Topical Tamoxifen Promising for Mastalgia

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — Afimoxifene, a novel tamoxifen gel applied directly to the breasts, performed favorably as topical therapy for moderate to severe cyclic mastalgia in premenopausal women in a phase II clinical trial.

Although the topical antiestrogen's developer, ASCEND Therapeutics Inc., plans to seek an initial indication for cyclic mastalgia, there also is strong interest in developing afimoxifene as a treatment for male gynecomastia as well as for breast cancer chemoprevention, Dr. Amit Goyal said at the San Antonio Breast Cancer Symposium.

Afimoxifene is 4-hydroxytamoxifen, a potent metabolite of tamoxifen, in a proprietary hydroalcoholic gel. Its binding affinity for the alpha– and beta–estrogen receptors is two- to threefold greater than that of estradiol, explained Dr. Goyal, of Cardiff (Wales) University.

Oral tamoxifen, bromocriptine, danazol, and progestins have demonstrated efficacy in treating cyclic mastalgia; however, their systemic side effects render them poorly suited for long-term treatment of a chronic problem. In contrast, transdermal afimoxifene is highly effective within the breast yet has very low systemic levels, thus reducing the risk of systemic toxicities, he continued.

After 4 cycles, pain intensity was 64% lower in women on afimoxifene than in the placebo group.

DR. GOYAL

In a pharmacokinetic study, 16 healthy premenopausal women applied 4 mg of afimoxifene to their breasts daily for 21 days. At steady state, achieved after 2 weeks of therapy, mean plasma 4-hydroxytamoxifen levels were just 1/18 of those measured in 19 healthy controls taking 20 mg/day of oral tamoxifen.

Based upon those encouraging findings, Dr. Goyal and colleagues next carried out the phase II trial involving 127 premenopausal women with moderate to severe cyclic mastalgia. They were randomized to placebo or either 2 mg or 4 mg of afimoxifene daily for 4 menstrual cycles.

Significant differences in efficacy between the 4-mg dose and placebo were documented after 2 cycles. After 4 cycles, mean pain intensity measured on a visual analog scale for the 7 worst days per cycle was 64% lower in women on 4 mg/day of afimoxifene than in the placebo group. Physician global assessments of breast nodularity and tenderness showed reductions of 70% and 67%, respectively, relative to placebo. The 2-mg dose showed less robust albeit favorable trends on all end points, he continued.

In an interview, Dr. Goyal said he has had some success in using oral tamoxifen in men with gynecomastia. He plans to study topical afimoxifene for this condition in a placebo-controlled trial.

Prevention of breast cancer is an exciting potential application for the topical selective estrogen-receptor modulator.

"The main reason why some women and some physicians are reluctant to use oral tamoxifen, even though we know from [a previous] study that it works, is because of side effects. If we can show afimoxifene works to prevent breast cancer as well as oral tamoxifen, I think that would be an important advance," Dr. Goyal said.

The mastalgia trial was supported by ASCEND Therapeutics. Dr. Goyal indicated he has received research funds from the company but has no other financial involvement with ASCEND. ■

Inflammatory Bowel Disease May Speed Ovarian Follicle Loss

SAN FRANCISCO — Inflammatory bowel disease does not severely alter ovarian reserve but may accelerate loss of primordial follicles in those aged 30 years and older, study results showed.

The investigators measured anti-müllerian hormone—a reliable hormonal marker for evaluating ovarian reserve independently of the menstrual cycle—in 44 women aged 20-41 years who had IBD and were in clinical remission after infliximab treatment for either Crohn's disease (37 patients) or ulcerative colitis (7 patients).

The hormone levels were compared with those of 163 age-matched women undergoing in vitro fertilization who had a normal ovarian response to controlled ovarian stimulation (5-15 oocytes retrieved) and a normal serum anti-müllerian hormone level (>1.5 mcg/L).

The anti-müllerian hormone levels did not differ significantly overall between the IBD and control patients (2.72 vs. 2.12 mcg/L), Dr. Thomas Fréour reported in a poster at the annual meeting of the American Society for Reproductive Medicine.

However, when the women were stratified by age 30 years and older vs. age less than 30 years, the anti-müllerian hormone levels were found to differ in the older women, with those aged 30 years and older having lower levels than controls (2 vs. 2.96 mcg/L). The levels in the younger patients remained comparable in the patients and controls, said Dr. Fréour of the University Hospital Center of Nantes (France).

