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FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

Role of Statin Drugs in Cardiovascular Health of Women



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INTRODUCTION

The statin drugs have revolutionized the medical treatment of atherosclerosis.¹ Lipid deposition in the arterial tree begins in childhood and is accelerated by smoking, hypertension, diabetes, hyperlipidemia, and in the female, menopause.² Statin drugs not only lower cholesterol levels but also restore vascular endothelial function, reduce inflammation, and stabilize atherosclerotic plaques.³ Over the past 20 years, multiple randomized clinical trials have demonstrated the safety of statins, the reduction of atherosclerotic progression, and the lowering of cardiovascular morbidity and mortality. This review will discuss the mechanisms of available agents and clinical indications for statin drugs.

MECHANISMS

Cholesterol is an essential substrate for hormones, cell membranes, and bile salts, the latter of which are nec-

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essary for lipid absorption from the intestinal tract. The liver is the major organ involved in the metabolism and production of various lipid components circulating in the blood. Statin drugs inhibit an enzyme (HMG-CoA reductase) involved in the final pathway of cholesterol production. When hepatic cholesterol metabolism is limited, the liver compensates by increasing the uptake of circulation lipids with a resultant decline in plasma levels.⁴ Sufficient reduction in plasma levels of cholesterol can promote reabsorption of cholesterol from the arterial tree. Statin drugs also restore production of nitric oxide, which induces arterial vasodilatation under stress. Vasodilatation of atherosclerotic vessels is impaired, and the unopposed vasoconstriction plays a critical role in the development of vascular complications. Statin drugs diminish the inflammatory process in the atherosclerotic plaque with resultant stabilization and prevention of plaque rupture, which is the underlying mechanism for acute coronary syndromes such as unstable angina and myocardial infarction.

FROM THE EDITOR

David F. Archer, M.D.

The turmoil created by the results of the Women's Health Initiative has resulted in women and their physicians turning to other therapeutic options. These have included prescription drugs, and alternative medicines. Non-prescription products used in menopausal women have limited data on which to base a medical judgment of efficacy and or safety. This issue addresses three alternatives to standard hormone therapy.

Charles E. Rackley, M.D., discusses statins. A relatively safe prescription product for treating elevated cholesterol and coronary heart disease. The magnitude of the sales for statins is in the billions of dollars, representing their extensive use by physicians in treating older women and men. Dr. Rackley provides the reader with an assessment of the currently available products and their starting dose. The issue of safety is addressed with the need for follow up liver function evaluations. Many of our patients are or will be requiring the use of statins as the recommendations for lower serum levels of LDL-cholesterol become mainline.

Ronald L. Young, M.D., provides an over-view to the use of Selective Estrogen Receptor Modulators in his article on Raloxifene. The utility of raloxifene in older women is limited to the indication for prevention of bone loss. Dr. Young provides us with the current knowledge from the completed clinical trials of raloxifene for prevention of bone loss, coronary heart disease, and breast cancer.

Veronica A. Ravnkar, M.D., tantalizes us again with the use of Dehydroepiandrosterone (DHA). This product, which has orphan drug status for Lupus Erythematosus, has been on the fringes in terms of use in postmenopausal women. The small studies that have been reported have indicated efficacy for general well being, and perhaps libido. Formal clinical trials of sufficient numbers are really needed to provide information on safety and efficacy, and a medical rationale for the use of DHA in older women.

Menopausal Medicine

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CLINICAL TRIALS

With the use of statin drugs, there has been a reported elevation of liver enzymes in less than 2% to 3% of the studies and no increased incidence of malignancies or lenticular opacities. The incidences of lenticular opacities were reported in earlier trials with cholesterol lowering drugs. Statin drugs primarily lower plasma cholesterol and the LDL component with minimal influence on HDL and triglyceride levels. Complications of skeletal muscle irritation and myositis have been reported in less than 1% of patients in clinical studies. However, the incidence of side effects of liver enzyme elevation or skeletal muscle irritation may increase with larger doses or when the statins are used in combination with other lipid-lowering agents such as niacin, gemfibrozil, and fenofibrates. High doses of statin drugs, when used in combination with other lipid lowering agents, necessitate periodic measurement of liver and skeletal muscle enzymes the initial three to four months to identify early manifestation of enzymatic disturbances.

AVAILABLE STATIN DRUGS

1. Lovastatin was the first FDA-approved statin drug and was introduced in 1987. It significantly lowers cholesterol and the LDL component. Lovastatin proved beneficial in clinical trials involving women, as well as men, with few cardiovascular risk factors and not clinical evidence of cardiovascular disease.⁵ Lovastatin has currently become a generic statin drug, and its doses range from 10mg to 80mg with the usual starting dose at 20mg.

2. Pravastatin was extensively tested in multiple primary and secondary prevention trials with consistent reduction in cardiovascular morbidity and mortality.⁶ Pravastatin is a water-soluble agent with possibly the lowest side effects of available statins. It can be used in combination with niacin and fibrates with a low side-effect

profile. Doses range from 10mg to 80mg, and the usual starting dose is 20mg to 40mg. Pravastatin recently has been reported to reduce cardiovascular events in elderly patients.

