Effects of High-Dose Simvastatin on Adrenal and Gonadal Steroidogenesis in Men With Hypercholesterolemia

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In view of the role of both the de novo biosynthesis and receptor-mediated uptake of cholesterol for normal steroidogenesis, we evaluated whether extending the therapeutic dose of the hepatic hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitor, simvastatin, to 80 mg/d would affect adrenal and gonadal steroid synthesis in men with hypercholesterolemia. To evaluate this question, we enrolled men into a multicenter randomized, placebo-controlled study lasting 12 weeks. Men with serum low-density lipoprotein cholesterol (LDL-C) more than 145 mg/dL after 6 weeks of a lipid-lowering diet were randomized to 80 mg simvastatin or placebo. Half of the subjects were asked to undergo a 6-hour infusion of corticotropin (ACTH) to evaluate cortisol synthesis, and the entire cohort received a human chorionic gonadotropin (hCG) stimulation test to assess gonadal hormone secretion using pooled serum samples taken 15 minutes apart. A total of 81 men (age, 45 ± 11 years; 93% Caucasian) with baseline serum LDL-C of 197 mg/dL (placebo, n = 39) and 184 mg/dL (simvastatin 80 mg, n = 42) completed the study. After 12 weeks, serum LDL-C, triglycerides, and high-density lipoprotein cholesterol (HDL-C) in the simvastatin group changed by −43%, −25%, and 8%, respectively (all *P* < .001). The basal cortisol level and the peak serum cortisol and area under the curve response to the 6-hour ACTH infusion were comparable between the two treatment groups at baseline and after 12 weeks. The pooled total testosterone level at baseline was 541 and 513 ng/dL in the placebo and simvastatin-treated groups, respectively, which declined to 536 ± 20.5 ng/dL (−1.5%) and 474 ± 30.4 ng/dL (−13.6%, *P* = .09) after treatment (mean ± SD). The pooled free testosterone declined by 6.3% in the simvastatin group, versus a 4.9% increase in the placebo group (*P* = .588), while pooled bioavailable testosterone declined 10.2% in the simvastatin group and increased 1.4% in the placebo group (*P* = .035). There were no changes in serum gonadotropin levels or sex hormone–binding globulin (SHBG). After administration of hCG, there were no differences in the peak total pooled testosterone level before or after 12 weeks of treatment. Simvastatin 80 mg was well tolerated compared with placebo. In conclusion, basal and stimulated cortisol production was unaffected by the use of simvastatin 80 mg versus placebo. As reported with other statins and cholestyramine, there were small declines in the simvastatin-treated group for pooled total, free, and bioavailable testosterone after 12 weeks, although there was no compensatory increase in serum follicle-stimulating hormone (FSH) or luteinizing hormone (LH) levels.

THE CURRENT National Cholesterol Education Program guidelines have defined specific target goals for reducing the plasma concentration of low-density lipoprotein cholesterol (LDL-C), which take into consideration the presence or absence of coronary heart disease and the number of cardiovascular risk factors.[1] Thus, there is a need for effective, well-tolerated medications that can be used as monotherapy. The maximum dose of simvastatin has recently been extended to 80 mg/d in the United States and other countries. In clinical trials involving over 1,100 patients, this dose was found to be effective (reducing LDL-C by 46% to 48%) and well tolerated.[2,3]

Since cholesterol is the precursor of steroid hormones, agents that decrease exogenous or intracellular free cholesterol levels could influence steroidogenesis.[4,5] Illingworth et al[6] have shown that patients with homozygous familial abetalipoproteinemia, on average, have a slight increase in plasma corticotropin (ACTH), normal basal levels of adrenal steroids, but a blunted cortisol response to prolonged ACTH stimulation. Similarly, there are concerns about gonadal status, with reports of normal testosterone levels and elevated serum gonadotropins[7] or testicular atrophy and amenorrhea in subjects with hypobetalipoproteinemia.[8]

Studies of basal and stimulated hormones have been used to evaluate steroidogenesis in subjects on hepatic hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors. Lovastatin at doses of up to 80 mg/d has been shown to have no effect on adrenal and gonadal steroid production.[9-12] Lovastatin 40 mg[13] or pravastatin 40 mg[14] had no effect on adrenocortical or testicular steroidogenesis even after maximal stimulation with ACTH and human chorionic gonadotropin (hCG), respectively.

