 26.0%), respectively (Fig 1).

Similarly, there were no significant differences between the placebo group and any of the active-treatment groups for the mean changes from baseline to week 24 in FSH or LH (Table 4). Small decreases relative to baseline for both gonadotropins were found in the simvastatin 20 mg group ($P < .05$); however, decreases of comparable magnitude also occurred in the placebo group. Moreover, the simvastatin 40 mg group showed small nonsignificant positive changes in both FSH and LH relative to baseline compared with the placebo group.

A small but significant ($P < .05$) reduction in SHBG (within-group and also *v* placebo) was observed for the 20 mg simvastatin group. However, no significant effect was observed either in the simvastatin 40 mg or pravastatin 40 mg groups.

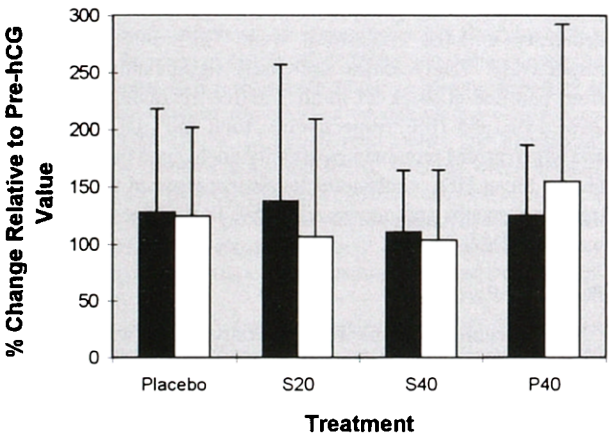


**Fig 1. Mean percentage increase in testosterone 72 hours after hCG administration at baseline (■) and after 24 weeks of treatment with simvastatin 20 mg, simvastatin 40 mg, pravastatin 40 mg, or placebo once daily (□). Bars represent standard deviations.**

*Semen Analyses*

Baseline values and changes at week 24 in sperm concentration, ejaculate volume, sperm motility, and sperm morphology are summarized in Table 5. Values at baseline were similar for the 4 treatment groups, and there were no statistically significant differences between the results for any active treatment and placebo at week 12 (data not shown) or week 24, except for a higher percentage of morphologically normal sperm in the simvastatin 20 mg group compared with the placebo group at week 24 ($P < .05$).

*Safety*

The percentage of patients with 1 or more adverse events during the study was 46% to 68% in the 4 treatment groups. None of the differences between groups were significant for the total incidence of adverse events or the incidence of adverse events considered by the investigator to be possibly, probably, or definitely drug-related (5% to 13%). No more than 1 patient in each treatment group experienced a serious adverse event or was withdrawn from therapy because of an adverse event. There were no between-group differences in the changes in vital signs.

## DISCUSSION

In this randomized placebo-controlled, double-blind trial, treatment with simvastatin 20 and 40 mg and pravastatin 40 mg did not result in clinically meaningful changes in serum testosterone, the hCG-stimulated increase in testosterone, gonadotropin levels, sperm concentration, or other measures of spermatogenesis (including semen volume and sperm morphology and motility). It is difficult to define "clinical significance" for serum testosterone, since it is unclear what is the "normal" serum testosterone level. Indeed, the threshold of normal may vary by age and the specific androgen-responsive end-organ. Therefore, our choice of 17% as clinically significant for the purpose of sample size calculations is an admittedly arbitrary but useful parameter. The changes at 24 weeks in measured hormonal and semen parameters among patients treated with simvastatin or pravastatin were not significantly different from those observed in patients receiving placebo, despite the expected substantial decreases in total and LDL cholesterol among patients in the active-treatment groups. Moreover, the observed (nonsignificant) changes did not follow a pattern