3. Simvastatin is a potent lipid-lowering agent that significantly reduces lipid levels and cardiovascular events. The Scandinavian Simvastatin Survival Study reported a reduction in cardiovascular events and mortality in females as well as males.⁷ The Heart Protection Study followed more than 20,000 patients with known coronary disease or who were at high risk for developing cardiovascular disease and reported a reduction in cardiovascular events in patients with elevated, as well as normal, cholesterol levels.⁸ Doses range from 5mg to 80mg, and the usual starting dose is 20mg to 40mg. Recently, the United Kingdom approved the over-the-counter sale of simvastatin.

4. Fluvastatin was the first synthetically produced statin drug. The agent is water-soluble and can also elevate the HDL component as well as reduce cholesterol and LDL. The LCAS trials reported a reduction in cardiovascular events particularly in patients with low baseline HDL cholesterol.⁹ The dose ranges from 20mg to an 80mg XL tablet.

5. Atorvastatin is the most potent of the statin drugs. It lowers LDL cholesterol more than that seen with lovastatin, pravastatin, simvastatin or fluvastatin. Recent trials in patients with an acute coronary syndrome compared atorvastatin to pravastatin, and atorvastatin proved to be superior in slowing coronary atherosclerotic progression and reducing ischemic events.¹⁰ Currently, atorvastatin is the most widely prescribed statin drug in clinical practice. The dose ranges from 10mg to 80mg, and the usual starting dose is 10mg to 20mg. However, in patients with a recent acute coronary syndrome, the initial dose may be 80mg.

6. Rosuvastatin, introduced in the past year, is the newest statin agent and may be more potent than atorvastatin in the reduction of cholesterol and LDL component.¹¹ Rosuvastatin may also elevate the HDL component more than the other statin agents. Doses range from 5mg to 40mg, and the usual starting dose is 10mg.

Lipid-versus-water solubility is one characteristic of several of the statin drugs. This may limit systemic uptake in skeletal muscle and the central nervous system. Lovastatin, simvastatin, and atorvastatin are lipid-soluble agents, whereas pravastatin, fluvastatin, and rosuvastatin are water-soluble drugs. Water-soluble agents may be better tolerated with fewer side effects when used in combination with other cholesterol-lowering agents and may result in a lower incidence of myalgias and skeletal muscle irritation.

INDICATIONS

In women as well as in men, elevated cholesterol and LDL components are major clinical indications for consideration of statin therapy. During the childbearing years, statin drugs should be restricted to unusually high-risk patients such as those with familial hypercholesteremia, diabetes, or cigarette use. If a statin drug is indicated during the childbearing years, there should be assurance of adequate birth control measures. If a decision is made for family planning, statin drug use should be interrupted. In the postmenopausal female, abnormal lipid values accompanied by other cardiovascular risks are indications for prescribing a statin drug.¹² Smoking, hypertension, and diabetes accelerate the atherosclerotic process in postmenopausal females. The metabolic syndrome is a recently emphasized clinical combination consisting of obesity, hypertension, elevated triglycerides, low HDL component, and glucose intolerance.¹³ Obesity is defined in the female as waist circumference greater than 35 inches, blood pressure greater than 130/85 mm/Hg,

triglycerides higher than 150 mg/dl, HDL cholesterol less than 50 mg/dl, and fasting glucose greater than 100 mg/dl. In the Heart and Estrogen Replacement Study (HERS), women assigned to the hormone treatment arm using statin drugs exhibited no increase in cardiovascular events.¹⁴ Even though the numbers in the subgroup are too small for statistical significance, these observations suggest that the statin drugs could protect against potential cardiovascular events in postmenopausal females using hormone therapy.

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For the postmenopausal female with abnormal elevated cholesterol or two or more cardiovascular risk factors, an initial statin might be lovastatin, pravastatin or fluvastatin. When multiple cardiovascular risks exist, or if the patient has known coronary artery disease, a more potent agent such as simvastatin, atorvastatin, or rosuvastatin might be considered. A recent update by the National Cholesterol Education Program suggested that the optimal level for the LDL value falls below 70 mg/dl.¹⁵ Such severe high-risk patients would be those with known coronary disease plus either diabetes, smoking, metabolic syndrome, or a recent acute coronary

while on a large-dose statin such as atorvastatin or rosuvastatin. Again, when larger doses are initiated, liver enzymes should be obtained at baseline with a three-month follow-up measuring CPK in anyone experiencing muscle aches.

In initiating a statin agent, the Food and Drug Administration does not recommend baseline liver enzymes if a single statin is employed without other cholesterol-lowering agents. If the statins are used in combination with other lipid lowering agents, the enzymes should be repeated at three months to assure there are no underlying potential side effects. If there are no disturbances in liver enzymes with combination therapy, only periodic lipid profiles are necessary at three- to four-month intervals without liver function studies.

