Effects of tibolone and raloxifene on health related quality of life and sexual function

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Abstract

Objectives: Study to compare the effects of tibolone and raloxifene on health related quality of life, sexuality and vaginal atrophy.

Methods: A double-blind, randomized study was conducted in 308 osteopenic, but otherwise healthy, postmenopausal women (mean age 66 years) who received tibolone 1.25 mg/day or raloxifene 60 mg/day for 2 years. Health related quality of life was assessed by the Women's Health Questionnaire (WHQ), sexual function by the McCoy Female Sexuality Questionnaire (MFSQ) and vaginal atrophy by assessing the Karyopycnotic Index (KI) and Vaginal Maturation (VM).

Results: At week 104, the tibolone group showed a trend towards an improved health related quality of life (HRQoL) mean score in eight out of nine WHQ domains. HRQoL scores approximated values for premenopausal women, being pre-defined as “clinically relevant.” The raloxifene group showed a trend to a diminished HRQoL mean score from baseline to week 104. No difference could be assessed between the tibolone and raloxifene group in mean total score and separate domains scores of the MFSQ, except for the vaginal lubrication domain (p= 0.037). The increase in KI and VM was statistically significantly greater with tibolone than with raloxifene (for both KI and VM p<0.0001). Tibolone and raloxifene were equally well tolerated.

Conclusions: In older postmenopausal women, tibolone treatment showed a trend towards an improvement in quality of life and sexuality when compared to raloxifene.
Introduction

The publication of the Women’s Health Initiative\(^1\) and Million Women Study\(^2\) studies led to a change in thinking about the use of hormone therapy (HT) for osteoporosis prevention and prompted consideration of other available strategies such as bisphosphonates, parathyroid hormone, selective estrogen receptor modulators (SERMs) and the selective tissue estrogenic activity regulator (STEAR) tibolone.\(^3,4\)

Tibolone regulates estrogenic activity in a tissue selective manner, resulting in estrogenic activity in certain tissues, like bone, vagina and the brain, hereby improving vasomotor symptoms, whilst avoiding it in the endometrium and breast.\(^5\) This tissue selective action of tibolone and its metabolites is a result of a number of mechanisms, depending on the target tissue, and include local metabolism, inactivation or activation of steroid metabolizing enzymes and differential receptor binding.

In contrast, the tissue selective action of the SERMs is solely a consequence of receptor binding which results in estrogenic agonist or antagonist effects, depending on the target tissue. Tibolone therefore differs from the SERMs, not only because it has no antagonistic effect on the estrogen receptor, but also because it acts via a variety of mechanisms.\(^6\)

Efficacy in the prevention and treatment of osteoporosis in postmenopausal women has been confirmed in randomized controlled studies with raloxifene\(^7-11\) and with a standard 2.5 mg/day dose of tibolone.\(^12-14\) A lower dose of 1.25 mg/day tibolone has also proved consistently effective\(^15-17\) and is now considered to be the optimal dose for osteoporosis prevention. Raloxifene has the benefit of reducing the risk of invasive breast cancer, but suggestions that it has beneficial effects on coronary heart disease have not been confirmed.\(^18\)

In common with conventional estrogen and estrogen-progestogen therapy (EPT), tibolone relieves climacteric symptoms and vaginal atrophy\(^19-22\) and there is evidence that it has beneficial effects on sexual function and mood.\(^22\) Unfortunately, SERMs such as raloxifene may cause or exacerbate hot flushes.\(^8,9,24\) This may deter many postmenopausal women, as the most common reason for taking HT is to alleviate climacteric symptoms.

The primary objective of the Study of Tibolone’s Effects on osteoPenia (STEP) study was to compare the effects of tibolone 1.25 mg/day and raloxifene 60 mg/day on lumbar vertebrae bone mineral density (BMD) in osteopenic women. These findings have been published elsewhere.\(^25,26\) The secondary objectives include determination of health-related quality of life, sexual function and vaginal atrophy, the results of which are presented here.