**Table 4. LH, FSH, and SHBG at Baseline and Change From Baseline After 24 Weeks of Treatment**

| Parameter | No. | Baseline (mean ± SD) | Week 24 (mean ± SD) | Change From Baseline | 95% CI for Change | *P* Relative to Placebo |
|---|---|---|---|---|---|---|
| LH (U/L) | | | | | | |
| Placebo | 29 | 2.94 ± 1.57 | 2.59 ± 1.25 | −0.35* | −0.70-−0.01 | |
| Simvastatin 20 mg | 32 | 2.78 ± 1.24 | 2.39 ± 0.79 | −0.39* | −0.69-−0.09 | .814 |
| Simvastatin 40 mg | 30 | 2.76 ± 1.34 | 2.70 ± 1.33 | −0.06 | −0.31-0.19 | .345 |
| Pravastatin 40 mg | 33 | 2.89 ± 1.38 | 2.70 ± 1.25 | −0.19 | −0.57-0.20 | .439 |
| FSH (U/L) | | | | | | |
| Placebo | 29 | 5.93 ± 3.88 | 5.59 ± 3.20 | −0.34 | −0.85-0.17 | — |
| Simvastatin 20 mg | 32 | 4.28 ± 2.90 | 3.75 ± 2.45 | −0.53* | −0.95-−0.10 | .452 |
| Simvastatin 40 mg | 30 | 3.74 ± 2.72 | 3.91 ± 2.48 | 0.17 | −0.40-0.73 | .231 |
| Pravastatin 40 mg | 33 | 4.58 ± 2.53 | 4.47 ± 2.83 | −0.10 | −0.39-0.19 | .459 |
| SHBG (mmol/L) | | | | | | |
| Placebo | 29 | 20.3 ± 12.4 | 21.3 ± 14.0 | 1.0 | −1.12-3.06 | — |
| Simvastatin 20 mg | 32 | 17.6 ± 8.3 | 16.0 ± 8.3 | −1.6* | −2.91-−0.21 | .035 |
| Simvastatin 40 mg | 30 | 17.4 ± 8.5 | 16.2 ± 7.5 | −1.2 | −2.80-0.37 | .091 |
| Pravastatin 40 mg | 33 | 19.4 ± 11.5 | 18.4 ± 10.3 | −0.9 | −2.30-0.45 | .118 |

*$P < .05$ for within-group change from baseline.

suggestive of any consistent trend. Both simvastatin and pravastatin were well tolerated.

Our findings are consistent with those of prior studies, most of which found no effect of HMG-CoA reductase inhibitors on male gonadal function.[6-10,12] This is not unexpected, considering the pharmacokinetic characteristics of pravastatin and simvastatin at the dosages used to treat hypercholesterolemia. After oral administration, both agents are selectively taken up by the liver, the target organ for the therapeutic effect on LDL cholesterol; thus, systemic exposure to active drug is limited, minimizing the chances that either compound would significantly impair gonadal function.[24]

Some studies have nonetheless recorded small effects of HMG-CoA reductase inhibitor therapy on testosterone production, spermatogenesis, or sperm characteristics. For example, Farnsworth et al[14] found a trend for lower plasma testosterone levels in 16 male hypercholesterolemic patients who received lovastatin 40 mg daily for 4 months. However, they did not find any compensatory increase in gonadotropins. Changes from baseline in the median serum testosterone levels after 24 weeks of treatment with simvastatin 40 or 80 mg/d were measured in male patients in two large randomized, multicenter trials in the United States[25] and multinationally.[26] Among 288 male patients in the US trial, serum testosterone decreased by 10% in both treatment groups, and among 292 male patients in the multinational trial, by 10% in the 40 mg and 12.5% in the 80 mg group. There were no significant between-group differences, nor were there any compensatory increases in LH or FSH levels in either study. The incidence of adverse experiences related to sexual function was very low in these studies, suggesting that the