The general dose range for the statin drugs is 5mg to 80mg. Some experts have recommended starting a larger dose and then reducing the dose as a future measure to ensure compliance. More frequently, initial doses are initiated in the range of 10mg to 40mg of the statin drug. However, should the patient be at very high risk with known coronary disease plus diabetes, smoking, metabolic syndrome, or recent coronary event, a dose of atorvastatin 80mg or rosuvastatin 40mg should be considered. Patients should be warned about the infrequent side effects of gastrointestinal irritation, myalgias, and muscle tenderness. Liver or systemic skeletal muscle side effects have been reported in less than 1% to 2% in extensive trials involving both men and women.

Although some patients may be sensitive to potential side effects, helpful clinical advice is to assure the patients that the drug can be discontinued for one or two weeks with further observation. The drug can then be restated after this period of interruption, and if the sensations recur, that particular drug should either be reduced in dose or discontinued with trial of another statin agent. In those

patients on high-dose statin drugs or those with combination drugs, reduction in the dose or change from a lipid-soluble to a water-soluble agent may eliminate the sensations or side effects.

CONCLUSION

The statin class of drugs has made a major impact on lowering cholesterol and stabilizing the atherosclerotic process with significant reduction in cardiovascular events. Postmenopausal females are at risk for accelerated atherosclerotic disease, and statin drugs should be considered in all postmenopausal females with cardiovascular risk factors, as well as those with clinical cardiovascular disease. Finally, the addition of a statin drug to women electing to remain on hormone replacement therapy may eliminate any increase in cardiovascular complications reported with the use of female hormones.

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The Role of SERMs in the Menopause



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THE CHANGING WORLD OF MENOPAUSE

Since publication of the findings of the Women's Health Initiative (WHI),¹ the Hormone and Estrogen Replacement Study (HERS),² and a series of additional investigations with estrogen-unfavorable conclusions, a barrage of negative publicity has dogged the practice of prescribing hormones for menopausal women. The door has thus been thrown wide open to a myriad of considerations aimed at filling the vacuum created by the retreat of traditional hormone therapy. That is not to say that estrogen and the progestogens are being, or ought to be, totally abandoned, but it would be irresponsible to fail to recognize that entirely new treatment approaches to menopause therapy are now being devised. That these new constructs are rising on constantly shifting sands makes our tasks as clinicians all the more difficult to digest them and apply them to our practices.

One natural outgrowth of the alarmist clamor has been to oppose virtually any and all therapies for the menopause, accepting the fact that the condition is, after all, a natural consequence of aging and not a disease as such. Another approach has been to look toward "natural" or "bio-equivalent" compounds, placing one's faith in the precept that these are somehow safer than estrogen. This concept is not without some merit in view of the fact that many of these products are dosed homeopathically thus assuring "safety" as a trade off for any degree

of efficacy. And, finally, there is the approach of accepting the new challenge by reverting to a more traditional, individualized practice, accepting that hormone therapy may be unsafe for some patients, and thus gearing protocols toward specific signs and symptoms unique for each patient.

A perhaps more logical response is to consider estrogen or estrogen/progestogen as the most reasonable bridging intervention through the menopausal transition, especially for the very subjective vasomotor and emotional symptoms of the early menopause. Accepting that, however, one must also accept that there have been important changes in traditional dosing protocols based on the new standard that less is better and shorter is better still. As a consequence, the current unwritten code for the use of hormones stresses that these should be delivered “in the lowest possible dose and for the shortest possible time.”

The true tragedy of WHI is not that it proved conclusively that hormones are harmful, but rather showed that, at least for coronary and cerebral vascular disease, they do not appear to be in any way helpful. And so, we are forced to abandon the concept of a holistic, “all-encompassing” single pill approach to the menopause. This, in turn, has forced us to further individualize menopausal cases to a degree that has not been prior practice. We thus avoid “treating” patients with no clear indication for intervention. In truth, the “one pill fits all” theory was perhaps a bit too simplistic and, over time, lent to the false concept of how “easy” it was to treat the menopause.

SERMS: BACKGROUND AND HISTORY

The Selective Estrogen Receptor Modulators (SERMs) may have some relation to a few of the above ideologies. From a more pro-active and interventional standpoint, they certainly seem to be potential and natural extenders of steroid hormone therapy. As representatives of the family of

antiresorptive drugs they unarguably have specific indications in both the prevention and treatment of osteoporosis. And, finally, many clinicians hold out hope that they may yet fill a broader, more holistic role through the mechanisms of cardiac protection and breast cancer risk reduction

The history of the SERMs goes back further than is commonly held. A representative of these compounds, ethamoxytriphetol, was tested in the 1960s for its potential in fertility control. It inhibited post-mating implantation in rats but proved to be of low potency and was associated with per-