The available data suggest that simvastatin has no effect on steroidogenesis. In the Scandinavian Simvastatin Survival Study (4S), there was no difference between simvastatin and placebo in the incidence of sexual adverse experiences in approximately 2,000 men treated with simvastatin 20 to 40 mg for up to 6 years.[15] A rigorous placebo-controlled study revealed no effect of simvastatin at doses of 20 and 40 mg/d on semen production or gonadal steroidogenesis.[16] In a 3-period crossover study, simvastatin 40, 80, and 160 mg was associated with a marginally significant reduction in basal serum testosterone levels.[17]

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The purpose of this study was to evaluate the effect of higher doses of simvastatin on the capacity of the adrenal cortex to synthesize corticosteroid and of the testes to produce gonadal steroids.

SUBJECTS AND METHODS

Subjects

Men 21 to 50 years of age with primary hypercholesterolemia were eligible for enrollment if, on diet only, their LDL-C was greater than 145 mg/dL and triglycerides less than 350 mg/dL. Subjects were required to have normal levels of cortisol (5 to 25 μg/dL), total testosterone (300 to 1,000 ng/dL), prolactin (3 to 18 ng/mL), fasting blood glucose (≤140 mg/dL), and thyrotropin (0.3 to 5 μU/mL). Treatment with any androgenic, estrogenic, progestogenic, antiandrogenic, or antiestrogenic agents or medications that can alter the gonadal steroid milieu or modulate the neuroendocrine regulation was not allowed. None of the subjects were using systemic immunosuppressants or anticoagulants. At baseline, their liver transaminases and creatine kinase (CK) were required to be less than 20% and less than 50% above the upper limit of normal, respectively.

Study Design

This was a multicenter (US centers) double-masked clinical trial in which patients with hyperlipidemia were randomized to receive simvastatin 80 mg daily versus a matching placebo for 12 weeks. Due to varying sample size requirements for the different hormones under evaluation, the study had a dual-format design. Half of the cohort underwent ACTH and hCG testing and half had hCG testing only. Some clinical centers performed both forms of testing, while others performed only the hCG evaluations.

Endocrine Testing

Endocrine testing was performed twice in all subjects, at baseline and after 12 weeks of treatment. A 6-hour intravenous infusion of ACTH was used to evaluate adrenal function. Exactly 0.250 mg Cortrosyn (synthetic ACTH; Organon, West Orange, NJ) was reconstituted in 1 mL saline and infused in 1 L normal saline through a metered intravenous pump. Blood samples were obtained for plasma cortisol in the basal state and at 2-, 4-, and 6-hour intervals.

To evaluate testicular function, basal levels of total, bioavailable, and free testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and sex hormone–binding globulin (SHBG) were obtained by pooling serum from 3 samples drawn at 15-minute intervals. Bioavailable testosterone includes the free hormone plus that which is loosely bound to albumin. The hCG test was performed on the day after Cortrosyn infusion by administering hCG 5,000 IU intramuscularly (Profasi; Serono, Rome, Italy) and obtaining a pooled blood sample again at 72 hours.

Assays

Total cholesterol and triglyceride levels were measured in a centralized laboratory (Medical Research Laboratories, Cincinnati, OH) using colorimetric enzymatic methods (Boehringer Biochemia, Mannheim, Germany). High-density lipoprotein cholesterol (HDL-C) was determined after precipitation of the β-containing lipoproteins (LDL and VLDL) in whole plasma by heparin-manganese chloride. LDL-C cholesterol was calculated by the Friedewald formula.[18]

Total and bioavailable testosterone levels were measured by radioimmunoassay kits (Diagnostic Products, Los Angeles, CA and Diagnostics Systems Laboratories, Webster, TX, respectively). Serum cortisol was determined by a glucometric enzyme immunoassay (Baxter Diagnostics, Deerfield, IL). Gonadotropins and prolactin were determined using the Ciba Corning Automated Chemiluminescence System (Medfield, MA).

