

Simvastatin Trial Suggests Statins May Treat PCOS

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LOS ANGELES — Simvastatin lowered testosterone levels by 41%, normalized gonadotropin levels, and reduced cardiovascular risk factors in a small, randomized, controlled trial, suggesting that statins may be a potential treatment for polycystic ovarian syndrome.

“Statins would improve the metabolic profile in those patients in terms of lipid

levels as well as improve the hormonal problems,” study investigator Antoni J. Duleba, M.D., said during the annual meeting of the Society for Gynecologic Investigation.

The study is the first to demonstrate these benefits in women with polycystic ovarian syndrome (PCOS). Dyslipidemia is common with PCOS, but statins are almost never used in PCOS, because the patients are typically young women trying to get pregnant or are at risk of getting preg-

nant. Statins are contraindicated in pregnancy, said Dr. Duleba of Yale University, New Haven.

The study eliminated pregnancy as a consideration by placing all 48 study participants on oral contraceptive pills (OCP) containing 20 mcg of ethinyl estradiol and 150 mcg of desogestrel. One 24-patient cohort was treated with 20 mg of simvastatin daily, along with OCP; the other 24 patients received only OCP.

Investigators from Yale and Poznan

University of Medical Sciences in Poland are conducting the ongoing trial in that country. The women are about 23 years old on average. None received any hormonal treatment or OCPs for at least 3 months before enrollment. Organon Inc. supplied the OCP Marvelon, and Polfa, a Polish pharmaceutical company, provided simvastatin.

A comparison of hormonal levels at baseline and 12 weeks showed total testosterone fell significantly—an average of 34.6 ng/dL (41%) in the OCP/simvastatin group. By contrast, in the OCP-alone group, levels fell by only 10.9 ng/dL (14%).

Average dehydroepiandrosterone sulfate (DHEA-S) fell 26% in the OCP/simvastatin patients and 28% in the OCP-alone group. Luteinizing hormone (LH), however, was reduced 43% in the OCP/simvastatin group vs. 9% in the OCP-alone cohort.

FSH declined 8%, which was not significant, in the OCP/simvastatin patients, but it increased 21% in those taking just OCPs.

The LH:FSH ratio declined significantly in the OCP/simvastatin group (44%) and fell by 12% in the OCP-alone group—not a statistically significant decline.

As expected, the simvastatin group had a significantly improved metabolic profile: Total cholesterol was 10% lower with simvastatin/OCP vs. 8% higher with OCP alone. Low-density lipoprotein (LDL) cholesterol dropped a significant 24% in the simvastatin/OCP patients, but stayed the same in the control group. Conversely, triglyceride levels increased 21% in the OCP-only patients but were not much changed in simvastatin/OCP patients.

Increases in HDL cholesterol levels were similar: 9% with simvastatin/OCP and 13% with OCP alone. Neither group had a significant improvement in insulin sensitivity or change in body mass index.

Dr. Duleba reported that hyperandrogenia declined dramatically in the simvastatin/OCP arm, but he said 3 months is too early to determine whether this will lead to improvements in excessive hair growth or other clinical conditions associated with PCOS.

The trial employs a crossover design by which the groups have since switched regimens. The investigators also are looking at biochemical markers of endothelial function and cardiovascular risk, which Dr. Duleba said is increasingly a patient concern.

“We used to only see women who wanted to get pregnant and, on occasion, because of complaints of hirsutism,” he said. “Now, with greater understanding of cardiovascular risk factors, people come to the office and say, ‘What can we do to protect ourselves from heart disease, diabetes, high blood pressure—all the cardiovascular problems that our mothers, aunts, and grandmothers had?’”

Although he would not recommend statins to women trying to get pregnant, he concluded that statins could eventually prove to be the answer to their question about cardiovascular risk. “In the long term, I hope to show clinical end points,” he said.

ENABLEX® (darifenacin)

Extended-release tablets

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE

ENABLEX® (darifenacin) extended-release tablets are indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.