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sistent side-effects. Tamoxifen also began its run as a compound looked at for fertility regulation but, by the early 1970s, was being studied for its anti-estrogenic effects in the area of breast cancer therapy. Its described mechanism of action was via blockade of breast cancer cell replication in the G1 phase of the cell cycle. By 1987 both raloxifen and tamoxifene were shown to have anti-resorptive properties by maintaining bone density in ovariectomized rats. Neither caused an increase in uterine weight although tamoxifen has subsequently been shown to be an endometrial stimulant with potentially hazardous consequences. We had previously reported on SERM-like effect of clomiphene citrate on gonadotropins and the uterus in the castrate rat

model and in human subjects as early as 1979.^{3,4} By 1983, in a similar model, we had also reported on clomiphene's positive bone effects. Tamoxifen, of course, has since been limited to the field of breast cancer while clomiphene has remained in its fertility treatment niche. The point to this abbreviated historical review is to underscore the similarities and dissimilarities among the various SERMs compounds. They may have between them varying estrogen-agonistic and -antagonistic effects. Each individual SERM may have, within itself, differing effects on different tissues and organs. This is what makes them so interesting. As many have pointed out, if a compound interacts with the estrogen receptor, then it is a SERM. This may include estrogen itself, certainly an excellent model for tissue and organ selectivity. Thus, the definition of an estrogen is rooted in its function and not in its chemical formula and this certainly describes some aspects of the SERMs.

SERMs encompass a group of chemically unrelated or loosely related compounds that all interact with the estrogen receptor. Most of the presently available SERMs were known before the actual term came into general use. The somewhat bizarre concept of simultaneous estrogenic and anti-estrogenic activity had been employed to describe their actions and, therefore, as an example, in the earliest days of its use, clomiphene citrate was described somewhat enigmatically as “an anti-estrogen with weak estrogenic properties.” The advent of receptor chemistry has thrown light on the mechanisms of their actions and what actually was happening. The SERMs compete with estrogen via binding with its receptor. The resulting estrogen-agonistic or -antagonistic activity of the SERMs is tissue and organ dependent. The complexity of these interactions is further confounded by the fact that different SERMs may act similarly in certain tissues, as is the case with

tamoxifen and raloxifene in the breast, and dissimilarly in others, as seen with these same two in the endometrium. The mechanism of the receptor interaction has been described as a distortion of the ligand-binding domain of the receptor that, in turn, interferes with coactivator binding and activity. The similarities between tamoxifen and raloxifene are easily understood though similar effects on the receptor. Differences between the two have been more difficult to explain.

BONE

Raloxifene is the sole SERM currently on the market for the treatment of bone loss and, therefore, the only SERM available on a routine basis for menopausal therapy. It had been previously suggested via analysis of breast cancer studies data that tamoxifen may protect against bone loss and fracture. Having launched with an indication for the prevention of osteoporosis, within a few years raloxifene also obtained one for the treatment of osteoporosis. It is thus one of the few agents with both these indications. Its effectiveness in this area has been proven in a number of large clinical studies, the first of which was published in 1997.⁵ In this study of Delmas et al, on data generated in France, it was shown that raloxifene, in doses of 30mg, 60mg, and 150mg effectively reduced radiographically diagnosed primary vertebral fracture by 55% and secondary vertebral fracture by 30% after three years. This study involved at-risk women, with a mean age of 67 years and a mean menopausal age of 19 years. In this same study, symptomatic vertebral fractures were reduced by 41%. Bone mineral density in spine and hip were increased by 2% to 3% over the same three-year period. The 60mg dose effected a 2.4% bone mineral density (BMD) increase in the lumbar spine and a 2.0% increase in the hip.

Subsequently, a larger and longer study was carried out that substantiated earlier findings. This study is

known as the Multiple Outcomes of Raloxifene Evaluation (MORE) and enrolled 7,705 women receiving 60 or 120mg of raloxifene over a four-year period of evaluation.⁶ In this, 6,828 of the enrollees obtained lumbar spine x-rays at baseline and at 36 months. At the 60mg dose, the incidence of vertebral fracture was 6.6%, and for those on 120mg, this number was 5.4%. By comparison, the placebo group had a vertebral fracture incidence of 10.1%.

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Non-vertebral fracture incidence was similar among those treated and those on placebo. BMD differences were 2.0% in the lumbar spine and 2.7% in the femoral neck when raloxifene was compared to placebo over 24 months. Over the four-year period raloxifene 60mg decreased vertebral fracture compared to placebo by 36%, RR = 0.64 (95% CI = 0.48-0.76). Again, there was no parallel reduction in non-vertebral fractures except for those with the radiographically most severe vertebral fractures as seen in post-hoc analysis.

The Continuing Outcomes of Raloxifene Evaluation Study (CORE) is a follow-up to MORE in which 4,007 patients, previously enrolled in MORE were followed for 48 addition-

al months. The primary endpoint shifted from bone to breast cancer reduction but non-traumatic, non-vertebral fractures were also followed. Vertebral fractures are reported only as adverse events. Patients were placed on raloxifene 60mg versus placebo and were given 500mg of calcium and 4-600mg of Vitamin D per day. In addition, they were allowed other anti-resorptive agents excepting estrogen or hormone therapy. The program has completed and publication of data should be shortly forthcoming.