Statistical Analyses

The primary hypothesis was that there would be no difference between the groups in the peak cortisol response to Cortrosyn stimulation. Based on the sample size of 15 per group, the study was powered at 80% to find a difference of 8.5 μg/dL between treatment groups in the primary endpoint of the peak cortisol response to Cortrosyn. With a sample size of 30 per group, a 25.6% and 44.9% difference in basal testosterone and stimulated testosterone, respectively, could be observed. The median testosterone is presented as a more robust indicator of testosterone levels, since testosterone values did not follow a normal distribution. The results were analyzed using analysis of covariance modeling. A P value .05 was considered statistically significant. The data are expressed as the mean ± SD, or as the median for variables that were not normally distributed. For all variables, there were no statistical differences noted among the separate clinical sites, and the data are thus presented for the group as a whole.

The primary analysis was ''per-protocol,'' a method considered as a more conservative approach for analyzing safety data. Data on subjects were excluded if they did not comply with the protocol based on prespecified criteria, ie, medication compliance less than 75%, systemic and inhaled steroid use, or no valid baseline cortisol level. In addition, all variables were analyzed by an intent-to-treat approach as a corroborative analysis.

RESULTS

Patient Population

Of 83 men (93% Caucasian) randomized to simvastatin 80 mg (n = 42) or placebo (n = 39), 81 (98%) completed the study. Their mean age (mean ± SD) as a group was 45.4 ± 11.46 years and there were no significant differences in the group demographics. Of the 2 subjects who discontinued participation in the study, both were on placebo—one withdrew consent and the other was removed because of a protocol violation.

Changes in Serum Lipids

The baseline serum LDL-C of patients randomized to placebo or simvastatin 80 mg was 197 and 185 mg/dL (nonsignificant [NS]), respectively. LDL-C declined by a mean of 0.4% ± 11.5% and 42.9 ± 15.2% in subjects randomized to placebo or simvastatin 80 mg, respectively ($P < .001$). Serum triglycerides declined by a median (SD median) of 25% (29.4%) in the simvastatin treatment group and increased by 13.8% (36.9%) in the placebo group ($P < .001$, between-group). HDL-C increased by a mean of 7.9% ± 13.9% from 45 to 48 mg/dL in the simvastatin group. There was no significant change in HDL-C in placebo-treated subjects from a baseline of 47 mg/dL ($P < .001$, between-group). The LDL-C/HDL-C ratio diminished by 46% in the simvastatin group ($P < .001$).

Adrenocortical Function

In the baseline state before therapy, the plasma cortisol level was comparable between the active and placebo treatment groups. After 12 weeks of treatment, there were no significant differences between the simvastatin and placebo groups in the

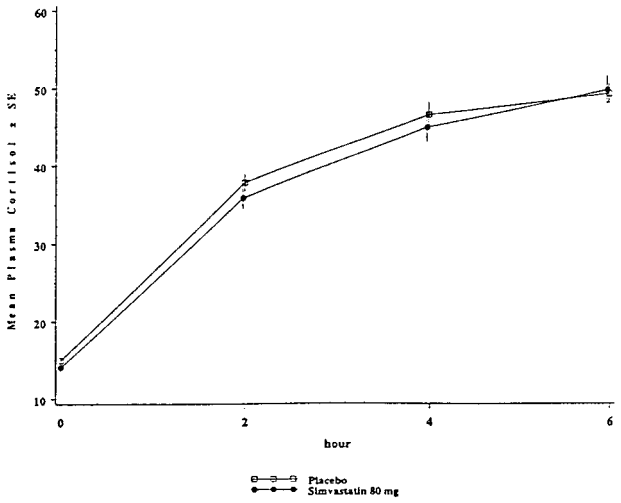

Fig 1. Cortisol response to Cortrosyn (mean ± SE) over the 6-hour infusion before and after 12 weeks of treatment with simvastatin 80 mg (n = 37) or placebo (n = 39). There were no differences between groups.

primary endpoint of the peak response to a 6-hour ACTH infusion. Compared with the response before initiation of treatment, the stimulated cortisol peak response to ACTH infusion among subjects randomized to active simvastatin or placebo declined by 1.7 and 1.2 μg/dL, respectively. The between-group comparison was not significant. After 12 weeks of treatment, there was no significant difference in the mean percent change from baseline in serum cortisol in the simvastatin group (−5.2% ± 26.8%) and the placebo group (+4.9% ± 47.8%) or the change in the area under the curve for the simvastatin (+1.4%) or placebo (+3.4%) groups (Fig 1).