Inflammatory bowel disease has been shown in previous studies to be associated with female subfertility, mainly through tubal dysfunctions, extensive adhesions, or chirurgical consequences on pelvic function, but alteration of ovarian reserve in those with IBD had not been previously studied, Dr. Fréour noted.

The findings suggest that in reproductive age women 30 years and older who have IBD, a substantially accelerated loss of primordial follicles may occur. This loss might be due to chronic inflammation or to IBD treatments, he noted.

—Sharon Worcester

BMI Greater Than 25 May Increase Risk of Miscarriage of a Normal Fetus

BY SHARON WORCESTER
Southeast Bureau

SAN FRANCISCO — The risk of miscarriage of a genetically normal fetus is significantly increased in overweight women, compared with normal weight women, the findings of a retrospective case-control study of 204 miscarriages suggest.

The rate of euploid miscarriage among 204 first trimester missed abortions that occurred between 1999 and 2008 in women at a single center was 53% in those with a body mass index of 25 or greater, compared with 37% in those with a BMI of less than 25. The difference was statistically significant, Dr. Innes V. Landres reported at the annual meeting of the American Society for Reproductive Medicine.

The mean age of the women in both groups was the same (34 years). Those over age 39 years were excluded because of the increased risk of miscarriage in women with advanced maternal age, noted Dr. Landres, a chief resident in obstetrics and gynecology at Stanford (Calif.) University.

The groups also were similar in types of assisted reproductive technologies used and in pregnancy history.

The study was undertaken to explore the cytogenetic results of miscarriages in relation to maternal weight and insulin resistance, Dr. Landres explained.

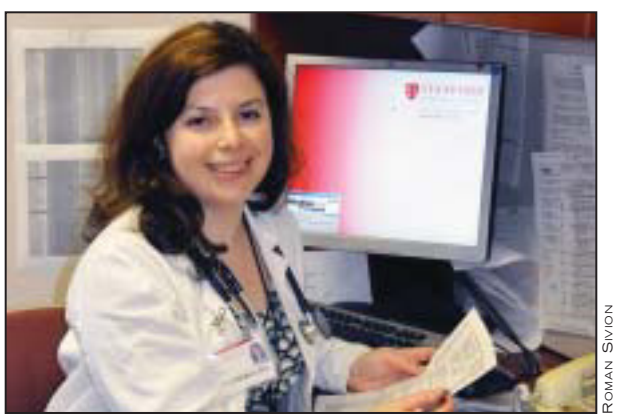
Both obesity and insulin resistance have been linked with spontaneous abortion and recurrent pregnancy loss. Most spontaneous abortions are a result of fetal aneuploidy, as was the case in 59% of patients overall in this study—67% in those over age 34 years, and 50% in those 34 years and younger. There is some evidence, however, that obesity predisposes women to euploid miscarriage, and that there is an increased rate of spontaneous abortion even among obese women with ovum donation.

For the current study, the medical records of women with first trimester missed abortion, subsequent dilation and curettage, and karyotype analysis of the products of conception were reviewed. Among the patients excluded—other than those older than 39 years—were those patients with a history of diabetes, those using steroids or narcotics, and those with donor eggs or preimplantation genetic diagnosis.

In addition to an increase in euploid miscarriage risk based on BMI, a trend toward increased risk among women with polycystic ovary syndrome, compared with those without PCOS, was observed (48% vs. 39%, respectively), but the difference did not reach statistical significance. Also, no significant differences in euploid miscarriage were seen based on insulin resistance status. However, because all but one of the women with insulin resistance were on insulin-lowering therapy at the time of conception, the conclusions in these populations are limited, Dr. Landres noted.

The findings, which suggest that BMI over 25 is a risk factor for euploid miscarriage, are important, given the fact that BMI (unlike age) is a modifiable risk factor. Although the study is limited by its retrospective nature, lack of power, and multiple confounders for which the investigators could not control, it is nonetheless important that elevated BMI be identified as a risk factor for euploid miscarriage, and that women with elevated BMI be counseled about the importance of lifestyle modification. Also, although more study is needed on the effects of insulin-lowering medications in this population, treatment should be considered.

Additional study of the effects of BMI on endometrial dysfunction and miscarriage rates, as well as on the effects of lifestyle modification, is needed, Dr. Landres concluded. ■



ROMAN SIVION

Elevated BMI should be seen as a risk factor for euploid miscarriage, said Dr. Innes V. Landres.