It is important that, for the time being, we continue to consider raloxifene solely as a bone drug. While it is tempting to speculate on its breast cancer reduction powers as well its coronary and other effects, we have to bear in mind that raloxifene has only two indications, namely the prevention and treatment of osteoporosis. Therefore we are bound to use it only in the bone arena and we are further compelled to take its measure against other antiresorptive and anabolic agents presently available. In that case there are the following facts to consider. Raloxifene is an impressive antiresorptive. Its reduction of vertebral fracture rate should cause no hesitation to using it where deemed appropriate. In BMD enhancement it ranks near the bottom of the antiresorptives but there is growing appreciation of other aspects of bone quality that are as equally important as BMD and this fact allows us to rest firmly on its vertebral fracture data alone.

In the world of medical marketing there is enormous pressure brought on raloxifene because of its lack of hip fracture data. It stands alone with calcitonin sharing this problem. The other antiresorptives all have some kind of data supporting hip fracture reduction, the last coming on behalf of estrogen out of the Women’s Health Initiative (WHI).¹ In truth, many of these results are challenged because of lack of sufficient numbers or poor study design. How important is this? It is a question without any answer. It has been specu-

lated that all of the other agents may also have some untoward side effects, thus making them risky for decades-long use.

On the other hand, alendronate now has 10-year data emphasizing both safety and maintenance of BMD. It can also be concluded that raloxifene fits nicely into the bone scheme as an intermediate agent to be used after hormones and before the bisphosphonates or newer anabolics may be needed.

BREAST

Tamoxifen has long been established as a routine adjuvant agent in the treatment of estrogen receptor positive (ER+) breast cancers. The weight of evidence was affirmed in the Breast Cancer Prevention Trial in America⁷ and in the International Breast Intervention Study-I (IBIS-I). The former showed around a 50% reduction in incidence rate and the latter study, around a 30% reduction. While these findings were not corroborated in the smaller Royal Marsden Hall (Great Britain) and the Italian Tamoxifen Prevention Study, it is widely held that these two were flawed by patient numbers or certain selection issues.

The association between raloxifene and breast health has intrigued clinicians from the beginning. A post hoc analysis of MORE patient data indicated a reduction in the incidence of ER+ invasive breast cancer reaching 76% over four years for patients receiving 60mg or 120mg of raloxifene daily.⁸ Best results were seen in patients with highest levels of endogenous estrogen. As is the case with tamoxifen, there were no positive effects on estrogen receptor negative (ER-) tumors.

This is not to say that cautionary positions have not existed regarding the relationship between raloxifene and breast cancer. There have been questions raised about the potential for interference with subsequent tamoxifen efficacy in patients who had previously taken raloxifene. Conversely, there have been concerns

voiced about giving raloxifene to patients who have completed a course of tamoxifen knowing that tamoxifen use, at least for the present, is limited to five years and that continuation with another SERM afterward might also be risky. There are no hard data to support these fears but they persist nevertheless. It has been my experience that at least some oncology centers have no reservations about con-

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tinuing such patients on raloxifene but, again, hard data is lacking.

The hope is that most if not all of the questions regarding raloxifene and breast cancer will be answered with the data generated from two studies yet to be made public. These are the CORE study and the Study of Tamoxifen And Raloxifene (STAR). The CORE study is completed and preliminary data indicate a reduction in the incidence of invasive breast cancer of 58% (HR =0.42, 95% CI = 0.23-0.75). STAR should have results soon. STAR is a direct head-to-head comparison of the two drugs. Other SERMs are also being studied in the area of breast cancer. Arzoxifene is being looked at in tamoxifen-resistant patients with metastatic breast cancer. In addition, aromatase inhibitors are being tested for their usefulness in treating breast cancer survivors.

ENDOMETRIUM

Tamoxifen is associated with stimulation of the endometrium and resulting hyperplasia and carcinoma. This drug has, in addition, been found to increase the risk of uterine sarcoma. Raloxifene escapes sharing these most unfavorable side effects as it is felt to be neutral vis-à-vis the uterus and especially the endometrium.⁸ Earlier findings of fluid present in the endometrial cavities of raloxifene users are rarely reported today. This may be because of work showing that the fluid is not associated with cancerous or pre-cancerous lesions. Raloxifene is felt not to be a carcinogen in the uterus.

HEART

Cardiovascular disease (CVD) is another area where raloxifene is actively studied and where past results indicate some similar as well as some disparate results when raloxifene is compared to estrogen. Prior studies had shown that in breast cancer patients being treated with tamoxifen, use of that drug was associated with a reduced risk of coronary heart disease (CHD).⁹ These conclusions were limited by patient numbers and the fact the CHD was not a primary study endpoint. On the other hand, two large studies in which heart disease was assessed in post hoc analysis showed neither risk nor benefit with tamoxifen use. These were the breast cancer prevention (NSABP P-1) trial, with over 13,000 subjects and the Early Breast Cancer Trialist's Collaborative Group, with around 36,000 subjects.