CONTRAINDICATIONS

ENABLEX® (darifenacin) extended-release tablets are contraindicated in patients with urinary retention, gastric retention or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions. ENABLEX is also contraindicated in patients with known hypersensitivity to the drug or its ingredients.

PRECAUTIONS

General

Risk of Urinary Retention

ENABLEX® (darifenacin) extended-release tablets should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Decreased Gastrointestinal Motility

ENABLEX should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention. ENABLEX, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as severe constipation, ulcerative colitis, and myasthenia gravis.

Controlled Narrow-Angle Glaucoma

ENABLEX should be used with caution in patients being treated for narrow-angle glaucoma and only where the potential benefits outweigh the risks.

Patients with Hepatic Impairment

There are no dosing adjustments for patients with mild hepatic impairment. The daily dose of ENABLEX should not exceed 7.5 mg for patients with moderate hepatic impairment. ENABLEX has not been studied in patients with severe hepatic impairment and therefore is not recommended for use in this patient population (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations and DOSAGE AND ADMINISTRATION in the full prescribing information).

Information for Patients

Patients should be informed that anticholinergic agents, such as ENABLEX, may produce clinically significant adverse effects related to anticholinergic pharmacological activity including constipation, urinary retention and blurred vision. Heat prostration (due to decreased sweating) can occur when anticholinergics such as ENABLEX are used in a hot environment. Because anticholinergics, such as ENABLEX, may produce dizziness or blurred vision, patients should be advised to exercise caution in decisions to engage in potentially dangerous activities until the drug's effects have been determined. Patients should read the patient information leaflet before starting therapy with ENABLEX.

ENABLEX extended-release tablets should be taken once daily with liquid. They may be taken with or without food, and should be swallowed whole and not chewed, divided or crushed.

Drug Interactions

The daily dose of ENABLEX should not exceed 7.5 mg when coadministered with potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, neflavir, clarithromycin and nefazadone) (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in the full prescribing information).

Caution should be taken when ENABLEX is used concomitantly with medications that are predominantly metabolized by CYP2D6 and which have a narrow therapeutic window, such as flecainide, thioridazine and tricyclic antidepressants (see CLINICAL PHARMACOLOGY in the full prescribing information).

The concomitant use of ENABLEX with other anticholinergic agents may increase the frequency and/or severity of dry mouth, constipation, blurred vision and other anticholinergic pharmacological effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to effects on gastrointestinal motility.

Drug Laboratory Test Interactions

Interactions between darifenacin and laboratory tests have not been studied.

Carcinogenesis/Mutagenesis/Impairment of Fertility

Carcinogenicity studies with darifenacin were conducted in mice and rats. No evidence of drug-related carcinogenicity was revealed in a 24-month study in mice at dietary doses up to 100 mg/kg/day or approximately 32 times the estimated human-free AUC₀₋₂₄ reached with 15 mg, the maximum recommended human dose (AUC at MRHD) and in a 24-month study in rats at doses up to 15 mg/kg/day or up to approximately 12 times the AUC at MRHD in female rats and approximately eight times the AUC at MRHD in male rats.

Darifenacin was not mutagenic in the bacterial mutation assays (Ames test) and the Chinese hamster ovary assay, and not clastogenic in the human lymphocyte assay, and the *in vivo* mouse bone marrow cytogenetics assay.

There was no evidence for effects on fertility in male or female rats treated at oral doses up to 50 mg/kg/day. Exposures in this study correspond to approximately 78 times the AUC at MRHD.

