Exenatide Plus Metformin Aids Ovulation in PCOS

BY MIRIAM E. TUCKER Senior Writer

ROME — Treatment of polycystic ovary syndrome with exenatide plus metformin was more effective than either medication alone in improving menstrual cycle frequency and in ameliorating hormonal and metabolic derangements, a study has found.

The study findings were presented at the annual meeting of the European Association for the Study of Diabetes by Dr. Ted Okerson of Amylin Pharmaceuticals Inc. on behalf of the scheduled presenter, Dr. Rajat Bhushan of the Metabolic Center of Louisiana Research Foundation, Baton Rouge, who was unable to attend the meeting because of a hurricane. Dr. Karen Elkind-Hirsch of the same institution was the principal author of the study, which was published in the Journal of Clinical Endocrinology and Metabolism (2008;93: 2670-8).

Metformin has been shown to reduce insulin resistance and androgen levels while increasing ovulation in women with polycystic ovary syndrome (PCOS). However, metformin does not alter insulin secretion. Exenatide (Byetta), used to treat type 2 diabetes, has been shown to restore first- and second-phase insulin secretion, which is attenuated in women with PCOS, as well as promote weight loss, thereby potentially further improving insulin sensitivity, Dr. Okerson said.

An open-label, prospective 24-week pilot study of 60 obese oligo-ovulatory women with PCOS was funded by a grant from Amylin Pharmaceuticals and Eli Lilly & Co. In the study, 40 white and 20 African American women with PCOS were randomized to receive either 1,000 mg metformin twice daily, exenatide 10 mcg twice daily, or a combination of the two, for 24 weeks. All were aged 18-40, with a body mass index above 27 kg/m² and six or fewer menses per year. Forty-two patients (14 in each group) complet- ed the study, with equal racial distribution across groups.

Menstrual cycle frequency, the primary study end point, was significantly increased in all treatment groups at 24 weeks and to a significantly greater degree with the combination, compared with metformin alone. The proportion of normal cycles in the group increased from a mean of 22% at baseline to 57% with exenatide alone, from 21% to 49% with metformin alone, and from 29% to 83% with both drugs. Ovulatory rates also improved with all three regimens, but significantly more so with the combination. Ovulation occurred in 12 of the combination patients (86%), compared with 7 who received exenatide alone (50%) and 4 (29%) with metformin alone.

Body weight changes were significant in both groups receiving exenatide, but not in those receiving metformin alone. At 24 weeks, mean weight loss was 6 kg in the combination group and 3.2 kg with exenatide alone, vs. just 1.6 kg with metformin alone. Similar reductions were seen in body mass index. Abdominal girth diminished slightly in both exenatide groups but increased slightly between weeks 12 and 24 among the metformin-alone patients, Dr. Okerson reported.

Total testosterone was significantly decreased from baseline in all treatment groups, by 10.2 ng/dL with exenatide alone, 3.6 ng/dL with metformin alone, and 18.4 ng/dL with the combination. The free androgen index was significantly more reduced with the combination, compared with metformin alone but not compared with exenatide alone. Levels of sex hormone–binding globulin were increased, but not significantly, with all treatments, while levels of dehydroepiandrostosterone sulfate and thyroid-stimulating hormone were not significantly altered in any group.

Insulin sensitivity improved significantly with all treatments, and was significantly higher in the combination group than in the metformin group at 24 weeks. After therapy, the calculated mean insulin secretion sensitivity index was 516 with combination therapy, 395 with exenatide alone, and 212 with metformin alone. Total cholesterol and triglycerides decreased significantly with combination therapy vs. metformin monotherapy, which did not consistently improve those levels, while HDL and LDL cholesterol levels did not change significantly with treatment. Adiponectin levels increased significantly with all treatments, while other inflammatory markers did not change.

Testosterone Patch Boosts Sex In Women, but Safety Is Issue

BY MARY ANN MOON Contributing Writer

The testosterone patch improves sexual function in postmenopausal women who have hypoactive sexual desire disorder, but the patch’s long-term safety needs to be studied, according to a report.

The improvement in frequency of satisfying sexual episodes was “numerically modest,” at 1.4 more such episodes per month, but this amount has been shown to be clinically meaningful in previous studies, said Dr. Susan R. Davis of Monash University, Prahran, Victoria, Australia, and her associates.

This is the first large-scale, phase III clinical trial of testosterone therapy that involved postmenopausal women who were not taking concomitant estrogen.

Testosterone without concomitant estrogen may have adverse effects on the breast and endometrium.

In this study, four cases of breast cancer occurred in women on active treatment, compared with no cases in women taking placebo, and vaginal bleeding also was significantly more common with active treatment.

The study involved women aged 20-70 years who had surgically induced menopause at least one year’s duration, and women aged 40-70 years who had natural menopause of at least 2 years’ duration. The women all had hypoactive sexual desire and were treated at 65 medical centers in the United States, Canada, Australia, the United Kingdom, and Sweden between 2004 and 2006 (N. Engl. J. Med. 2008;359:2005-17).

The study was sponsored by Procter & Gamble Pharmaceuticals Inc., which also was involved in study design and data collection, and conducted the data analysis. Procter & Gamble makes Intrinsa, a testosterone patch that has been approved by the European Medicines Agency for treatment of hypoactive sexual desire.

A Food and Drug Administration advisory committee recommended against approval of the drug for the U.S. market in 2004.

In the study, 814 women were randomly assigned to use a 150-mcg testosterone patch, a 300-mcg testosterone patch, or a placebo patch every day for 1 year.

The efficacy analysis was performed at 24 weeks, after which the effect of testosterone tends to plateau; the safety analy- sis was performed at 1 year. A total of 71% of the women completed 24 weeks, and 57% completed the full year.

Compared with the placebo group, both groups on active treatment report- ed significant increases in sexual desire and frequency of satisfying sexual episodes, as well as decreases in personal distress related to sexual function.

The overall incidence of adverse ef- fects was similar among the three groups.

The most common reasons for withdrawal from the study were patch-site re- actions and androgenic events, princi- pally the growth of facial hair.

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