Although the broad spectrum of recent studies with clinical endpoints have indirectly cautioned against relying too heavily on surrogate marker data when attempting to predict coronary events, it is worth mentioning how raloxifene affects them. In general, raloxifene has a most favorable profile regarding cardiovascular intermediate markers, the most notable exception being its neutrality versus HDL. This, in turn, should predict a

favorable risk profile in cardiovascular events.¹⁰ Raloxifene lowers total cholesterol and LDL. Failing to elevate HDL overall, it does elevate HDL-2, the active oxidative component. Raloxifene is also neutral versus triglycerides, C-reactive protein, and PAI-1.

Additional encouraging findings include lowering of lipoprotein (a), homocysteine and plasma fibrinogen. Furthermore, raloxifene may have a positive effect on insulin resistance in hyperinsulinemic women.

Does this carry forward to positive clinical endpoints? To begin with, we have known from the start that raloxifene increases the risk of thromboembolic disease with a RR of around 3.0. This parallels the findings with both tamoxifen and estrogen. This adverse venous thromboembolism (VTE) effect has hounded raloxifene to some extent since its introduction. There are mitigating circumstances, however, in that the absolute risk for VTE is small as is overall mortality.

More optimistic findings are revealed in the paper published by Barrett-Connor et al in 2002.¹¹ She analyzed data from the MORE patients and concluded that, overall, raloxifene neither improved nor worsened the risks for cardiovascular disease. There was no early rise in the incidence of CVD as had been the case in WHI and HERS. This relative neutrality was sustained for the four years of observation. More impressive was the finding that, in the subset of osteoporotic patients at highest risk for cardiovascular disease, raloxifene was associated with a 40% decrease in risk that impacted on both the cardiovascular and cerebrovascular areas. It is hoped that the Raloxifene Use in The Heart (RUTH) study with over 10,000 women enrolled will further clarify the SERM effect on the heart. The data from RUTH are still a few years away.

OTHER AREAS OF CONCERN

Inevitably, raloxifene, or any of the future SERMs, will be held up to the

standards of estrogen to assess therapeutic value in areas other than bone. What exactly these standards are is now, of course, subject to much discussion and we are learning that estrogen was never quite the panacea many held it to be. Heart benefits have been pared away as have been cognitive and Alzheimer's benefits. Pelvic floor function and urinary disorders are other areas where the benefits of estrogen are in question. As for the SERMs, while broader claims paralleling those of hormone therapy have never really been made, speculation

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abounds as to what their potential might be. As yet we have little data on cognition. While raloxifene as yet has not been shown to have positive effects of cognition, it has not been found to be inhibitory either.¹² We have a mixed bag of results on pelvic floor and urinary function with both SERMs and estrogen with some of the next generation of SERMs actually being held back by unfavorable findings in this area. Raloxifene, on the other hand, has not been found to have any negative impact on these functions. There are no positive findings available for SERMs in some of the other areas where estrogen has had a constructive impact, among them skin quality, vaginal atrophy, age-related macular degeneration and colon cancer.

THE FUTURE

A great many SERMs exist under development in this country and many hundreds more outside of America are presently in use. In view of their myriad and unpredictable actions in the body it is perhaps not too surprising that they are employed for a number of uses around the world. These include not only menopause therapy and particularly bone loss prevention, but also menstrual cycle regulation, fertility control, weight control, and as nutritional supplements. Cyclofenil, a SERM used for ovulation induction in Sweden and Japan, one that I experimented with over 20 years ago, has now emerged in the world of body building as some sort of anabolic agent and testosterone enhancer.

It is probably not too far fetched to imagine a more perfect SERM that will one day fulfill the secret wish many may have to come up with another one-pill approach to menopause therapy that successfully replaces estrogen. Raloxifene's causing or exacerbating hot flashes has been a major problem in broadening its acceptance. The two newest SERMs probably closest to the market, lasofoxifene and basodoxifene, will both claim to not cause hot flashes, or at least not as much as raloxifene. It is unlikely that they will do much better in the area of VTE and the lesser problematic leg cramps associated with SERMs use. Arzoxifene is being tested in both endometrial as well as breast cancer treatment and has shown a great deal of promise.^{13,14}

Can any SERM actually treat hot flashes? Apparently none that we know of at the present time. Perhaps such a pill will one day emerge from the laboratory. On the other hand, if it is indeed borne out that raloxifene or any future SERMs reduce the risk of breast cancer by 50% or 60%, and may be taken over a longer course, much will be forgiven regarding side effects. It will become very hard to market against such a family of drugs.