Pregnancy Category C

Darifenacin was not teratogenic in rats and rabbits at doses up to 50 and 30 mg/kg/day, respectively. At the dose of 50 mg/kg in rats, there was a delay in the ossification of the sacral and caudal vertebrae which was not observed at 10 mg/kg (approximately 13 times the AUC of free plasma concentration at MRHD). Exposure in this study at 50 mg/kg corresponds to approximately 59 times the AUC of free plasma concentration at MRHD. Dystocia was observed in dams at 10 mg/kg/day (17 times the AUC of free plasma concentration at MRHD). Slight developmental delays were observed in pups at this dose. At 3 mg/kg/day (five times the AUC of free plasma concentration at MRHD) there were no effects on dams or pups. At the dose of 30 mg/kg in rabbits, darifenacin was shown to increase post-implantation loss but not at 10 mg/kg (nine times the AUC of free plasma concentration at MRHD). Exposure to unbound drug at 30 mg/kg in this study corresponds to approximately 28 times the AUC at MRHD. In rabbits, dilated ureter and/or kidney pelvis was observed in offspring at 30 mg/kg/day and one case was observed at 10 mg/kg/day along with urinary bladder dilation consistent with pharmacological action of darifenacin. No effect was observed at 3 mg/kg/day (2.8 times the AUC of free plasma concentration at MRHD). There are no studies of darifenacin in pregnant women. Because animal reproduction studies are not always predictive of human response, ENABLEX should be used during pregnancy only if the benefit to the mother outweighs the potential risk to the fetus.

Nursing Mothers

Darifenacin is excreted into the milk of rats. It is not known whether darifenacin is excreted into human milk and therefore caution should be exercised before ENABLEX is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of ENABLEX in pediatric patients have not been established.

Geriatric Use

In the Phase III fixed-dose, placebo-controlled, clinical studies, 30% of patients treated with ENABLEX were over 65 years of age. No overall differences in safety or efficacy were observed between these patients (n=207) and younger patients <65 years (n=464). No dose adjustment is recommended for elderly patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations and CLINICAL STUDIES in the full prescribing information).

References: 1. Chapple CR, Yamanishi T, Chess-Williams R. Muscarinic receptor subtypes and management of the overactive bladder. *Urology*. 2002;60(suppl 5A):82-89. 2. Federal Interagency Forum on Aging-Related Statistics. Older Americans 2000: key indicators of well-being. August 2000. Available at: <http://www.agingstats.gov/chartbook2000/healthstatus.html#Indicator%2014>. Accessed November 4, 2004. 3. Feinberg M. The problems of anticholinergic adverse effects in older patients. *Drugs Aging*. 1993;3:335-348.

ADVERSE REACTIONS

During the clinical development of ENABLEX® (darifenacin) extended-release tablets, a total of 7,363 patients and volunteers were treated with doses of darifenacin from 3.75 mg to 75 mg once daily.

The safety of ENABLEX was evaluated in Phase II and III controlled clinical trials in a total of 8,830 patients, 6,001 of whom were treated with ENABLEX. Of this total, 1,069 patients participated in three, 12-week, Phase III, fixed-dose efficacy and safety studies. Of this total, 337 and 334 patients received ENABLEX 7.5 mg daily and 15 mg daily, respectively. In all long-term trials combined, 1,216 and 672 patients received treatment with ENABLEX for at least 24 and 52 weeks, respectively.

In all placebo-controlled trials combined, the incidence of serious adverse events for 7.5 mg, 15 mg and placebo was similar.

In all fixed-dose Phase III studies combined, 3.3% of patients treated with ENABLEX discontinued due to all adverse events versus 2.6% in placebo. Dry mouth leading to study discontinuation occurred in 0%, 0.9%, and 0% of patients treated with ENABLEX 7.5 mg daily, ENABLEX 15 mg daily and placebo, respectively. Constipation leading to study discontinuation occurred in 0.6%, 1.2%, and 0.3% of patients treated with ENABLEX 7.5 mg daily, ENABLEX 15 mg daily and placebo, respectively.

Table 4 lists the adverse events reported (regardless of causality) in 2% or more of patients treated with 7.5-mg or 15-mg ENABLEX extended-release tablets and greater than placebo in the three, fixed-dose, placebo-controlled Phase III studies (Studies 1, 2 and 3). Adverse events were reported by 54% and 66% of patients receiving 7.5 mg and 15 mg once-daily ENABLEX extended-release tablets, respectively, and by 49% of patients receiving placebo. In these studies, the most frequently reported adverse events were dry mouth and constipation. The majority of adverse events in ENABLEX-treated subjects were mild or moderate in severity and most occurred during the first two weeks of treatment.

