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SERMs Still Have Value for Breast Ca Prevention

— Treatment with selective estrogen receptor modulators (SERMs) led to long-term protection against breast cancer, authors of a meta-analysis concluded.

by Charles Bankhead, Staff Writer, MedPage Today

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Treatment with selective estrogen receptor modulators (SERMs) led to long-term protection against breast cancer, authors of a meta-analysis concluded.

SERM therapy was associated with about a 40% reduction in the risk of breast cancer for up to 10 years after diagnosis and treatment, and the benefit was greatest during the first 5 years, reported Jack Cuzick, PhD, of Queen Mary University of London, and colleagues online in The Lancet.

While SERMs increased the risk of thromboembolic events ($P<0.0001$), they reduced the risk of vertebral fractures, they added.

In spite of the demonstrated efficacy, SERMS continue to be ignored by patients and primary care physicians alike, "mainly because of concern about toxic effects and perceived unfavorable balance between benefits and harms," the authors noted.

"Unfortunately, at the present time, none of these drugs are being actively marketed for breast cancer prevention," they said. "Our longer-term assessment shows that the benefit-harm balance is now more favorable than that calculated for short-term follow-up, and, in view of this new evidence, assessment of these drugs, especially lasofoxifene, should be continued."

Almost 30 years ago, studies of tamoxifen showed a reduced incidence of contralateral tumors in breast cancer patients. Subsequent trials confirmed a protective effect against breast cancer. Trials of SERMs in osteoporosis also suggested a potential to prevent breast cancer, the authors noted.

A randomized comparison of tamoxifen and the SERM raloxifene (Evista) showed the former more effectively prevented breast cancer but the latter caused fewer side effects. A meta-analysis of breast cancer prevention trials showed that tamoxifen reduced the risk of estrogen receptor (ER)-positive tumors by 48% but had no effect on ER-negative tumors.

Limited data on breast cancer prevention exist for the newer SERMs lasofoxifene and arzoxifene. Cuzick and colleagues included data for both drugs in an update of previous meta-analyses of breast cancer prevention with SERMs.

Their analysis comprised nine randomized trials (eight placebo controlled and one with tamoxifen as active control) in 83,399 women and 306,617 patient-years of follow-up. Collectively, the trials had a median follow-up of 65 months.

SERM treatment duration was 5 years in most of the studies. The studies involved patients with a breast cancer risk ranging between normal and high.

Overall, SERMs were associated with a 38% reduction in the risk of breast cancer at 10 years ($P<0.0001$ versus control). The cumulative 10-year incidence of breast cancer was 6.3% in control groups and 4.2% in SERM groups. The benefit was greater during the first 5 years (42%) than in years 5 to 10 (25%).

SERM treatment was associated with a 2.1% incidence of ER-positive breast cancer versus 4% in control groups ($P<0.0001$).

The number needed to treat (NNT) to prevent one breast cancer over 10 years was 42, increasing to 53 when the analysis was limited to invasive ER-positive breast cancer.

With respect to the individual agents, trials of tamoxifen showed a 33% reduction in breast cancer incidence (44% in invasive ER-positive breast cancer). Raloxifene demonstrated a smaller, but significant benefit, which did not differ significantly in comparison with tamoxifen.

The 5-year follow-up with lasofoxifene showed a significant reduction in breast cancer versus placebo ($P<0.0001$) with the 0.5 mg dose but only a small effect with a lower dose. Arzoxifene was associated with an overall reduction in breast cancer occurrence of 58% ($P=0.001$), including a 70% reduction in occurrence of ER-positive breast cancers ($P=0.002$).

Finally, thromboembolic events were significantly increased with all SERMs (odds ratio 1.73, 95% CI 1.47 to 2.05), but the authors highlighted a reduction of 34% in vertebral fractures (OR 0.66, 95% CI 0.59 to 0.73). The effect for nonvertebral fractures was small (OR 0.93, 95% CI 0.87 to 0.99).

Limitations of this analysis were many of the trials were done on average-risk women with osteoporosis. Also, longer follow-up is needed for the lasofoxifene and arzoxifene trials.

Long-term follow-up is key to determine the effects of SERMS, wrote Anthony Howell, MD, and D. Gareth Evans, MD, from the University Hospital of South Manchester in England, in an accompany editorial.

"Most of the trials stopped at, or even before, the 5-year SERM treatment period was completed," they wrote. "This cutoff not only precludes data for long-term risk, but, because of crossover of controls and insufficient follow-up, it also limits long-term assessment of benefit."

Nevertheless, they said the "present study is testament to the persistence of clinical trials groups, industry, investigators, and the women volunteers, who have now collectively shown the long-term effectiveness of the original SERM hypothesis," adding that the future of breast cancer prevention "will depend on prediction of breast cancer risk and responsiveness with more precision."

Although the study provided useful information, whether the results will have an impact in clinical practice remains to be seen, according to Peter Ravdin, MD, of the University of Texas Health Science Center at San Antonio.

"Over the last decade there have been FDA-approved medicines for the reduction of breast cancer (tamoxifen and raloxifene) but because of uncertainties about their long-term effectiveness and concerns about their side effects they have not been widely adopted," Ravdin said via email. "The good news is that it appears that the effect will last out to 10 years, although there is a suggestion that the reduction was larger in the first 5 years of follow-up than in years 5–10," he added. "This is similar to the impact of adjuvant hormonal therapy, which, after giving tamoxifen for 5 years, has its biggest impact in the first 5 years, and then there is a carry-over into years 5 to 10."

The principal downside of SERMs is their side-effect profile. The agents studied in the trials universally about double the risk of thrombotic events, and tamoxifen increased the risk of endometrial cancer, said Ravdin. Reassuringly, none of the agents increased the incidence of cardiovascular or cerebrovascular events.

"Still, there are uncertainties remaining," he said. "Ideally, one would like to know the time course of the risk of these noncancer events."

Cuzick disclosed a relationship with AstraZeneca. Co-authors included current and past employees and shareholders of Eli Lilly.

Howell and Evans reported no conflicts of interest.

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