PRESENT RECOMMENDATIONS

As I see it there is still a piece of the pie for everybody. How long this situation lasts is anyone's guess. For the present time there is really no adequate substitute for estrogen in the transitional phase of the early menopause. It is probably still the cheapest and most effective approach to the problems associated with this period although it is not felt to be as safe as previously held. If estrogen is begun, how long should it be given?

The latest paradigm allows for estrogen use in the lowest dose for the shortest time. The former value is easy to determine, the latter less so. Many women who might benefit from hormones may never take them, but many who start them will not want to quit. With proper informed consent, these choices will remain to a great degree with the patient herself.

I see a role for raloxifene, or future SERMs, after estrogen use has stopped. This would be for those patients in whom maintenance of bone mass is desired and for whom stronger antiresorptives are not yet indicated. One counter argument is that bisphosphonates may be given safely over the long course and there is no need for a SERM. with its potential side effects. Advocates of these two families of drugs, SERMs and bisphosphonates, may argue interminably about their relative merits and dangers. The clinician has to be conversant with the data and make a personal choice for recommendation. These choices will not be easy.

If one chooses to go with raloxifene, thought should be given as to not stopping estrogen abruptly but rather going through a step down from estrogen into a step up to the SERM. Since there is no hard science behind this thought one would have to develop a personal protocol to enforce it. A review of the literature for WHI close-out recommendations failed to substantiate any differences between abrupt or step-wise cessation for estrogen use. On the other hand the concept of a type of estrogen "withdrawal syndrome" has existed for some time.

The further question as to whether estrogen and SERMs can be given together is frequently raised and is presently being studied. The rationale might involve vasomotor control but the issue of combining two agents with VTE risk gives reason for caution.

So, estrogen or hormones for four to five years, raloxifene or a successor SERM for another five to 10 and then bisphosphonates and statins for whatever the duration. Does this make sense? On the surface it appears to a tossing of sops to all parties, akin to political pork barreling. I see it as being as rational as any alternative agenda. Marketing forces have launched potent campaigns for and against nearly every therapeutic agent in this arena. And I repeat, if the breast cancer prevention data are sustained, and, if cardiac protection or even neutrality is maintained, a very large piece of the pie will eventually belong to the family of SERMs.

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Use of DHEA in Menopause Practice



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DHEA (Dehydroepiandrosterone) is an adrenal androgen that is used as an over the counter dietary supplements. Recently, a pharmacologic grade of DHEA has been approved by the U.S. Food and Drug Administration. This is therefore an appropriate time to reassess the use of over the counter DHEA supplements.

A review of recent studies in lupus patients and in healthy menopausal women using DHEA for symptom relief will be discussed. Theories behind the benefits of DHEA in clinical practice will also be reviewed. Finally, a review of the new data measuring endogenous DHEA in different ethnic perimenopausal populations will be discussed.

Recently oral Prestara (aka Prasterone) GL701 (DHEA 100mg, 200mg, Genelabs*) received orphan drug status for its use in systemic lupus erythematosus. A clinical trial performed by the Lupus Study Group used oral DHEA at a dose of 200mg. The subgroup of women on DHEA required less than 7.5mg of prednisone was used over a sustained amount of time in a larger proportion of patients. The added DHEA therefore decreased the need for high dose prednisone.¹ On a 200mg DHEA dose, serum DHEA levels changed from 66.2 ± 329.9 $\mu\text{g/dl}$ to $784.9 \pm 1,029.9$ $\mu\text{g/dl}$. Therefore, serum levels achieved were very high and extremely variable. Additionally testosterone levels increased from 16.7 ± 13.2 ng/dl to 56.9 ± 60.2 ng/dl on 200mg prasterone.

Lowering the dose of corticosteroids (prednisone) should lead to positive outcomes in lupus patients with fewer side effects from steroid use, less bone loss, cataracts etc. However, the levels of DHEA achieved were high and variable especially on the 200mg dose. In another analysis doses up to 1000mg of DHEA were needed to treat lupus patients.² In this particular study from the GL 701 Lupus Study Group, the majority of women were also on hormone therapy. The data resurrect the subject of the use of DHEA (now in pharmacological grade) for many of its purported benefits in menopausal patients (documented in the past) by a number of prominent

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OB/GYN investigators in the field).³⁻⁵ Needless to say, the doses used in lupus patients are much higher than the doses anyone would use in menopausal patients. The pharmacologic grade DHEA may not be transferred easily to the menopausal patient seeking treatment for her symptoms.

DHEA is currently considered an over the counter dietary-supplement and consistent grade/quantity of these preparations is questionable. Also doses for healthy menopausal replacement should be “physiologic,” and the amount and the form of therapy are still in question (oral or transcutaneous).