Methods

Subjects

Osteopenic, but otherwise healthy, postmenopausal women (aged 60-79 years) were included in this randomized, double-blind, double-dummy, parallel group comparative
study conducted in eight centers in Australia, France, Germany, Italy and the USA. The study was conducted in compliance with the Declaration of Helsinki, International Conference of Harmonisation guidelines and Good Clinical Practice; the protocol was approved by the Independent Ethics Committee or Institutional Review Board of each center. All women provided written informed consent. The women were recruited through investigator’s practices, referrals and advertisements in the local press and broadcast media. Women were included if they had been amenorrheic for at least a year (if the date of last menstruation was unclear because of perimenopausal HT use, HT had to have been used for at least 2 years), were ambulatory, and had a lumbar vertebrae bone mineral density of -2.5 to -1.0 standard deviations of the T-score and a body mass index of >19 to ≤30 kg/m². Exclusion criteria included history/presence of malignancy (or current suspicion of malignancy) or thromboembolic disorders, abnormal Pap smear or transvaginal ultrasound (TVUS), undiagnosed abnormal vaginal bleeding in the previous year, uncontrolled hypertension, type I diabetes mellitus, serious decompensated renal or hepatic disease, abnormal laboratory values, X-ray showing symptomatic vertebral fracture, history of bilateral hip replacement, bone disease other than osteoporosis, and use of >20 cigarettes or 4 alcoholic drinks per day. Other reasons for exclusion included current or recent prolonged use of drugs that affect steroid pharmacokinetics, use of anabolic steroids, calcitonin or raloxifene in the last 6 months, use of alendronate or risedronate for >6 months (12 month washout if >6 months), use of etidronate (6 or 12 month washout if used for ≤1 year or >1 year, respectively), use of fluoride for ≥2 weeks, systemic glucocorticoid treatment for >1 month in the past 6 months, a change in thyroid medication in the last 6 weeks, and ever use of estrogen and/or progestin implants. Washout periods were 8 weeks for oral estrogen and/or progestin, 4 weeks for transdermal HT or local estrogen, and 20 weeks for medroxyprogesterone acetate-containing contraceptives.

**Treatment**
The women were randomized to treatment with oral tibolone 1.25 mg or raloxifene 60 mg once daily for 2 years. Treatment was taken in the evening and a double-dummy technique was used to preserve blinding. Concomitant use of sex hormones or anabolics, hepatic enzyme inducing drugs, cholestyramine, colestipol, coumarin products or medication for osteoporosis (except calcium/vitamin D) was not permitted.

**Assessments**
Following screening and baseline visits, assessments were performed after 4, 12, 24, 52, 76 and 104 weeks of treatment. Health related quality of life, assessed by the Women’s Health Questionnaire (WHQ) was measured at baseline and each follow up visit. The WHQ is a self-administered questionnaire consisting of 36 items, which are divided into 9 subscales: somatic symptoms, depressed mood, memory/concentration, anxiety/fears, sexual behavior, vasomotor symptoms, sleep problems, menstrual symptoms and attractiveness. Changes from baseline in the various WHQ domains are expressed in terms of clinical relevance when compared to pre-menopausal values, which is the valid standard to analyze the WHQ.
Sexual function was assessed by the McCoy Female Sexuality Questionnaire Short Form (MFSQ) at baseline and at each follow-up visit. The MFSQ questionnaire consists of four domains created from 9 items: sexual interest, vaginal lubrication, orgasm and sexual partner. A global score is based on the sum of all 9 items.28 A vaginal smear was obtained at baseline and after 52 and 104 weeks and vaginal atrophy was assessed by the Karyopycnotic Index (KI) and Vaginal Maturation (VM). Vaginal smears were analyzed by a central cytology/pathology laboratory. The percentage of superficial, intermediate and parabasal cells in the smear was determined. The KI was defined as the percentage of superficial cells. VM was calculated by multiplying the percentage of superficial cells by 1, intermediate cells by 0.5 and parabasal cells by 0 and summing the total. VM values ranged from 0, when only parabasal cells were present (atrophic specimen), to 100 when only superficial cells were present (mature specimens). Physical and gynecological examinations, including TVUS and mammography were performed at baseline and after 52 and 104 weeks. Information on possible adverse events was obtained at each visit.

