2. Future PCI/stent use among stable angina patients could depend on COURAGE: managed care first report. (Accessed July 25, 2008, at http://www.mccfirstreport.com/show_story.php?newsid=1172.)
3. Weintraub WS, Spertus JA, Kolm P, et al. Effect of PCI on quality of life in patients with stable coronary disease. N Engl J Med 2008;359:677-87.
4. Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. J Am Coll Cardiol 1995;25:333-41.
5. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Ann Med 2001;33:350-7.
6. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation 2008;117:1283-91.
7. ACC NCDR data. Durham, NC: Duke Clinical Research Institute, 2008.

Tibolone and the Promise of Ideal Hormone-Replacement Therapy

Ghada El-Hajj Fuleihan, M.D., M.P.H.

Since the mean life expectancy at menopause is 32.7 years, women spend more than one third of their lives in the estrogen-deficient postmenopausal state.[1] Of the majority of menopausal women who have climacteric symptoms, 20% describe them as intolerable, and one third have such symptoms for up to 5 years.[2] During her lifetime, one of every two women will have an osteoporotic fracture, one third will have coronary heart disease, one fifth will have a stroke or Alzheimer's disease, and one eighth will have breast cancer.

Whereas hormone-replacement therapy was once accepted as the ideal strategy for optimizing postmenopausal health outcomes, randomized trials have challenged that view and have led to a marked decrease in the use of such therapy[3] and a heated search for alternatives. To date, alternative therapies have included the selective estrogen-receptor modulators (SERMs) and selective tissue estrogenic activity regulators (STEARs).[4] Tibolone, a synthetic STEAR with differential effects in target organs due to tissue-specific metabolism, enzyme regulation, and receptor activation,[4] seems attractive. After ingestion, tibolone is converted to three metabolites. The 3α- and 3β-hydroxy metabolites exert an estrogenic effect through activation of the estrogen receptor, with positive effects on climacteric symptoms, the skeleton, and the vagina, whereas the Δ^4 isomer binds to progesterone and androgen receptors, thus inhibiting endometrial stimulation and enhancing libido. The Δ^4 isomer also inhibits sulfatases and thus the formation of active estrogens in the breast.

The efficacy of tibolone in the treatment of climacteric symptoms and the prevention of bone loss has led to its formal approval in many countries but not in the United States. However, the effect of tibolone on major health outcomes has been unclear. In this issue of the *Journal*, Cummings et al.[5] report the results of the Long-Term Intervention on Fractures with Tibolone (LIFT) trial (ClinicalTrials.gov number, NCT00519857), a randomized, double-blind, placebo-controlled study that was designed to show the efficacy of tibolone in reducing vertebral fractures in women with osteoporosis. The LIFT trial was planned as a 3-year study with a 2-year extension, and 4538 women (mean [±SD] age, 68±5 years) were randomly assigned to receive either 1.25 mg of tibolone or placebo once daily. All the women also received 600 to 1200 mg of calcium citrate and 400 to 800 IU of vitamin D. Tibolone was associated with a 45% decrease in the relative risk of morphometric vertebral fracture, the primary outcome of the study. It was also associated with a reduced risk of nonvertebral fracture (26%), invasive breast cancer (68%), and colon cancer (69%). It appeared to have no deleterious effect on coronary heart disease or venous thromboembolism. However, the study was halted by the data and safety monitoring board at a median follow-up of 3 years because of a doubling of the risk of stroke, a risk that was most substantial within the first year and in women more than 70 years of age. Endometrial bleeding and endometrial biopsies were three times as frequent in the tibolone group as in the placebo group; four cases of endometrial cancer were reported in the tibolone group but none in the placebo group. Other

adverse events in the tibolone group included a mean weight gain of 0.6 kg (as compared with that in the placebo group), breast discomfort, vaginal discharge and infection, pelvic pain, and elevations in liver aminotransferase levels.

The efficacy of tibolone in reducing fractures was anticipated, because previous trials of tibolone had shown a reduction in bone turnover and modest increments in bone mineral density.[6] In the LIFT study, the reductions in the risks of vertebral and nonvertebral fractures were higher in the subgroup of women who had already had a vertebral fracture at study entry; such reductions were similar to those associated with other approved osteoporosis therapies.[7] Although there were fewer hip fractures in the tibolone group than in the placebo group, the results were not significant.

Previous surrogate-end-point studies evaluating the effects of tibolone on markers of thromboembolic and arterial disease were inconclusive. Tibolone has been associated with decreased levels of fibrinogen, factor VII, plasminogen activator inhibitor 1, homocysteine, and tissue plasminogen activator and with increased levels of C-reactive protein, antithrombin III, and D-dimer.[6,8] In the Osteoporosis Prevention and Arterial Effects of Tibolone (OPAL) study, tibolone (at a dose of 2.5 mg per day) that was administered to women with a mean age of 58 years increased the annual progression of common carotid intima–media thickness, as compared with placebo, an effect similar to that of hormone-replacement therapy.[9] Although there was no significant increase in cardiovascular disease in the LIFT trial, such disease was a secondary end point for which the study was not adequately powered. The antiproliferative and proapoptotic activities of tibolone in breast-cancer cells[6] would be expected to result in a reduction in the risk of breast cancer, as was shown in the LIFT trial. The Livial Intervention following Breast Cancer; Efficacy, Recurrence, and Tolerability Endpoints (LIBERATE) trial (ClinicalTrials.gov number, NCT00408863), which was investigating the efficacy and safety of tibolone in controlling climacteric symptoms in postmenopausal women with a history of breast cancer, was halted prematurely because of a trend toward an excess rate of breast-cancer recurrence in women taking tibolone, as compared with placebo.[10] The possibly increased risk of endometrial cancer that was reported in the LIFT trial was not observed in smaller randomized trials involving younger women receiving a 2.5-mg dose of tibolone.[11,12] In the observational Million Women Study, the use of tibolone was associated with an increased risk of both endometrial and breast cancer.[13,14] However, the study had several limitations, including the fact that information regarding medication use was gathered several years before the diagnosis of cancer.

