Monotherapy Option for Type 2 Diabetes Patients

Muraglitazar effectively lowered hemoglobin A_{1c} and triglycerides while raising HDL cholesterol levels.

BY MIRIAM E. TUCKER
Senior Writer

WASHINGTON — Muraglitazar, a novel agent targeting both glucose and lipid levels, is an effective monotherapy option for patients with type 2 diabetes, Robert Frederich, M.D., and his associates reported at the annual meeting of the American Association of Clinical Endocrinologists.

In the first phase III data to be released by comarketers Bristol-Myers Squibb Co. and Merck & Co., muraglitazar effectively lowered hemoglobin A_{1c} and triglycerides and raised HDL cholesterol levels in a 24-week, randomized, double-blind, placebo-controlled trial of drug-naive adults with type 2 diabetes who were inadequately controlled with diet and exercise alone, said Dr. Frederich, of Bristol-Myers Squibb in Princeton, N.J., and his associates.

The New Drug Application for muraglitazar is under review by the Food and Drug Administration. If approved, the drug would be the first of the new class called "glitazars," agents that activate both α and γ peroxisome proliferator-activated receptors (PPARs).

The PPARs, members of the steroid hormone nuclear receptor family, are already established as therapeutic targets for treating diabetes and dyslipidemia: The thiazolidinedione class of glucose-lowering agents are PPAR-γ agonists, while fibrates improve lipid profiles via PPAR-α activation, Jorge Plutzky, M.D., explained at a satellite symposium sponsored by Bristol-Myers Squibb and Merck held during the AACE meeting.

"Such drugs hold out the potential for combining PPAR-α's lipid improvements, the PPAR-γ's insulin-sensitizing effects, and the possible anti-inflammatory/antiatherosclerotic effects of both receptors," said Dr. Plutzky, director of The Vascular Disease Prevention Program at Brigham and Women's Hospital, Boston.

According to AACE past president Paul Jellinger, M.D., "combo pills are becoming more common and more accepted by many [physicians] largely because of reduced copayment.

Dual PPARs may be useful because the triglyceride/HDL part of diabetic dyslipidemia often gets overlooked in favor of straight LDL lowering with statins," he told this newspaper after the meeting.

Most diabetics are already on lipid-lowering therapy, and statin therapy sometimes adequately addresses diabetic dyslipidemia, but often it does not. "On balance, I believe dual PPAR's will be a sensible and useful addition," said Dr. Jellinger, of Hollywood, Fla.

The study patients were adults aged 18-70 years who had a mean baseline hemoglobin A_{1c} between 7% and 10%. None were on antihypertensive therapy in the 4-6 weeks before the study. Therapy with a stable dose of statins was allowed through the first 12 weeks of the trial.

A total of 111 patients were randomized to receive 2.5 mg of muraglitazar daily, 114 took 5.0 mg, and 109 received placebo. In a separate open-label trial, another 109 patients with baseline A_{1c} values of 10%-12% received 5.0 mg of muraglitazar daily, Dr. Frederich and his associates reported in a poster presentation.

At 24 weeks, the mean A_{1c} values dropped from 8.02% to 6.96% (–1.05) in the 2.5-mg muraglitazar group, from 7.89% to 6.68% (–1.23) in the blinded 5.0-mg patients, and from 10.68% to 8.06% (–2.62) in the open-label 5.0-mg group. In contrast, A_{1c} levels among the placebo patients fell by an insignificant 0.32 percentage points, from 7.99% to 7.67%.

In the randomized trial, 67% of the 2.5-mg group and 74% of the 5.0-mg group achieved the American Diabetes Association's A_{1c} target of less than 7.0%, compared with 32% of the placebo patients. The proportions who dropped below the AACE's 6.5% cutoff were 58%, 36%, and 18%, respectively. Fasting plasma glucose and insulin levels also were significantly reduced in both muraglitazar dosage groups in the double-blind trial, they said.

Triglyceride levels in the double-blind trial decreased significantly by 18% with 2.5 mg of muraglitazar and by 27% with 5.0 mg, compared with just 2% for placebo. In the open-label trial, triglycerides were reduced by 31%. Among the patients with baseline triglycerides of 150 mg/dL or above, reductions at 24 weeks were 24.8% with 2.5 mg of muraglitazar, 30.4% with 5.0 mg, 13.2% with placebo, and 31% in the open-label trial with 5.0 mg.

Mean HDL cholesterol levels rose by 10% and 16% with 2.5 mg and 5.0 mg of muraglitazar, respectively, in the blinded trial, both significant increases compared with the 2% rise with placebo. Levels of LDL cholesterol didn't change significantly with muraglitazar, but levels of apolipoprotein B, free fatty acid, and non-HDL cholesterol did, Dr. Frederich and his associates reported.

