Selective estrogen receptor modulators in chronic renal failure

JOSE´ R. WEISINGER, ITA PFEFFERMAN HEILBERG, EDDY HERNÁNDEZ, RAUL CARLINI, and EZEQUIEL BELLORIN-FONT

Division of Nephrology, Hospital Universitario de Caracas, Universidad Central de Venezuela, Caracas, Venezuela; and Division of Nephrology, Universidade Federal de Sao Paulo, Sao Paulo, Brazil

Selective estrogen receptor modulators in chronic renal failure.

Background. In addition to renal osteodystrophy, postmenopausal women on dialysis could be at risk of osteoporosis. Hormone replacement therapy (HRT) could have beneficial effects as well as potentially serious risks, especially in uremic women, due to the pharmacokinetics of estradiol in renal failure. Therapeutic alternatives, such as the selective estrogen receptor modulators (SERMs), have shown the benefits of estrogen on bone and serum lipid levels, without its adverse effects on the breast and endometrium, in nonuremic women.

Methods. Recent data on the effect of the SERM raloxifene in bone and lipid metabolism in osteoporotic postmenopausal women on dialysis is reviewed. Since the estrogen receptor (ER) gene has been suggested as a candidate marker for osteoporosis, we investigated whether ER polymorphism could have predicted the BMD response to raloxifene.

Results. Hemodialyzed women on raloxifene demonstrated increased trabecular bone mineral density (BMD) and decreased bone resorption markers. Similarly, LDL-cholesterol values dropped significantly. ER gene polymorphism analysis of baseline BMD parameters did not differ between PP/xx or Pp/Xx groups. Nevertheless, patients on raloxifene with PP/xx genotypes, but not those with Pp/Xx, showed a higher trabecular BMD after one year on treatment, suggesting that homozygous women for P or x alleles of the ER have a better BMD response to raloxifene.

Conclusion. Raloxifene and, most likely, other SERMs, could represent a good alternative to HRT in postmenopausal uremic women.

ESTROGEN AND BONE IN UREMIA

The term osteoporosis must be applied with caution in both uremic and patients on dialysis, who have a complex range of metabolic bone disease [1]. Nevertheless, osteoporosis could begin early in time. An important proportion of young women on dialysis (<50 years old) are already amenorrheic and relatively hypoestrogenic with significantly lower bone mineral density (BMD) and higher bone resorption markers, compared to similar women with normal menstruation [2]. At the same time, only a few postmenopausal uremic women are being offered hormone replacement therapy (HRT), indicating that these patients are managed differently than nonuremic women. Apart from the lack of awareness of the treating physicians, women with end-stage renal failure are usually stoic and rarely complain about gynecologic problems that may seem trivial in comparison to their renal disease burden [3–6].

The adverse effects of hypoestrogenism on bone have been widely recognized. Lack of estrogens is associated with increased osteoclastic bone resorption [7–10]. In addition, estrogen may affect parathyroid hormone action by increasing PTH mRNA at the parathyroid gland [11] and modulating PTH action on bone. Clinical evidence in favor of an effect of estrogen in uremic bone disease has been recently suggested in a controlled study of a small group of postmenopausal women on dialysis, in which treatment with transdermal estradiol and the cyclic addition of norestisterone acetate significantly increased lumbar spine BMD after one year [12].

Nevertheless, there could be some problems with the use of HRT in uremic women. First, it has been demonstrated that women on dialysis, when compared to nonuremic women, showed elevated baseline estradiol levels which increased significantly after the ingestion of estradiol. This could suggest that renal failure may decrease estradiol catabolism and affect the pharmacokinetics of exogenous estradiol [13]. Second, a recent study on the risks and benefits of estrogen plus progesterin in healthy postmenopausal women has introduced a word of caution in HRT therapy [14]. In this randomized controlled primary prevention trial of the Women’s Health Initiative, in which 16,608 postmenopausal women were followed for 5.2 years, it was demonstrated that the outcomes were more harmful than beneficial in the estrogen plus progesterin group versus the placebo group. Although the estrogen plus progesterin treatment reduced the observed hip and vertebral fracture rate and colon cancer by one third, the rate of women experiencing coronary

Key words: osteoporosis, bone mineral density, hemodialysis, menopause, hormone replacement therapy, selective estrogen receptor modulator, raloxifene.

© 2003 by the International Society of Nephrology
heart disease increased by 29%, venous thromboembolism was twofold greater, stroke rates were increased by 41%, and invasive breast cancer increased by 26%.