Table 4
Incidence of Adverse Events* Reported in 2.0% of Patients Treated with ENABLEX® Extended-Release Tablets and More Frequent with ENABLEX® than with Placebo in Three, Fixed-Dose, Placebo-Controlled, Phase III Studies (Studies 1, 2, and 3)

Body System	Adverse Event	Percentage of Subjects with Adverse Event (%)		
		ENABLEX® 7.5 mg N = 337	ENABLEX® 15 mg N = 334	Placebo N = 388
Digestive	Dry Mouth	20.2	35.3	8.2
	Constipation	14.8	21.3	6.2
	Dyspepsia	2.7	8.4	2.6
	Abdominal Pain	2.4	3.9	0.5
	Nausea	2.7	1.5	1.5
Urogenital	Diarrhea	2.1	0.9	1.8
	Urinary Tract Infection	4.7	4.5	2.6
Nervous	Dizziness	0.9	2.1	1.3
	Body as a Whole	1.5	2.7	1.3
Eye	Asthenia	1.5	2.1	1.3
	Dry Eyes	1.5	2.1	0.5

*Regardless of causality

Other adverse events reported, regardless of causality, by 1% of ENABLEX patients in either the 7.5 mg or 15 mg once-daily darifenacin-dose groups in these fixed-dose, placebo-controlled Phase III studies include: abnormal vision, accidental injury, back pain, dry skin, flu syndrome, pain, hypertension, vomiting, peripheral edema, weight gain, arthralgia, bronchitis, pharyngitis, rhinitis, sinusitis, rash, pruritus, urinary tract disorder and vaginitis.

Study 4 was a 12-week, placebo-controlled, dose-titration regimen study in which ENABLEX was administered in accordance with dosing recommendations (see DOSAGE AND ADMINISTRATION in the full prescribing information). All patients initially received placebo or ENABLEX 7.5 mg daily, and after two weeks, patients and physicians were allowed to adjust upward to ENABLEX 15 mg if needed. In this study, the most commonly reported adverse events were also constipation and dry mouth. The incidence of discontinuation due to all adverse events was 3.1% and 6.7% for placebo and for ENABLEX, respectively. Table 5 lists the adverse events (regardless of causality) reported in >3% of patients treated with ENABLEX extended-release tablets and greater than placebo.

Table 5
Number (%) of Adverse Events* Reported in >3% of Patients Treated with ENABLEX® Extended-Release Tablets, and More Frequent with ENABLEX® than Placebo, in the Placebo-Controlled, Dose-Titration, Phase III Study (Study 4)

Adverse Event	ENABLEX® 7.5 mg/15 mg N = 268	Placebo N = 127
Constipation	56 (20.9%)	10 (7.9%)
Dry Mouth	50 (18.7%)	11 (8.7%)
Headache	18 (6.7%)	7 (5.5%)
Dyspepsia	12 (4.5%)	2 (1.6%)
Nausea	11 (4.1%)	2 (1.6%)
Urinary Tract Infection	10 (3.7%)	4 (3.1%)
Accidental Injury	8 (3.0%)	3 (2.4%)
Flu Syndrome	8 (3.0%)	3 (2.4%)

*Regardless of causality

Acute urinary retention (AUR) requiring treatment was reported in a total of 16 patients in the ENABLEX Phase I-III clinical trials. Of these 16 cases, seven were reported as serious adverse events, including one patient with detrusor hyperreflexia secondary to a stroke, one patient with benign prostatic hypertrophy (BPH), one patient with irritable bowel syndrome (IBS) and four OAB patients taking darifenacin 30 mg daily. Of the remaining nine cases, none were reported as serious adverse events. Three occurred in OAB patients taking the recommended doses, and two of these required bladder catheterization for 1-2 days.

Constipation was reported as a serious adverse event in six patients in the ENABLEX Phase I-III clinical trials, including one patient with benign prostatic hypertrophy (BPH), one OAB patient taking darifenacin 30 mg daily, and only one OAB patient taking the recommended doses. The latter patient was hospitalized for investigation with colonoscopy after reporting nine months of chronic constipation that was reported as being moderate in severity.

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light.

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