Adverse events occurred in 71% of patients with 2.5 mg of muraglitazar, 77% with 5.0 mg, 69% with placebo, and 70% in the open-label 5.0-mg group, with serious adverse events in 3%-4% of all groups with no significant differences between them. There were no cases of heart failure.

Edema-related events occurred in 8% with 2.5 mg, 11% with 5.0 mg, 8% with placebo, and 9% in the open-label group. All events in the muraglitazar patients were mild to moderate, while one placebo patient experienced serious edema. No patient treated with muraglitazar discontinued the study due to edema, but two placebo patients did.

There were no confirmed cases of glucose values at or below 50 mg/dL, and no patient dropped out of the study due to hypoglycemia. Mean change in body weight from baseline were gains of 1.1 kg in the 2.5-mg muraglitazar group and 2.1 kg with 5.0 mg, while the placebo group lost a mean of 0.8 kg. The open-label patients gained 2.9 kg.

Adverse events led to discontinuation of the study in 3%-4% of all muraglitazar groups and the placebo group, while rates of discontinuation due to lack of efficacy in the double-blind patients were 8% for 2.5 mg and 6% for 5.0 mg, compared with 23% for placebo. ■

Little Data About Androgens In Postmenopausal Women

BY DOUG BRUNK
San Diego Bureau

LOS ANGELES — Despite growing interest in the use of androgens among postmenopausal women, there are few clinical data about their efficacy for this population of patients, Carol Havens, M.D., said at the annual meeting of the California Academy of Family Physicians.

"My patients are coming into me all the time with stuff off the Internet or out of magazines such as Ladies' Home Journal and People, promoting the use of androgens for impotence in women, mostly for libido," said Dr. Havens, a family physician who is director of clinical education for Kaiser Permanente's Northern California region. "There is lots of information out there in the lay press but very little in the medical press. Very few trials have actually been done. There's very little we actually know."

'Contrary to popular belief, androgen levels don't suddenly go down at the time of menopause like estrogen levels do. They actually decrease gradually.'

The theory behind androgen replacement is that androgen deficiency causes clinical symptoms such as dysphoria, fatigue, and low sex drive. However, androgen levels in women are highly variable, and they're not clearly linked to such symptoms, she said.

"Contrary to popular belief, androgen levels don't suddenly go down at the time of menopause like estrogen levels do. They actually decrease gradually," explained Dr. Havens, who also chairs the California Medical Association's Committee on CME. "The androgen level of a woman at the age of 50 is about half that of a woman at the age of 25."

Estratest is the only androgen-replacement preparation approved for women in the United States. It contains 0.625/1.25-mg esterified estrogen plus 1.25/2.5-mg methyltestosterone.

Transdermal androgen patches are not appropriately dosed for women. In fact, it's difficult to accurately measure testosterone in women because most of the assays were developed to test men.

"The available assays lack the sensitivity to be able to accurately measure the lower testosterone levels that are found in women," Dr. Havens said. "The other problem is that testosterone is highly bound to sex hormone–binding globulin and albumin. In women, 1% or less of total testosterone is actually available as free testosterone, which is the biologically active one. The free testosterone index is the test that's been widely advertised as being the most reliable, but your lab may not be able to give you an accurate level of free testosterone."

Key indications for androgen replacement in postmenopausal women with clinical symptoms of androgen deficiency include adequate estrogen status and having free testosterone levels at or below the lowest quartile for reproductive age. "The objective of replacement is to restore their testosterone levels to that of the mid-range for that of healthy young women," she said.

The effect of androgens on coronary heart disease is unknown, but oral androgens decrease HDL cholesterol (by up to 20%), LDL cholesterol, and triglycerides. "So they could have a significant effect on lipids," she noted.

Transdermal androgens, on the other hand, do not appear to affect lipid levels.

Estrogenic effects of androgens may include vaginal bleeding, endometrial hyperplasia, and the stimulation of breast epithelium, but there are no reports of direct links to breast or endometrial cancer.

Androgens appear to increase bone mineral density, but they have an unclear effect on fracture rate, muscle performance, and physical function. They also do not decrease visceral fat. "This is the opposite of what happens in men," Dr. Havens said. "Androgens in women may actually increase visceral fat."

As for the effect on sexuality, testosterone levels are not well correlated with libido in women, "although women who take testosterone do report an increase in libido and sexual activity," she noted. "The increase in sexual activity is pretty limited."

Other effects may include increases in erythropoiesis, hostility, hirsutism, and acne. (The transdermal form does not seem to affect hirsutism or acne.)

Pregnant and lactating women should not take androgens, nor should those with breast or endometrial cancer or polycythemia. Relative contraindications include moderate to severe acne, moderate to severe hirsutism, androgenic alopecia, and severe insulin resistance.

If you start postmenopausal women on androgens, ask them about their symptoms, and do follow-up lipid tests, liver function tests, and hemoglobin tests, Dr. Havens said. ■