Afinoxifene Effective Therapy for Cyclic Mastalgia

BY BRUCE JANCIN
Denver Bureau

San Antonio — Topical afinoxifene proved effective for the treatment of cyclic mastalgia and also showed potential for reduction of mammographic breast density in separate phase II clinical trials presented at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Afinoxifene is a highly potent tamoxifen metabolite formulated in a topical alcohol-based gel. Applied to the breast, it avoids first-pass liver metabolism, thus resulting in high levels of the antiestrogen in target breast tissue with low systemic exposure.

The result is an agent designed to have a far quicker onset of benefit than oral tamoxifen, which is prescribed for 5 years for chemoprevention—and afinoxifene also is intended to spare women from the side effects of the parent oral drug, including increased risks of venous thromboembolism, endometrial cancer, and hot flashes.

Dr. Robert E. Mansel reported on 130 premenopausal women with a history of moderate to severe cyclic mastalgia who were randomized to 2 mg or 4 mg/day of afinoxifene or placebo for four menstrual cycles in a double-blind multicenter trial. The primary end point was change in breast pain assessed by patients on a visual analog scale from baseline through the fourth treatment cycle. The 4-mg dose significantly outperformed placebo as evidenced by a mean 32-point reduction from a baseline of 72 points on the 0-100 scale vs. reductions of 19 points with placebo and 25 points with 2 mg/day of afinoxifene.

The 4-mg dose also outperformed placebo in the secondary end points of blinded physician-assessed breast pain, nodularity, and tenderness, with 67%-70% reductions being recorded relative to placebo in each of these domains, added Dr. Mansel, who is professor and chairman of the department of surgery at the University of Wales, Cardiff.

Rates of hot flashes, night sweats, and nipple discharge were similar in the three groups. Application site skin reactions occurred in 4% of women on 4 mg/day of the topical antiestrogen. Menses duration, cycle length, and estrogen and progesterone levels were unaffected in the three study arms. Mastalgia is experienced by an estimated 8 million premenopausal American women for at least 2 weeks during their menstrual cycles. There are at present no approved treatments, Dr. Mansel noted.

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DR. MANSEL

Dr. Jennifer A. Harvey reported on 61 premenopausal women with 50%-80% breast tissue density and 19 with greater than 80% breast density on a screening digital mammogram performed within the prior 42 days who were randomized to 2 mg/day of afinoxifene or placebo in a double-blind study.

Mammographic breast density in the 80% range has been shown to be a biomarker conferring a four- to fivefold increased risk of developing cancer. But unlike many breast cancer risk factors, such as age, family history, and early age at menarche, breast density is modifiable. Radiodense glandular epithelium and connective tissue also interferes with early diagnosis of breast cancer by hiding mammographic abnormalities, said Dr. Harvey of the University of Virginia Charlottesville.

Results of the trial were mixed: Five of 32 afinoxifene-treated patients and 0 of 29 placebo-treated patients with 50%-80% baseline mammographic breast density showed at least a 10% reduction in density after 4 months, but there was no significant difference between the two study arms at 6 months. None of the 19 patients with greater than 80% baseline breast density showed a 10% improvement at 4 months. In light of the success of 4 mg but not 2 mg/day of afinoxifene in the mastalgia trial, more breast density reduction studies with the higher dosage are planned.

An intriguing finding was that four of five afinoxifene responders were younger than 40 years, suggesting afinoxifene may have potential as a chemopreventive agent in young high-risk women who avoid oral tamoxifen because of side effects.

The trials were sponsored by Ascend Therapeutics. ■

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