The Biology Behind

Arzoxifene: A Promising New Selective Estrogen Receptor Modulator for Clinical Chemoprevention of Breast Cancer


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Despite numerous major advances in the diagnostic, medical, and surgical management of breast cancer, the morbidity and mortality from this disease continue to be unacceptable. The need for a preventive approach to control breast cancer remains of paramount importance. Indeed, in the entire field of chemoprevention of cancer, breast cancer has thus far led the way to show proof of principle, with the demonstration of the proven clinical efficacy of two agents, namely tamoxifen and raloxifene (1–3). Both of these agents are selective estrogen receptor modulators, which have the important property of having either proestrogenic or antiestrogenic activity in different target organs. Selective estrogen receptor modulators can even have either proestrogenic or antiestrogenic actions in the very same cell, depending on the overall context in which that particular cell finds itself. Thus, tamoxifen is proestrogenic for MCF-7 breast cancer cells in the absence of 17-β estradiol but antiestrogenic when estradiol is present. The ultimate selective estrogen receptor modulator for prevention of breast cancer should not only be antiestrogenic in the breast but also should be proestrogenic in all of the other targets in the body in which estrogen exerts beneficial effects, such as bone and the cardiovascular system. Neither tamoxifen nor raloxifene represent ideal selective estrogen receptor modulators, and at present, there is continuing major effort to develop new selective estrogen receptor modulators that will have a more acceptable pharmacodynamic profile.

Basis for the Multifunctionality of Selective Estrogen Receptor Modulators

Although the original discovery of the mixed functionality of an agent such as tamoxifen was extremely puzzling (at one time, it was thought that differential metabolism of tamoxifen accounted for its different actions in different organs), there is now a much better understanding of the molecular basis for the selective estrogen receptor modulator concept. Selective estrogen receptor modulators are ligands for the two estrogen receptors, estrogen receptor α and estrogen receptor β, which, in turn, are transcription factors controlling the expression of numerous genes. The main advance in understanding the complexity of the actions of selective estrogen receptor modulators has been the discovery that the functional transcriptional unit that enables an individual selective estrogen receptor modulator to regulate the activity of any specific gene is not merely the selective estrogen receptor modulator and its cognate estrogen receptor but rather a multimolecular transcriptional complex, which includes not only the selective estrogen receptor modulator and the estrogen receptor but also a series of coregulatory proteins known as coactivators or corepressors. These critical coregulators interact with the receptor and, in turn, with the response machinery that ultimately controls the expression of any specific gene (4–6). These coactivators and corepressors thus control the ultimate agonistic or antagonistic action of the selective estrogen receptor modulator in any particular organ. As an example, in an elegant series of experiments, Shang and Brown (7) have shown that both tamoxifen and raloxifene induce the recruitment of corepressors to the promoters of target genes in mammary cells, and thus both agents can act as estrogen antagonists in the breast. Conversely, they found that in endometrial cells, tamoxifen, but not raloxifene, is proestrogenic by stimulating the recruitment of coactivators to the transcriptional complex; this is presumed to be the basis of the undesirable proliferative and carcinogenic actions of tamoxifen in the uterus (8). However, raloxifene, which does not recruit these coactivators in uterine cells, does not stimulate proliferation in the uterus and does not cause uterine cancer (3). Coregulator function is now believed to be a critical modulator of the agonist or antagonist activity of an entire series of related transcription factors, all of which are members of the nuclear receptor superfamily (6).

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Arzoxifene, a Third Generation Selective Estrogen Receptor Modulator

Therefore, it is not surprising that there has been intense activity in the pharmaceutical industry directed toward synthesis and testing of new selective estrogen receptor modulators. Arzoxifene is an excellent example of this effort, and the article by Fabian et al. (9) in this issue represents the first report of the use...
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Arzoxifene is a potent inducer of the expression of transforming growth factor β (14); this action may contribute to the suppression of early lesions in the breast (15).

The Present Study

Arzoxifene thus is an ideal candidate for a clinical study of chemoprevention of breast cancer, and in this context, this first report from Fabian et al. (9) is most welcome. Two trials are reported, in which women with newly diagnosed ductal carcinoma in situ or T1/T2 invasive breast cancer were studied. In both trials, women were biopsied then treated with arzoxifene for between 2 and 6 weeks before re-excision of their lesion. A very large battery of both serum and tissue biomarkers have been evaluated, and with this short a treatment period, many of the results were negative. However, there were some strikingly positive findings, most notably decreases in serum insulin-like growth factor I (IGF-I) and serum IGF-1:IGF binding protein-3 ratio (IGF binding protein-3 is one of the specific binding proteins that maintain IGF-I in an inactive state), as well as a marked decrease in proliferation indices, especially as measured by proliferating cell nuclear antigen expression. The effects of arzoxifene on IGF-I are particularly notable, because there are extensive data to indicate that high levels of circulating IGF-I and low levels of IGF binding protein-3 are clinically associated with increased risk of breast cancer (16, 17). Moreover, in the second trial, a statistically significant decrease in estrogen receptor expression was found in the women treated with arzoxifene. In short trials such as those reported here, it is clearly impossible to evaluate long-term effects of a preventive agent on cancer incidence, but the authors conclude that, given the favorable side effect profile and the biomarker modulations, arzoxifene remains a reasonable candidate for additional study as a breast cancer chemopreventive agent.

Future Directions

Clearly this entire approach to prevention of breast cancer is now ready for additional clinical study. Synthetic chemistry continues to generate a large number of new selective estrogen receptor modulators that have yet to be explored in the clinic as preventive agents. Just as the second and third generation selective estrogen receptor modulators, raloxifene and arzoxifene represent a totally new class of chemical structures (benzothiophenes) that are chemically distinct from tamoxifen (a triphenylethylene), so there is now an even greater choice of new selective estrogen receptor modulators to consider for prevention studies. These include agents of very diverse structure, such as acolbifene (a benzopyran) and lasofoxifene (a tetrohydronaphthalene), both of which share the common property of being antiestrogenic in the breast and proestrogenic on bone in experimental animals; neither one has the undesirable uterotrophic effects of tamoxifen (18–21). The ultimate practical usefulness of any of these new agents no doubt will depend on their total selective estrogen receptor modifier profile, which has yet to be explored in a clinical context. Studies of the interaction of these drugs with coactivators and corepressors will be of major importance for the understanding of the selectivity, which is desired.

As can be seen from the present report by Fabian et al. (9), there is still a major need to develop new and better biomarkers to evaluate the efficacy of any selective estrogen receptor modulator in a clinical trial. Many of the biomarkers in present use are more than a decade old, and their sensitivity is hardly...
optimal. The recent emphasis on proteomics should offer better hope for the future (22, 23). Additional cooperation among academia, the pharmaceutical industry, and the Food and Drug Administration will be essential in achieving this desired goal of clinical chemoprevention of breast cancer. It is clear by now that we have the means to prevent breast cancer in numerous animal models, whether with single agents or with combinations of drugs (24, 25). The current challenge is to apply this knowledge in the clinic. The study by Fabian et al. (9) clearly shows that clinical evaluation of biomarkers can be an important component in this complex process.

REFERENCES


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