Third-Generation SERMs May Face Uphill Battle

By Charlie Schmidt

Lasofoxifene, a third-generation selective estrogen receptor modulator (SERM), has emerged from the phase III PEARL trial with what could be considered flying colors. Compared with placebo, the drug reduced breast cancer risk in postmenopausal women with osteoporosis as effectively as first-generation tamoxifen and second-generation raloxifene, prevented more kinds of fractures than raloxifene, and did not raise the risk of endometrial cancer like tamoxifen. As reported in this issue of the Journal, lasofoxifene was particularly effective in reducing risk in higher-risk women and those with high estradiol levels.

But don’t look for lasofoxifene as an immediate option in breast cancer chemoprevention. The drug, made by Pfizer, has approval in Europe, but only as an osteoporosis treatment. In the U.S., the company has withdrawn its application to the Food and Drug Administration despite the PEARL trial results. According to its most recent filing with the Securities and Exchange Commission, in August, Pfizer is now “exploring strategic options for [lasofoxifene], including but not limited to out-licensing or sale.”

Stalled SERMs

Lasofoxifene’s withdrawal marks yet another snag in the development of SERMs for breast cancer prevention. A decade ago, scientists were enthusiastically predicting that new designer SERMs targeting breast cancer risk factors and postmenopausal osteoporosis would soon be available. The National Surgical Adjuvant Breast and Bowel Project, a National Cancer Institute–sponsored cooperative group, had just released data showing that tamoxifen lowered the risk of breast cancer by 50%. Raloxifene also looked promising in chemoprevention, and scientists speculated that third-generation SERMs might help to stop breast cancer in its tracks.

But in 2010, tamoxifen and raloxifene are still the only two SERMs approved for reducing estrogen receptor (ER)-positive breast cancer risk in the United States. And still only a few women eligible for the drugs are using them.

As the terminology implies, SERMs modulate ERs selectively. They block ER activity in the breast, thus lowering cancer risk, but can stimulate it elsewhere, including bone, which improves mineral density and lessens the chance of fractures.

Third-generation SERMs are now in development mainly for osteoporosis treatment, with breast cancer prevention a secondary benefit. Last year Eli Lilly dropped arzoxifene, a third-generation SERM with promising results in chemoprevention, because it didn’t meet secondary endpoints in nonvertebral fractures. Another third-generation SERM, bazedoxifene by Wyeth (now Pfizer), is in development to protect the uterus in women facing postmenopausal symptoms.

No one answer explains why SERMs haven’t been more widely adopted for breast cancer chemoprevention or why companies aren’t developing third-generation SERMs for that purpose. Drug companies won’t address the matter publicly, but experts point to a complex web of factors, including regulatory hurdles, patent issues, a lack of awareness in the medical community, and insufficient marketing. Among other factors, public misperceptions about the risks of SERMs play an important role, as Victor Vogel, M.D., notes in an editorial in this issue of the Journal.

No Economic Incentive

One major problem is that drug companies have no economic incentive to pursue prevention indications, said Vogel, director of cancer services at Geisinger Health System in Danville, Penn.

Prevention trials take a lot of money and time—they require enormous cohorts, and detecting differences in cancer incidence takes many years. Given that, drug companies generally seek treatment-based approvals first. For tamoxifen, the treatment indication was breast cancer, and for raloxifene, it was osteoporosis.

“As after you get your treatment approval, you can start looking into a prevention indication,” Vogel said in an interview. “The problem is that the patent clock starts ticking as soon as you register the drug, and that doesn’t leave a lot of time to recoup your investment.”

That’s what happened with raloxifene. On the basis of results in the STAR trial, raloxifene—which was already approved for osteoporosis—gained a breast cancer prevention indication in 2007. But the drug’s patent runs out in 2014, which left Eli Lilly just 7 years to recover the millions that it spent on the study. Neither FDA’s approval nor the results of European studies generated sales beyond those already achieved in osteoporosis, however. Drug companies took note, and SERM prevention trials have been a low priority ever since.
Balancing Act

Other reasons involve public perceptions of SERMs. Deluged by conflicting reports on what causes cancer and what doesn’t, many otherwise healthy women won’t accept SERM side effects if they can’t measure benefits in real time (the way they might measure drops in cholesterol from taking statins, for example), said Leslie Ford, M.D., associate director in the NCI’s division of cancer prevention. SERMs can produce hot flashes, Ford said, in addition to slight elevations in both endometrial cancer risk and thrombotic events that can lead to stroke.

SERM development is in many ways an exercise in balancing the risks and benefits of differential estrogen binding. The most recent update of data from the STAR trial, which compared tamoxifen to raloxifene, show that tamoxifen is the more effective chemoprevention agent but that it also elevates risks for endometrial cancer and blood clots, albeit slightly. (These risks have been detected only in post-menopausal women, emphasized V. Craig Jordan, M.D., vice chair of oncology at the Lombardi Comprehensive Cancer Center of Georgetown University, who discovered tamoxifen’s cancer-preventing properties in 1990.)