Statistical analyses
Analyses were based on the Intent-to-treat principle (ITT analysis): all subjects treated who had at least one post-baseline assessment were included in the efficacy analysis. WHQ and MFSQ analyses were performed using the non-parametric Wilcoxon rank test using a complete case analysis (i.e. domain and global scores were only calculated when all the items were available for the subject). Statistical analyses of KI and VM were performed by an Analysis of Variance (ANOVA) model using the last observation carried forward (LOCF) approach. An imputed case analysis was used to account for subjects who did not complete the final visit at week 104. All tests were two-sided with statistical significance defined as $P<0.05$. Analyses were performed using SAS 8.2 software.

Results
In total, 310 women with a mean age of 66 years were enrolled and randomized to trial medication of which finally 153 in the tibolone group and 155 in the raloxifene group commenced treatment. The number of subjects at each stage of the study and their baseline demographic characteristics are shown in Figure 1 and in Table 1. There were no relevant differences between the groups. The ITT population consisted of 115 subjects on tibolone and 120 on raloxifene. The study was discontinued prematurely by 52 subjects in the tibolone group and 50 in the raloxifene group, resulting in 101 completers on tibolone and 105 on raloxifene.

Health-related quality of life
Baseline demographic data relating to quality of life, such as marital status, total family income, level of formal education and occupation, were comparable between the two treatment groups. The majority of women were married, retired, had attended primary or secondary high school and rated their health as good.
Tibolone showed statistically significant benefits (lower mean score) over raloxifene on a number of health-related quality of life domains (Table 2): In the raloxifene group, the WHQ vasomotor symptom domain showed consistently higher scores than in the

**Table 1. Demographic characteristics (AST)**

<table>
<thead>
<tr>
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<th>Tibolone (n=153)</th>
<th>Raloxifene (n=155)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>66.0 ± 4.6</td>
<td>65.9 ± 4.4</td>
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<tr>
<td>Weight (kg)</td>
<td>66.1 ± 8.7</td>
<td>64.8 ± 8.3</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.1 ± 6.0</td>
<td>160.7 ± 5.7</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>25.8 ± 2.8</td>
<td>25.1 ± 2.9</td>
</tr>
<tr>
<td>Time since menopause (years)</td>
<td>17.4 ± 6.5</td>
<td>17.8 ± 7.0</td>
</tr>
<tr>
<td>Number (%) of women who have ever used HT and/or bone agents</td>
<td>65 (42.5%)</td>
<td>63 (40.9%)†</td>
</tr>
<tr>
<td>Number (%) of hysterectomized women</td>
<td>40 (26.1%)</td>
<td>41 (26.5%)</td>
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†data missing for one woman

Values given as mean (±SD) except where stated
tibolone group reflecting a worsening of vasomotor symptoms in the raloxifene group during treatment. The differences were statistically significant at week 12 (p=0.005), week 24 (p=0.001) and week 52 (p=0.002) in favor of the tibolone group. Other domains showing statistically significant differences in favor of the tibolone group included depressed mood at week 24 (p=0.016) and week 104 (p<0.001), sexual behavior at week 52 (p=0.006) and week 104 (p=0.011), somatic symptoms at week 52 (p=0.048) and attractiveness at week 12 (p=0.04). There were no statistically significant advantages for raloxifene on any of the subscales.