Gonadal Function

The median baseline level of total testosterone in 3 pooled samples taken 15 minutes apart was 541.0 and 513.0 ng/dL for placebo- and simvastatin-treated patients, respectively (NS). After 12 weeks of therapy, the median in the placebo group was 536.0 ng/dL (−1.5% change), while the simvastatin-treated group median was 474 ng/dL (−13.6% change, between-group $P = .09$; Table 1).

The change in the median (SD median) basal free testosterone was −6.3% (43.5) versus 4.9% (44.4) in the simvastatin and placebo-treated subjects, respectively (NS), while the bioavailable basal testosterone was −10.2% (33.4) and 1.4% (22.9) in the active and placebo groups ($P = .035$). There were no significant differences in serum gonadotropins or SHBG (Table 1).

After intramuscular administration of hCG at baseline, the median peak total testosterone level increased by 99.6% in the placebo group, versus 87.8% in the simvastatin group (Fig 2). After 12 weeks of treatment, it increased by 108.6% in the placebo group and 89.7% in the treated group ($P = .293$, between-group). There were no statistically significant changes in the stimulated free or bioavailable testosterone after treatment.

Safety and Tolerance

Simvastatin 80 mg was well tolerated with a similar number of patients with drug-related clinical adverse events in the simvastatin group (11.9% of subjects with ≥1 adverse experiences) and the placebo group (4.9% of subjects with ≥1).

Two patients in the simvastatin group had an increase in alanine transaminase, with one judged to be drug-related. One patient in the placebo group experienced a CK elevation to 2,160 mIU/mL, which was probably exercise-induced and resolved spontaneously. The follow-up CK was 98 mIU/mL.

DISCUSSION

The current study was designed to evaluate whether treatment with simvastatin 80 mg/d influences steroid hormone production by the adrenal cortex or testes in men with primary hypercholesterolemia. The changes in serum lipids and lipoproteins observed in the present study were similar to those reported previously (46% to 48%) with simvastatin 80 mg in patients with primary hypercholesterolemia.[2,3,17]

We chose the 6-hour infusion of Cortrosyn, rather than shorter tests (60 or 90 minutes), to potentially elicit more subtle effects on corticosteroid production. In subjects with homozygous abetalipoproteinemia, a lipoprotein disorder in which patients have a complete absence of LDL-C and a reduced response to Cortrosyn, a deficient cortisol response was noted only beyond 2 hours.[9] The results of our study agree with previous reports in which steroidogenesis was examined in patients with hypercholesterolemia treated with lower doses of simvastatin (40 mg/d)[19,20] or lovastatin 80 mg/d[9,21] and in a smaller study in 8 patients with familial hypercholesterolemia

Table 1. Serum Hormones in Men Randomized to Placebo or Simvastatin 80 mg

Parameter	Treatment	No.	Baseline	Week 12	Change	SD	*P*
Total basal pooled testosterone (ng/dL)	Placebo	39	541.0	−1.5%	20.5	.091	
	Simvastatin	37	474.0	−13.6%	30.4		
Free basal pooled testosterone (pg/dL)	Placebo	39	131.0	118.0	4.9%	44.4	.588
	Simvastatin	37	122.0	101.0	−6.3%	43.5	
Bioavailable basal pooled testosterone (ng/dL)	Placebo	37	230.0	244.0	1.4%	22.9	.035
	Simvastatin	37	249.0	189.0	−10.2%	33.4	
Serum LH (mIU/mL)	Placebo	39	5.01	4.86	−0.14%	1.68	.841
	Simvastatin	37	4.90	4.56	−.034%	2.00	
Serum FSH (mIU/mL)	Placebo	39	5.09	5.05	−0.05%	1.10	.536
	Simvastatin	37	4.76	4.85	0.09%	0.90	
Serum SHBG (mg/dL)	Placebo	39	0.79	0.74	−0.05%	0.25	.614
	Simvastatin	37	0.84	0.76	−0.08%	0.27	