Raloxifene does not cause endometrial cancer and prevents vertebral fractures, but it’s also a less effective chemoprevention agent, with about 78% of tamoxifen’s cancer-reduction activity. Both drugs offer protection that lasts from 5 to 15 years after 5 years of use.

If one takes a SERM for longer than 5 years, risks begin to outweigh benefits, Ford said. “What you’re basically looking for in a SERM is a drug that prevents breast cancer and osteoporosis and that doesn’t increase risks of endometrial cancer and heart problems or pulmonary embolisms. And that also doesn’t cause hot flashes,” she added.

Lasofoxifene, which is considerably more powerful than raloxifene (compare the 0.5-mg daily dose with 60 mg for the latter), comes close to meeting those aims, Jordan said. In the PEARL trial, it reduced total and ER-positive breast cancer, prevented vertebral and nonvertebral fractures, and did not cause endometrial cancer, although it did increase blood clots. Jordan said that lasofoxifene “fulfills the promise of what I predicted could be done with SERMs back in 1990.”

Nevertheless, the FDA denied lasofoxifene’s approval for osteoporosis in 2005, and with the withdrawal of Pfizer’s FDA application this summer, the development of this third-generation SERM appears to have halted.

Promoting Chemoprevention

In lieu of new SERM development, Ford argues that the NCI can do a better job promoting chemoprevention with the agents available now. With an oft-cited comparison, she points out that statins and blood pressure drugs have gained broad acceptance for heart attack and stroke prevention, despite their own side-effect profiles. Like SERMs, statins lower risks for these leading killers by roughly 50%, but they can also cause memory loss; muscle and joint aches; and, in more extreme situations, liver and kidney damage and diabetes. (Some researchers also suggest that statins don’t work as well in women as they do in men.)

According to Ford, statins came into widespread use only after the National Heart, Blood, and Lung Institute pushed their adoption in a massive educational campaign that lasted 20 years. “We’ve got a lot of work to do in terms of showing the public that there are real ways to reduce breast cancer risk,” she said. “Right now, women get bombarded with advice that ranges from the ridiculous to the absurd, such as the notion that doing sit-ups or riding your bike 5 miles a day to stop breast cancer is somehow equivalent to taking a statin that reduces the risk of heart disease.”

Working with the NCI’s Office of Communications and Education, Ford is developing a prevention campaign based on FDA-approved drugs, including SERMs for breast cancer and finasteride for prostate cancer. She said the program will also educate primary-care doctors, who typically do not have training in how SERMs prevent breast cancer. The target population, she added, includes women deemed high risk according to the Gail model, a widely used breast cancer risk assessment tool.

Ford emphasized that SERM treatment may not extend to gene carriers for the illness, including women who test positive for BRCA1 and BRCA2 mutations. “There simply haven’t been enough gene carriers in prevention trials to draw any conclusions,” she said.

Measurable Marker Needed

Powel Brown, M.D., Ph.D., who chairs the Department of Clinical Cancer Prevention at the M. D. Anderson Cancer Center in Houston, argues that broadened use of SERMs in prevention will require a measurable marker, analogous to cholesterol or blood pressure. Such a marker has proven elusive, however. Histology markers, such as atypical ductal hyperplasia (a risk factor for breast cancer), might fluctuate in response to SERM treatment, Brown said, but these tests are invasive.

A noninvasive alternative, he added, is breast density, also a breast cancer risk factor. Along those lines, Jack Cuzick, Ph.D., who runs the Centre for Epidemiology, Mathematics, and Statistics at the Wolfson Institute in London, has generated preliminary findings to suggest that breast density fluctuates in response to circulating estrogen levels.

According to Cuzick, women with 50% breast density—a measure of stromal tissue—face a twofold elevation in cancer risk. That’s either because the tissue itself releases oncogenic factors, he said, or because stroma contains glandular epithelial tissues that are inherently more susceptible to cancer.

Two years ago, Cuzick presented provocative data at the San Antonio Breast Cancer Symposium showing that tamoxifen therapy reduces breast density at both 6 and 18 months. He said he’s now validating those results and hopes to have a final report soon.
“The big theme behind our research is that people will take blood pressure drugs and statins because they see measurable effects on established risk factors,” he said. “That’s what’s missing in cancer prevention, and it’s what we hope to provide with our breast density measurements. So there’s an enormous amount of interest in this.”

Cuzick was optimistic that cancer prevention has a future in public health. “We need two things for effective prevention therapy,” he said. “First, we need better ways to identify high-risk people. And second, we need to develop safer, more effective prevention agents. We’re making some progress, but we still have a ways to go with what statins have achieved. But I don’t want to leave with a negative view; we’re basically where cardiologists were 20 years ago, and that should encourage us to move forward.”

Dr. Vogel reported consulting agreements and research support from AstraZeneca, which markets tamoxifen and Eli Lilly, which markets raloxifene. Dr. Cuzick reported working in a consultant or advisory role to AstraZeneca and received researcher funding from Eli Lilly and AstraZeneca. Dr. Brown reported research funding from Eli Lilly and AstraZeneca.