**Table 5. Semen Variables: Baseline Values and Change From Baseline After 24 Weeks of Treatment**

| Parameter | No. | Baseline (mean ± SD) | Week 24 (mean ± SD) | Change From Baseline | 95% CI for Change | *P* Relative to Placebo |
|---|---|---|---|---|---|---|
| Sperm concentration ($10^6$/mL) | | | | | | |
| Placebo | 29 | 79.7 ± 57.5 | 78.0 ± 51.8 | −1.8 | −16.4-12.9 | — |
| Simvastatin 20 mg | 35 | 92.6 ± 61.5 | 74.7 ± 42.5 | −17.9* | −31.1-−4.7 | .158 |
| Simvastatin 40 mg | 31 | 99.2 ± 51.3 | 103.4 ± 66.9 | 4.2 | −19.0-27.4 | .780 |
| Pravastatin 40 mg | 33 | 83.6 ± 64.7 | 87.2 ± 72.3 | 3.6 | −12.0-19.3 | .449 |
| Ejaculate volume (mL) | | | | | | |
| Placebo | 29 | 2.51 ± 1.36 | 2.44 ± 1.33 | −0.07 | −0.34-0.20 | — |
| Simvastatin 20 mg | 35 | 2.57 ± 1.32 | 2.29 ± 1.21 | −0.28* | −0.53-0.02 | .280 |
| Simvastatin 40 mg | 31 | 1.96 ± 0.93 | 1.90 ± 0.97 | −0.06 | −0.33-0.21 | .863 |
| Pravastatin 40 mg | 33 | 2.86 ± 1.43 | 2.70 ± 1.30 | −0.16 | −0.49-0.18 | .651 |
| Sperm motility (% motile) | | | | | | |
| Placebo | 29 | 58.3 ± 16.4 | 58.4 ± 12.9 | 0.09 | −3.88-4.06 | — |
| Simvastatin 20 mg | 35 | 58.6 ± 13.8 | 58.7 ± 12.6 | 0.19 | −3.93-4.30 | .874 |
| Simvastatin 40 mg | 31 | 59.0 ± 11.7 | 57.8 ± 15.7 | −1.24 | −5.68-3.19 | .582 |
| Pravastatin 40 mg | 33 | 54.6 ± 14.0 | 57.2 ± 14.4 | 2.58* | 0.20-4.96 | .373 |
| Sperm morphology (% normal) | | | | | | |
| Placebo | 29 | 77.4 ± 10.0 | 76.4 ± 12.4 | −1.0 | −3.53-1.49 | — |
| Simvastatin 20 mg | 35 | 76.3 ± 11.2 | 78.7 ± 9.6 | 2.4*† | 0.11-4.71 | .036 |
| Simvastatin 40 mg | 30 | 77.7 ± 10.5 | 76.9 ± 11.5 | −0.87 | −3.12-1.39 | .827 |
| Pravastatin 40 mg | 33 | 74.6 ± 10.0 | 76.6 ± 8.7 | 2.07 | −0.10-4.24 | .117 |

*$P < .05$ for within-group change from baseline.

†$P < .05$ *v* placebo.

observed decreases are not clinically relevant. In 1 of the few placebo-controlled studies of gonadal function, Kjaer et al[27] found that SHBG was significantly ($P < .05$) reduced by 19% compared with placebo during 12 weeks of treatment with simvastatin 10 to 40 mg daily among 6 male patients with insulin-dependent diabetes mellitus. However, there were no significant changes in other hormones, including dehydroepiandrosterone sulfate, testosterone, estradiol, prolactin, LH, or FSH. In a study enrolling 8 patients receiving simvastatin 20 mg for 1 year, Azzarito et al[16] found mild declines in free testosterone. The declines were not associated with any compensatory increases in LH, although the absence of change in gonadotropins cannot exclude the possibility of an effect at the level of the hypothalamus/pituitary. Rossato et al[15] recorded statistically significant increases in androstenedione at 1, 2, and 12 months among 18 male patients with non–insulin-dependent diabetes mellitus receiving simvastatin 10 mg daily (plasma testosterone levels did not change). Others have found no changes in androstenedione.[8,16] Dobs et al[6] observed significant decreases in sperm motility at 6 and 12 months among a small number of men taking pravastatin 40 to 80 mg daily. However, Bernini et al[28] found no significant change in sperm motility among 8 men treated with pravastatin 20 mg daily for 6 months. In view of the lack of consistency of various isolated findings deriving from different studies in which multiple statistical comparisons were made, it is plausible that most or all of the "significant" findings were due to chance.

The prior studies, as well as the study reported here, enrolled men with normal testosterone levels. The possibility of unknown effects of HMG-CoA reductase inhibitors on men with baseline low serum testosterone levels or impaired fertility has not been addressed and therefore cannot be excluded.

The present study was conducted to more accurately detect any potential effects on male gonadal function by enrolling a larger number of patients and using a randomized placebo-controlled, double-blind design. The length of the study included 2 complete cycles of spermatogenesis (cycle estimated to be approximately 64 days),[29] thus improving the chance of detecting any potential adverse effect on spermatogenesis. We found no clinically relevant changes in testosterone levels in any treatment group. In addition, the mean changes from baseline for the free testosterone index were comparable among the 4 treatment groups. (The free testosterone index was calculated because the testosterone fraction that is not bound to SHBG correlates better with biologic activity than total testosterone.[30]) The active treatments were associated with slight decreases in SHBG; however, the small magnitude of the changes and the absence of a relation to the dose of simvastatin make it unlikely that there was a clinically meaningful effect on SHBG.