**SELECTIVE ESTROGEN RECEPTOR MODULATORS IN HEALTHY WOMEN**

Several alternatives are available for women who cannot, or refuse to, take estrogen. Two potential estrogen-like therapies include raloxifene and tamoxifen. These are selective estrogen receptor modulators (SERMs), and they possess tissue-selective estrogen agonist and antagonist properties [15]. In ovariectomized animals, raloxifene preserves bone density, lowers serum total cholesterol concentrations, and inhibits aortic cholesterol accumulation, without causing endometrial hyperplasia [16]. The mechanism responsible for the apparent tissue-selective activity of raloxifene is not completely understood. In vitro experiments suggest that raloxifene has different effects than estradiol at the estrogen receptor, including differential modulation of DNA response elements [17] and induction of a different conformational change in the transactivation domain of the ligand-binding domain [18]. A long-term (40 months) clinical trial, the Multiple Outcomes of Raloxifene Evaluation (MORE) study, involving 7705 postmenopausal women with osteoporosis, found that raloxifene’s antagonistic effect on the breast appeared to cause a reduction in the risk of breast cancer [19]. Raloxifene did not increase the risk of endometrial cancer, but there was an increased incidence of thromboembolic disease, hot flashes, influenza-like symptoms, peripheral edema, and leg cramps. In this same study, most of the women had lumbar spine x-rays at baseline and after 36 months of treatment. Among the women receiving 60 mg raloxifene, 6.6% had new vertebral fractures, compared with 10.1% in the placebo group, but the risk of nonvertebral fractures was similar. Thus, treatment of uremic women with a SERM, with their spectrum of breast and uterus antagonist effects, and action on bone as an estrogen agonist, seems a less harmful and more rational therapeutic strategy [20].

Baseline blood determinations and BMD analysis were obtained. Blood was drawn every three months, and BMD was evaluated after one year. To investigate whether the ER polymorphism could have predicted the response of BMD to raloxifene in those postmenopausal women in chronic hemodialysis, blood was obtained for genomic DNA extraction from peripheral leukocytes.

The ER gene polymorphic region for both PvuII and XbaI, located in part of intron 1 and exon 2, was amplified by PCR using the following primers:

$$5’ – CTG CCA CCC TAT CTG TAT CTT TTC CTG – 3’$$
$$5’ – TCT TTC TCT GCC ACC CTG GCG TCG ATT ATC TGA – 3’$$

After digestion, the products of PvuII and XbaI restriction fragment length polymorphism (RFLP) were submitted to agarose gel electrophoresis. The presence of the restriction site was labeled as $p$ or $x$ alleles (for PvuII and XbaI reactions, respectively), and its absence as $P$ or $X$.

Both groups of women were similar regarding age, time on dialysis, time after menopause, medical management of renal osteodystrophy, and degree of osteoporosis or osteopenia. Blood biochemical parameters, including serum creatinine, calcium, PTH, and phosphorus, as well as sexual hormone levels (total estradiol, follicle stimulating hormone, and luteinizing hormone) were also similar in both groups.

Bone mineral density at the lumbar spine improved significantly after one year of treatment with raloxifene, with no change in the placebo group (Fig. 1). No significant changes were observed at the femoral neck. Likewise, there was a decrease in markers of bone resorption.
the decrease in LDL-cholesterol and the fact that raloxifene in postmenopausal uremic women could be the decrease in LDL-cholesterol and the fact that raloxifene has been shown to be neutral overall, and protective in high-risk women with respect to coronary and cerebrovascular events. The long-term effect of SERMs in chronic renal failure patients remains to be determined.

CONCLUSION

Although fracture risk reduction data are needed, these preliminary observations on the effect of raloxifene on BMD and bone resorption markers in uremic women are interesting. Another important beneficial effect of raloxifene in postmenopausal uremic women could be the decrease in LDL-cholesterol and the fact that raloxifene has been shown to be neutral overall, and protective

ACKNOWLEDGMENTS

This study was supported by grant G-97-008808 of the Fondo Nacional de Ciencia, Tecnología y Innovación de Venezuela (FONACIT) and Fundarenal-HUC. The help of the physicians, nurses, and secretarial staff of our dialysis units is fully appreciated. We thank Samira A. Gomes and Larissa G. Ferreira for performing the estrogen receptor gene determinations. We acknowledge the contribution of Drs. Javier San Martin and Lee Kay Pen, from Ely Lilly and Co. for providing the study drug.

Reprint requests to José R. Weisinger, M.D., Hospital Universitario de Caracas, Division of Nephrology, Apartado Postal 47365, Los Chaguaramos, Caracas, Venezuela 1040.

E-mail: jweising@telcel.net.ve

REFERENCES