In Search of the Perfect SERM: Beyond Tamoxifen and Raloxifene

Never mind this spring's excitement over tamoxifen and raloxifene; they're just forerunners of designer estrogens to come. Second generation compounds are already in clinical trials. And with growing knowledge of how the estrogen receptor works, researchers say that new synthetic estrogens — known as selective estrogen receptor modulators or SERMs — will certainly be entering drug company pipelines over the next decade.

That long view may have been temporarily obscured by headlines emerging last month from the annual meeting of the American Society of Clinical Oncology in Los Angeles, where the two SERMs now on the market, tamoxifen (Nolvadex®) and raloxifene (Evista®), seemed to be competing stars.

Both drugs had slots at the plenary session and at an official ASCO press briefing. Reporting on tamoxifen was D. Lawrence Wickerham, M.D., associate director of the National Surgical Adjuvant Breast and Bowel Project, which conducted the Breast Cancer Prevention Trial. That trial showed that tamoxifen lowered the risk of breast cancer by 45% percent in high-risk women, compared to a placebo (see News, May 6, 1998). Both emphasized that the tamoxifen findings were based on mature, long-term data. In contrast, they said, much more research was needed on Indianapolis-based Eli Lilly's raloxifene before it could be recommended for the prevention of breast cancer.

For raloxifene, Steven Cummings, M.D., from the University of California at San Francisco, presented early data on the drug's ability to prevent breast cancer. After 2 years of follow-up among post-menopausal women taking it for osteoporosis, raloxifene appeared to lower the risk of breast cancer by 58% to 66% compared to a placebo. Moreover, it has so far not appeared to increase the risk of endometrial cancer, which is one of the drawbacks of tamoxifen.

The two SERMs are destined to meet head-to-head in a second breast cancer prevention trial, which will probably start recruiting patients this fall, according to Wickerham. The Study of Tamoxifen and Raloxifene (STAR) will enroll about 22,000 post-menopausal women who will be randomly assigned to receive either one drug or the other, he added.

While tamoxifen-versus-raloxifene may have been the issue of the week, other ASCO speakers made it clear that eventually there should be more to the SERM story. "The perfect SERM... has not yet been developed," said C. Kent Osborne, M.D., of the University of Texas Health Science Center in San Antonio, the discussant for both the tamoxifen and raloxifene presentations. He added that "modern drug discovery techniques offer promise for its synthesis."

The perfect SERM would be a compound that acts as a potent anti-estrogen in the breast and uterus to prevent estrogen-driven cell proliferation and, at the same time, has strong estrogenic effects in bone, the cardiovascular system, and the central nervous system, where hormones can help prevent a variety of post-menopausal conditions.

Second Generation

It is not clear that anything approaching the perfect SERM is now in the pipeline, but a second generation of synthetic estrogens, most of them variations on tamoxifen and raloxifene, are in development.

At Eli Lilly, for instance, drug designers have taken raloxifene's structure as a starting point and are developing a variation that they call SERM III. Their aim, said Dalil Dhingra, M.D., an oncologist and clinical research physician at Lilly, is to optimize the drug's anti-estrogen effects in breast and endometrial tissue.

So far, in preclinical data, the compound does look like a more potent anti-estrogen than raloxifene, Dhingra said. In the clinic, two trials with SERM III are just getting under way; one is a phase II
breast cancer treatment trial and one an early trial of the drug's ability to prevent breast cancer. Lilly is also planning a trial of SERM III to prevent osteoporosis.

**Perhaps a Preventive**

Another synthetic estrogen in the pipeline is droloxifene, being developed by Pfizer, Inc., New York City. The company originally envisioned droloxifene as a therapeutic drug in breast cancer, but interim data from a phase III trial was discouraging, showing that droloxifene "offered no benefit beyond the current therapy," according to Brian McGlynn, director of corporate media relations.

Pfizer had originally planned to file a New Drug Application for droloxifene with the Food and Drug Administration this year. Now it has dropped that plan, McGlynn said, and decided instead to evaluate droloxifene in the prevention of breast cancer and to accelerate development efforts in osteoporosis, where the data are more promising.

A third SERM in clinical trials is SmithKline Beecham's idoxifene, also designed as a variation on existing SERMs. It is now in a phase III trial for the prevention of osteoporosis and a phase II trial for the treatment of advanced breast cancer. The Philadelphia-based company says idoxifene appears to be estrogenic in bone and anti-estrogenic in the breast, and so far does not increase the risk of endometrial hyperplasia.

If SERM III, droloxifene, idoxifene, and other tamoxifen-like drugs are considered second-generation SERMs, what will the third generation be like?

"A fundamental change" is needed, said Donald P. McDonnell, Ph.D., a Duke University investigator who has been working on preclinical studies of a SERM called GW5638. (If GW5638 works out in clinical trials, it could offer an option for tamoxifen-resistant cancers, McDonnell said, but it too is basically a variation on current SERMs.)

The next generation of SERMs should be based on new knowledge about estrogen and estrogen receptor biology, McDonnell said, and that is turning out to be much more complex than once thought. For one thing, the different ligands, whether natural estrogens or SERMs, appear to interact with the receptor in different ways.

Knowing the intricacies of those interactions could help in designing new SERMs. For example, recent research using crystallography has clarified the way in which raloxifene and estradiol interact with the estrogen receptor. As Jordan points out in this issue (page 967), that knowledge has provided insight into the mechanisms of anti-estrogenic activity.

But SERM-receptor interactions are not the only events that need to be understood. There are a bevy of other molecules that get involved in a cell's response to estrogen. For instance, scientists recently discovered that there are actually two estrogen receptors, alpha and beta, that occur in different quantities in different cells and tissues. And, as Osborne pointed out, there are at least 20 different receptor interacting proteins that bind to the estrogen receptors and function either as co-activators to enhance estrogen's effect or as co-repressors to inhibit it.

"The estrogen receptor does not work in a vacuum," said McDonnell, speaking at a symposium last March in Chantilly, Va. "It has lots of dancing partners."

And that's not all. There are probably more than 50 transcription activating factors, TAFs, that interact to regulate the effects of estrogen on its target genes. Also at the DNA level, response elements in the promoter regions of the target genes may be involved in the complex process that determines what effect a given SERM will have on tissues.

"Many biologists now feel it is the particular ensemble of ligands, receptors, receptor interacting proteins, and response elements, that determine whether there will be a predominantly agonist or antagonist signal on a given tissue or gene," said Osborne. One of the challenges facing the designers of third-generation SERMs will be defining the workings of these ensembles and developing drugs that target them.

**Multiple Options**

The third-generation drugs that emerge from this process may be some years away. But the intense interest in SERMs makes it seem certain that eventually clinicians can expect to have an increasing number of options.

"It will be like antibiotics," said Jordan, envisioning a time when there will be many more than two SERMs on the market. In an interview at ASCO, he compared tamoxifen and raloxifene to penicillin, which over the years has been joined by a host of other antibiotics, each with its own indications. One SERM is not necessarily going to replace another, he predicted. Instead, "there will be a menu of options for specific subsets of patients."

— Caroline McNeil