No clinical relevant changes based on normative WHQ domain scores for premenopausal women when compared to baseline were found in any of the two groups. However, tibolone treatment resulted in a trend towards an improved quality of life from baseline to week 104 on eight of the nine WHQ subscales: somatic symptoms, depressed mood, memory/concentration, anxiety/fears, sexual behavior, vasomotor symptoms, sleep problems and menstrual symptoms. In contrast, women treated with raloxifene showed a trend towards a poorer health-related quality of life over the same time period on six subscales: somatic symptoms, depressed mood, sexual behavior, vasomotor symptoms, menstrual problems and attractiveness. A clinically relevant “worsening” was found for the attractiveness domain in the raloxifene group from week 52 onwards.

**Sexual function**

Only 58 (38%) women in the tibolone group and 65 (42%) women in the raloxifene group provided data for the MFSQ. The main reason for not completing this questionnaire was absence of sexual activity. Figure 2 shows the scores in each of the four domains and the total score at baseline and after 52 and 104 weeks of treatment. Generally, there was little to no difference between the tibolone and raloxifene group in mean and median scores for the 4 domains (sexual interest, sex with partner, orgasm and vaginal lubrication) and the global score of the McCoy Female Sexuality Questionnaire, Short Form at any of the post-baseline visits.

A statistically significant difference in favor of the tibolone group was only found for the vaginal lubrication domain at week 52 where for tibolone a 47% improvement and for raloxifene a 8% improvement from baseline was observed (p=0.037).

A post-hoc separate item analysis showed statistically significant differences in favor of the tibolone treated women on a few questions including the presence of sexual thoughts and fantasies (week 104: p=0.047), feeling aroused/excited (week 24: p=0.038) and a decrease in pain during intercourse (week 52: p=0.02).

**Vaginal atrophy**

There were no statistically significant differences between the tibolone and raloxifene groups in baseline KI (4.69% and 4.92%, respectively) or VM (18.06% and 17.74%, respectively). Vaginal atrophy was improved by tibolone, but remained unchanged in the raloxifene group. The increase from baseline in both KI and VM was statistically significantly (p<0.0001) greater with tibolone than with raloxifene after 52 and 104 weeks (Figure 3).
Figure 2. Mean MFSQ actual domain scores and global score (center) at baseline and after 52 and 104 weeks of treatment with tibolone or raloxifene: ITT population (complete case analysis)

Effects of tibolone and raloxifene on health related quality of life and sexual function
Safety and tolerability

Tibolone and raloxifene were equally well tolerated. The incidence of adverse events (AEs) was similar in both groups. AEs that were reported in >10% of subjects in any or both of the two treatment groups were: muscle spasms (tibolone 25.5%; raloxifene 26.5%), arthralgia (tibolone 16.3%; raloxifene 12.9%), hyperhidrosis (tibolone 13.7%; raloxifene 16.1%), back pain (tibolone 13.1%; raloxifene 11.6%), weight increase (tibolone 12.4%; raloxifene 13.5%), nasopharyngitis (tibolone 11.1%; raloxifene 11.6%), menopausal symptoms (tibolone 10.5%; raloxifene 18.1%), hypertension (tibolone 11.8%; raloxifene <10%), arthralgia (tibolone <10%; raloxifene 12.9%). Adverse events classified as menopausal symptoms (including night sweats and hot flushes) occurred in 23 women (15%) treated with tibolone compared with 37 (24%) treated with raloxifene. AEs accounted for the withdrawal of 27.5% of women in the tibolone group and 23.2% in the raloxifene group; the most common reasons for withdrawal were reproductive system and breast disorders (9.2%), weight increase (3.9%) and gastrointestinal disorders (3.9%) with tibolone and vascular disorders (4.5%) and weight increase (3.2%) with raloxifene. One subject in the raloxifene group died after a fall causing a subarachnoid bleeding. Drug-related (defined as definitely, probably or possibly related to study medication according to the investigators) serious adverse events (each of which occurred in one subject) were postmenopausal bleeding, uterine polyp/vaginal bleeding, endometrial disorder, hydrometra, meningioma, breast cancer and transient ischemic attack in the tibolone group and benign breast neoplasm, dystonia and exanthema/pruritis in the raloxifene group.