General dosages for “physiologic” replacement have been 25mg-50mg

orally (micronized) or DHEA 10% cream. The published benefits of DHEA have included a decrease in insulin resistance, a decrease in obesity, beneficial immunomodulatory effects, and beneficial bone effects. The risk benefit ratio for breast protection and cardiovascular protection, however, remain controversial.⁶⁻¹¹

More recently, Genazzani et al studied two groups of postmenopausal women in a prospective case study design. Women were divided into two groups (10 apiece) (50-55 and 60-65) and treated with 25mg DHEA.^{12,13} The surprising findings were that with this low dose there were alleviation of climacteric symptoms, and changes in mood (increasing levels of beneficial anxiolytic substances such as allopregnanolone and beta-endorphin). There was no change in the endometrium, with no bleeding and no change in endometrial thickness over a six- and 12-month period of time. At 12 months, serum DHEA levels rose to about 2-5 $\mu\text{g/ml}$ in both groups with testosterone levels rising to 1.5 $\mu\text{g/dl}$. Estradiol levels rose to 100 pg/ml and progesterone levels showed a slight increase to 1.0 ng/ml . Cortisol levels were slightly suppressed to 150 $\mu\text{g/d}$ while allopregnanolone levels rose to 300 pg/ml and Beta-endorphin levels to 60 pg/ml . Labrie et al, using percutaneous administration of DHEA in elderly postmenopausal females (60-70 years) over one year, showed beneficial effects on more parameters; with bone density increased, vaginal maturation indices improved and with no endometrial stimulation.¹⁴⁻¹⁵

For sexual dysfunction acute dosing of DHEA of 300mg showed improvement in subjective and physiologic sexual responses and an increase in mental and physical sexual arousal ratings.¹⁶ Again, this dose is much higher than what has been routinely used in postmenopausal women. Dr. Spark at last year’s “Androgen Insufficiency in Women: The Princeton Conference” highlighted the probable importance of DHEA supplementation

in female sexuality but also spoke of the variable potencies of over the counter DHEA preparations.¹⁷ Moreover, the pharmacology and the lowest possible effective dose is not known. Doses of DHEA for hot flash relief are significantly lower than the doses for sexual dysfunction. The latter doses approach the values used in lupus patients.

All the drug intervention regimens quoted in the literature used different patient populations and a whole variety of different doses (25mg-200mg). It appears that the 25mg-50mg dose is optimal in early/late postmenopausal women. Higher doses at this point should be reserved for medical management of patients with autoimmune disease such as lupus.

Dr. Ferdinand Labrie and associates have coined the phrase “intracrinology” to denote “individualized” extragonadal synthesis of hormones.¹⁸ Transformation of adrenal precursor steroids such as DHEAS and DHEA into androgen and estrogens varies at peripheral sites dependent on various steroidogenic and metabolizing enzymes in particular peripheral target issues. His theory is that the best hormonal combination maybe DHEA and a Selective Estrogen Receptor Modulator (SERM). He maintains that DHEA in combination with a SERM would be the most appropriate hormone combination. This has yet to be proven in a clinical trial. His belief is that androgens inhibit breast cancer and therefore combining with a SERM that also does so would be of benefit since you would achieve beneficial estradiol and progesterone levels at appropriate end organ sites. Again, this is still not fully tested in clinical trials.

Despite the fact that DHEA is the most abundant steroid in human serum, we know little about normal levels during the menopausal transition. The Melbourne Women’s Study is a prospective study of biologic life style factors associated with the normal menopausal transition. Women in this

cohort experienced natural menopause sometime within the seven-year of followup. DHEAS levels decreased significantly with age and BMI but had no relationship to menopausal status in the study.¹⁹

Recently, 3,029 women between the ages of 42-54 from five ethnic groups were studied for two years in the Swan Study (Study of Women’s Health Across the Nation).²⁰ During the menopausal transition, changes in testosterone and estradiol were correlated with changes in DHEAS. Prior observations had suggested that the ovary is devoid of gonadotropin receptors and steroidogenic enzymes. The parallel changes in DHEAS and testosterone in this database would then suggest that most of the testosterone postmenopausally is produced from peripheral conversion of DHEAS.

Circulating levels of DHEAS in the Swan Study Group exhibited marked ethnic variations. Chinese and Japanese women had the highest levels whereas the lowest were observed in African American and Hispanic women. So contrary to the Melbourne Study, DHEAS levels in the Swan Study did correlate with menopausal status. The authors warn that the two-year time period of the study may be too short to make an absolute conclusion at this point. Needless to say, it would point to DHEA as an important source of androgen in postmenopausal women and suggests that ethnicity and BMI play an important role in the amount of androgens produced postmenopausally and by inference the amount of DHEA that would need to be replaced.

Since DHEA appears to have a relevant function as an immune modulator and since it appears to be an important source of androgens postmenopausally, further work in this area is definitely needed. Dosing and route of administration (oral vs. transcutaneous) are still unresolved. Levels as high as those used in lupus patients and in some of the studies for sexual dysfunction should not be

used. The genotype of the individual that may best benefit from such therapy is also still in question. Studies comparing transcutaneous testosterone vs DHEA as an androgen supplement are needed. We should pursue further research in this area but pharmacologic dosing in all menopausal women is still premature.

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