The Women's Health Initiative (WHI) trials taught us many things, including the importance of relying on prospective, randomized, clinical trials rather than on observational studies to elucidate risks and benefits of a specific therapy. The WHI trials also showed us the importance of appreciating the modulation of outcomes by predictors such as the patient's age at the start of therapy,[15] baseline risk factors for outcomes of interest, specific formulations and doses, and the duration of therapy. Equally important is the recognition of the sustained, delayed, and resolving health benefits or risks after discontinuation of hormone-replacement therapy on the various outcomes of interest.[16] In older women, the advantage of tibolone over hormone-replacement therapy and raloxifene includes the apparent lack of a prothrombotic effect. In addition, as compared with raloxifene, tibolone reduced the risk of nonvertebral fracture; as compared with hormone-replacement therapy, tibolone was not associated with an increase in the incidence of cardiovascular disease and breast cancer in women without a history of breast cancer. Such comparison is limited by the lack of trials directly evaluating these therapies concomitantly. Indeed, women who participated in the WHI trial of combination hormone-replacement therapy were heavier than those in the LIFT trial and did not have osteoporosis. Furthermore, one third of the women in the WHI trial were receiving statins. Thus, despite their younger age, these women may have had a higher baseline risk of both cardiovascular disease and breast cancer than women in the LIFT trial.

The long-term safety and efficacy of tibolone on major health outcomes in younger postmenopausal women are unknown. In older, mostly white women with osteoporosis, tibolone at a dose of 1.25 mg daily for 3 years seemed to have a beneficial effect on the breast and skeleton and did not appear to have a deleterious effect on cardiovascular outcomes or thrombosis. However, the study was not adequately powered to evaluate

the effect of tibolone on these outcomes. The use of tibolone should be avoided in older women, those at a high risk for stroke, and those who have breast cancer or are at high risk for the disease.

The ideal postmenopausal hormonal therapy, which has yet to be identified, should achieve several benefits, minimize risks, and enhance adherence in the individual patient while optimizing cost-effectiveness — a formidable medical and societal challenge. The health risks and needs of a woman vary greatly during her 30 years of expected life after menopause, and health-risk profiles among women also differ. Therein lies the conundrum in searching for an ideal hormonal therapy.

Dr. El-Hajj Fuleihan reports receiving consulting and lecture fees from Eli Lilly, lecture fees from Novartis and Merck, and grants from Novartis and Sanofi-Aventis. No other potential conflict of interest relevant to this article was reported.

From the Calcium Metabolism and Osteoporosis Program, the American University of Beirut Medical Center, Beirut, Lebanon.

1. Kung HC, Hoyert DL, Xu J, Murphy SL. Deaths: final data for 2005. Natl Vital Stat Rep 2008;56(10):1-120.
2. Hickey M, Davis SR, Sturdee DW. Treatment of menopausal symptoms: what shall we do now? Lancet 2005;366:409-21.
3. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA 2004;291:47-53.
4. Kloosterboer HJ, Ederveen AG. Pros and cons of existing treatment modalities in osteoporosis: a comparison between tibolone, SERMs and estrogen (±progestogen) treatments. J Steroid Biochem Mol Biol 2002;83:157-65.
5. Cummings SR, Ettinger B, Delmas PD, et al. The effects of tibolone in older postmenopausal women. N Engl J Med 2008;359:697-708.
6. Modelska K, Cummings S. Tibolone for postmenopausal women: systematic review of randomized trials. J Clin Endocrinol Metab 2002;87:16-23.
7. Rosen CJ. Postmenopausal osteoporosis. N Engl J Med 2005;353:595-603.
8. Campisi R, Marengo FD. Cardiovascular effects of tibolone: a selective tissue estrogenic activity regulator. Cardiovasc Drug Rev 2007;25:132-45.
9. Bots ML, Evans GW, Riley W, et al. The effect of tibolone and continuous combined conjugated equine oestrogens plus medroxyprogesterone acetate on progression of carotid intima-media thickness: the Osteoporosis Prevention and Arterial effects of tiboLone (OPAL) study. Eur Heart J 2006;27:746-55.
10. Mols M. Tibolone study in breast cancer patients to close ahead of schedule. Auckland, New Zealand: Drugs.com. (Accessed July 25, 2008, at http://drugs.com/news/tibolone-study-breast-cancer-patients-close-ahead-schedule-6164.html.)
11. Langer RD, Landgren BM, Rymer J, Helmond FA. Effects of tibolone and continuous combined conjugated equine estrogen/medroxyprogesterone acetate on the endometrium and vaginal bleeding: results of the OPAL study. Am J Obstet Gynecol 2006;195:1320-7.
12. Archer DF, Hendrix S, Gallagher JC, et al. Endometrial effects of tibolone. J Clin Endocrinol Metab 2007;92:911-8.
13. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419-27. [Erratum, Lancet 2003;362:1160.]
14. *Idem*. Endometrial cancer and hormone-replacement therapy in the Million Women Study. Lancet 2005;365:1543-51.
15. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007;297:1465-77. [Erratum, JAMA 2008;299:1426.]
16. Heiss G, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA 2008;299:1036-45.