Topical Tamoxifen Benefits Cyclic 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 highly 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, a surgical oncologist at 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.

Transdermal afimoxifene is highly effective within the breast yet has very low systemic levels.

DR. GOYAL

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.

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 his coinvestigators 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 four menstrual cycles.

Significant differences in efficacy between the 4-mg dose and placebo were documented after two cycles.

After four 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, a condition for which the only established therapy at present is surgery.

Dr. Goyal said he plans to study topical afimoxifene for this condition in a placebo-controlled trial.

Chemoprevention of breast cancer is a particularly 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 the National Surgical Adjuvant Breast and Bowel Project 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.

That will require a large, lengthy, and costly phase III clinical trial, he noted.

The mastalgia trial was supported by ASCEND Therapeutics.

Dr. Goyal indicated that he has received research funds from the company but has no other financial involvement with ASCEND. ■