The percentage changes in serum testosterone after hCG stimulation were quite variable, as evidenced by the high SD for hCG-stimulated testosterone. The general magnitude of the changes observed, the variability in response, and the lack of statistically or clinically meaningful effect on hCG-stimulated testosterone are consistent with the results of other studies using hCG testing for patients receiving simvastatin or pravastatin.[6,8,9]

The small but statistically significant mean decreases in LH and FSH relative to baseline among patients receiving the lower dose of simvastatin are most likely chance findings or the result of a period effect, because the placebo group also showed a significant decrease from baseline in LH, none of the comparisons with the placebo group were statistically significant, and there was no significant change from baseline for either the simvastatin 40 mg or pravastatin 40 mg groups. Other studies have found no consistent effect of simvastatin or pravastatin on serum gonadotropin levels.[6,9,10,12,15]

There were no significant differences in sperm concentration between any of the active-treatment groups and the placebo group. The variability of sperm concentration is well recognized and reflects both biologic and laboratory variability. Repeat samplings at 3-day intervals and rigorous standardized sample collection and laboratory procedures were used to minimize variability in this study. The SDs recorded for semen concentration in the current study were similar to those in an earlier study examining within-subject variability for the sperm count.[31] Of the assessments of semen volume and sperm morphology and motility, only the comparison between simvastatin 20 mg and placebo groups for morphology reached statistical significance, with the simvastatin group showing an increase in the percentage of normal forms. In the absence of a biologically plausible explanation or a consistent result at the 40-mg simvastatin dose, this most likely represents a chance finding reflecting multiple statistical comparisons.

In conclusion, we found no evidence for clinically meaningful effects of simvastatin or pravastatin on gonadal testosterone production, testosterone reserve, or multiple parameters of semen quality in this double-blind, placebo-controlled study.

## APPENDIX

Simvastatin-Pravastatin Male Gonadal Function Study Group: Carlos R. Ayers, MD, University of Virginia Medical Center, Charlottesville, VA; Michael H. Davidson, MD, Chicago Center for Clinical Research, Chicago, IL; Adrian S. Dobs, MD, The Johns Hopkins University School of Medicine, Baltimore, MD; Jack C. Rutledge, MD, University of California, Davis, Medical Center, Sacramento, CA; Sam S. Miller, MD, SAM Clinical Research Center, San Antonio, TX; Gilberto Neri, MD, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL; J. Edward Pickering, MD, Lankenau Medical Research Center, Wynnewood, PA; Sherwyn L. Schwartz, MD, Diabetes and Glandular Disease Clinic, San Antonio, TX; Philip D. Toth, MD, Midwest Institute for Clinical Research, Indianapolis, IN; J. David Wallin, MD, Louisiana State University School of Medicine, New Orleans, LA; and Stuart R. Weiss, MD, The San Diego Endocrine and Medical Center, San Diego, CA.

## REFERENCES

1. Scandinavian Simvastatin Survival Study Group: Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). Lancet 344:1383-1389, 1994

2. Shepherd J, Cobbe SM, Ford I, et al: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 333:1301-1307, 1995

3. Pedersen TR, Tobert JA: Benefits and risks of HMG-CoA

reductase inhibitors in the prevention of coronary heart disease. A reappraisal. Drug Saf 14:11-24, 1996

4. Hubbard SC, Ivatt RJ: Synthesis and processing of asparagine-linked oligosaccharides. Annu Rev Biochem 50:555-583, 1981

5. Matsumoto AM, Bremner WJ: Endocrinology of the hypothalamic-pituitary-testicular axis with particular reference to the hormonal control of spermatogenesis. Baillieres Clin Endocrinol Metab 1:71-87, 1987

6. Dobs AS, Sarma PS, Schteingart D: Long-term endocrine function in hypercholesterolemic patients treated with pravastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. Metabolism 42:1146-1152, 1993

7. Azzarito C, Boiardi L, Zini A, et al: Long-term therapy with high-dose simvastatin does not affect adrenocortical and gonadal hormones in hypercholesterolemic patients. Metabolism 41:148-153, 1992

8. Bernini GP, Argenio GF, Gasperi M, et al: Effects of long-term simvastatin treatment on testicular and adrenal steroidogenesis in hypercholesterolemic patients. J Endocrinol Invest 17:227-233, 1994

9. Travia D, Tosi F, Negri C, et al: Sustained therapy with 3-hydroxy-3-methylglutaryl-coenzyme-A reductase inhibitors does not impair steroidogenesis by adrenals and gonads. J Clin Endocrinol Metab 80:836-840, 1995