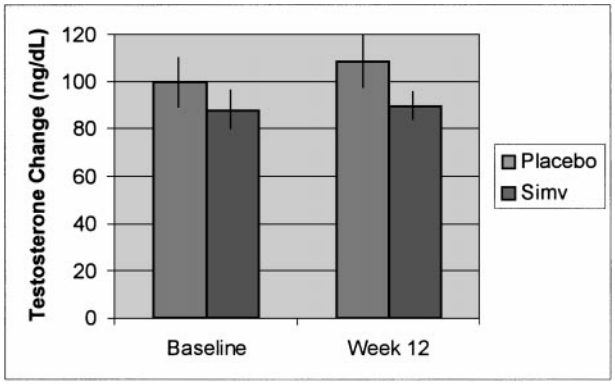

Fig 2. Absolute median changes in total testosterone (basal *v* stimulated) at baseline and 12 weeks of placebo (n = 39) or simvastatin 80 mg (n = 37) treatment.

treated with simvastatin at a dose of 80 mg/d.[22] In these studies, treatment with simvastatin or lovastatin did not result in any differences in basal cortisol or the weighted area under the curve between patients studied while on and off treatment with simvastatin or lovastatin. In our study, we found no differences in basal cortisol, the peak level, or the area under the curve during the 6-hour infusion.

Testicular steroidogenesis depends on a continuous supply of cholesterol derived either from de novo Leydig cell synthesis or from uptake of circulating LDL. In previous studies, there has been no change[23] or a small reduction[24] in serum testosterone with the statin class. These changes were not associated with an increase in gonadotropins and were also observed with cholestyramine. As there have been no complaints of hypogonadism in several large clinical studies with statins,[15,25] these small changes in serum testosterone with lipid-lowering therapy do not appear clinically relevant. Additionally, in a study in 160 men without evidence of hypogonadism treated with simvastatin 20 or 40 mg/d, pravastatin 40 mg/d, or placebo for 24 weeks, no effects were found on semen analysis or basal or hCG-stimulated testosterone.[14]

In the present study, we rigorously assessed gonadal function by using pooled serum samples, measuring total, bioavailable, and free testosterone, and performing hCG stimulation. In the basal state, there was a small NS decrease in median total testosterone in the simvastatin versus placebo group, respectively. Similarly, changes in free testosterone were not statistically significant ($P = .588$). However, the change in basal bioavailable testosterone for the simvastatin group did reach statistical significance ($P = .035$). There was no compensatory increase of gonadotropin in simvastatin-treated patients. We found no difference in hCG-stimulated testosterone in these eugonadal subjects treated with simvastatin or placebo.

These results are consistent with those obtained in 2 phase III studies with simvastatin 80 mg versus 40 mg that included more than 1,100 patients and 640 men. There was an approximate 10% reduction in total testosterone observed in men in both groups.[2,3] However, the absence of a placebo group in that study left the significance of those reductions uncertain. These investigators also found no elevation of gonadotropin in either group, and the incidence of sexual adverse experiences was low for both groups (0.4% for 40 mg and 0.8% for 80 mg). It is difficult to interpret the clinical significance of mild decrements in free testosterone within the context of normal serum gonadotropins. Since the mean age in the phase III studies was 53 years and in the current study 45 years, a clinically significant decrease in testosterone should have been accompanied by an increase in gonadotropins, which was not apparent. It is possible that simvastatin affects the hypothalamic/pituitary secretion of gonadotropins, or that simvastatin enhances the sensitivity of testosterone to its receptors, perhaps through increased conversion to dihydrotestosterone. However, there is no evidence for either of these possibilities. Lastly, it may be that the hypothalamus is not sufficiently sensitive to detect small changes in circulating testosterone.

The level of circulating serum testosterone needed for its end-organ effects is now being debated. The relationship of serum testosterone required for adequate sexual activity and maintenance of bone density may be a function of age, serum concentrations, and the inherent sensitivity of the androgen receptor. Although supplemental testosterone is of benefit in hypogonadal men[26] or the elderly,[27,28] the level of serum testosterone may[29,30] or may not[31] directly correlate with the level of sexual functioning. This study was designed to evaluate subtle changes in serum hormone levels, and thus questionnaires documenting libido and erectile function were not used. Similarly, the exact threshold needed for the maintenance of bone density or body composition is not known.

In conclusion, simvastatin 80 mg was well tolerated. There were no changes in the basal or Cortrosyn-stimulated cortisol peak response in men randomized to 80 mg simvastatin. In addition, there was a slight decrease in total, free, and bioavailable testosterone with no compensatory increase in FSH or LH. The existing data suggest that the small changes in androgens observed with cholesterol reductions would not be clinically relevant.

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