10. Jay RH, Sturley RH, Stirling C, et al: Effects of pravastatin and cholestyramine on gonadal and adrenal steroid production in familial hypercholesterolemia. Br J Clin Pharmacol 32:417-422, 1991

11. Prihoda JS, Pappu AS, Smith FE, et al: The influence of simvastatin on adrenal corticosteroid production and urinary mevalonate during adrenocorticotropin stimulation in patients with heterozygous familial hypercholesterolemia. J Clin Endocrinol Metab 72:567-574, 1991

12. Purvis K, Tollefsrud A, Rui H, et al: Short-term effects of treatment with simvastatin on testicular function in patients with heterozygous familial hypercholesterolaemia. Eur J Clin Pharmacol 42:61-64, 1992

13. Illingworth DR, Corbin D: The influence of mevinolin on the adrenal cortical response to corticotropin in heterozygous familial hypercholesterolemia. Proc Natl Acad Sci USA 82:6291-6294, 1985

14. Farnsworth WH, Hoeg JM, Maher M, et al: Testicular function in type II hyperlipoproteinemic patients treated with lovastatin (mevinolin) or neomycin. J Clin Endocrinol Metab 65:546-550, 1987

15. Rossato M, Guarneri G, Lavagnini T, et al: Simvastatin influences testicular steroidogenesis in human. Horm Metab Res 25:503-505, 1993

16. Azzarito C, Boiardi L, Vergoni W, et al: Testicular function in hypercholesterolemic male patients during prolonged simvastatin treatment. Horm Metab Res 28:193-198, 1996

17. Hildebrand RD, Hepperlen TW: Lovastatin and hypospermia. Ann Intern Med 112:549-550, 1990 (letter)

18. Levine RJ, Mathew RM, Chenault CB, et al: Differences in the quality of semen in outdoor workers during summer and winter. N Engl J Med 323:12-16, 1990

19. Smals AGH, Kloppenborg PWC, Benraad TJ: Circannual cycle in plasma testosterone levels in man. J Clin Endocrinol Metab 42:979-982, 1976

20. Griffin JE, Wilson JD: Disorders of the testes and male reproductive tract, in Williams RH, Wilson JD, Foster DW: Williams' Textbook of Endocrinology (ed 7). Philadelphia, PA, Saunders, 1985, pp 259-311

21. Krauss RM, Deckelbaum RJ, Ernst N, et al: Dietary guidelines for healthy American adults. A statement for health professionals from the Nutrition Committee, American Heart Association. Circulation 94:1795-1800, 1996

22. Cunningham SK, McKenna TJ: Evaluation of an immunoassay for plasma sex hormone–binding globulin: Comparison with steroid-binding assay under physiological and pathological conditions. Ann Clin Biochem 25:360-366, 1988

23. Friedewald WT, Levy RI, Frederickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 18:499-502, 1972

24. Germershausen JI, Hunt VM, Bostedor RG, et al: Tissue selectivity of the cholesterol-lowering agents lovastatin, simvastatin and pravastatin in rats in vivo. Biochem Biophys Res Commun 158:667-675, 1989

25. Stein EA, Davidson MH, Dobs AS, et al: Efficacy and safety of simvastatin 80 mg/day in hypercholesterolemic patients. Am J Cardiol 82:311-316, 1998

26. Ose L, Kastelein JJP, Scott EA, et al: Efficacy and six-month safety of simvastatin 80 mg/day: Results from the Worldwide Simvastatin Expanded Dose Program (WSEDP). Nutr Metab Cardiovasc Dis 8:143-151, 1998

27. Kjaer K, Hangaard J, Petersen NE, et al: Effect of simvastatin in patients with type I (insulin-dependent) diabetes mellitus and hypercholesterolemia. Acta Endocrinol (Copenh) 126:229-232, 1992

28. Bernini GP, Brogi G, Argenio GF, et al: Effects of long-term pravastatin treatment on spermatogenesis and on adrenal and testicular steroidogenesis in male hypercholesterolemic patients. J Endocrinol Invest 21:310-317, 1998

29. Heller CG, Clermont Y: Spermatogenesis in man: An estimate of its duration. Science 140:84-86, 1963

30. Nanjee MN, Wheeler MJ: Plasma free testosterone—Is an index sufficient? Ann Clin Biochem 22:387-390, 1985

31. Schwartz D, Laplanche A, Jouannet P, et al: Within-subject variability of human semen in regard to sperm count, volume, total number of spermatozoa and length of abstinence. J Reprod Fertil 57:391-395, 1979