There were no clinically relevant differences between the groups with regard to physical and gynecological examinations, cervical Pap smear, TVUS, mammography, vital signs or laboratory parameters. Mean double layer endometrial thickness for tibolone and raloxifene at week 52 were: 1.50 mm and 0.40 mm respectively and at week 104: 1.34 and 0.29 respectively.

Figur 3. Mean change from baseline in Karyopycnotic Index and Vaginal Maturation after 52 and 104 weeks of treatment with tibolone (n=112) or raloxifene (n=118): ITT population (LOCF)
Discussion

The recent controversies surrounding conventional HT and the risk of breast cancer and cardiovascular disease have resulted in many women stopping treatment.\textsuperscript{29,30} The need remains, however, for effective ways of relieving vasomotor symptoms, improving quality of life and preventing mediate to long term consequences of menopause such as vaginal atrophy and osteoporosis. Amongst the alternative options are the STEAR tibolone and the SERM raloxifene, which have been directly compared in this 2 year study in osteopenic postmenopausal women. Tibolone 1.25 mg/day effectively prevented bone loss and resulted in a larger increase of BMD at the lumbar spine and hip than standard dose raloxifene and less risk of ongoing bone loss from the lumbar spine.\textsuperscript{25}

There were a number of other distinctions between the two treatments. Tibolone improved health-related quality of life, with WHQ values approximating those for premenopausal women, whilst women treated with raloxifene showed a trend towards a poorer quality of life.\textsuperscript{27} Changes from baseline of a few WHQ domains were statistically significantly larger in favor of the tibolone group when compared to the raloxifene group, particularly the sexual behavior, attractiveness and vasomotor symptoms all showed a statistically significant improvement from baseline. Of note, however, is that results of questionnaires, especially when analyzed at various time points during the study, should be interpreted with caution as a statistically significant difference at only one measured time point without being maintained over the duration of the study and/or without approximating values predefined as being clinically relevant, are likely to be subject to chance. Vasomotor symptoms were consistently worse with raloxifene throughout the study. This was confirmed by the higher incidence of vasomotor symptoms reported as adverse events with raloxifene. Vasomotor effects, which are experienced by more than 80% of untreated postmenopausal women, are often considered the most disturbing symptom of the menopause.\textsuperscript{30,31}

Although this is the first direct comparison of the efficacy of tibolone and raloxifene in postmenopausal women, studies in estrogen-deficient rats have shown that tibolone, in common with estrogen and clonidine, restored tail temperature to that seen in non-ovariectomized animals, whilst no change occurred with raloxifene.\textsuperscript{32} Previous clinical studies have demonstrated that raloxifene causes or worsens vasomotor symptoms, whilst tibolone provides a similar level of relief to that achieved with conventional HT.\textsuperscript{19,33,34} The lower 1.25 mg dose of tibolone, as used in the current study, has also been shown to be effective in controlling hot flushes, sweating and other symptoms, resulting in significantly greater relief than that seen with placebo.\textsuperscript{21,22}

No statistically significant differences between the two treatment groups regarding changes in sexual function, measured by the MFSQ total score and domain scores, could be observed except for some separate item scores for the tibolone treated women. This is remarkable as it is thought that the reduction in sex hormone binding globulin levels (resulting in increased free testosterone) caused by tibolone, together with the direct androgenic effects of the $\Delta 4$ metabolite, contribute to the beneficial effects on sexual well-being reported in previous studies.\textsuperscript{23}
In the current study, measures of vaginal atrophy showed improvement with tibolone, whilst there were no meaningful changes in the raloxifene group. Both KI and VM were increased with tibolone, resulting in a significant difference from the raloxifene-treated women. Most likely the improvement in the vaginal lubrication domain of the MFSQ is a result of the improved condition of the vaginal tissue after estrogenic exposure.

Tibolone and raloxifene were equally well tolerated in these elderly postmenopausal women. A number of previous studies have also directly compared various safety and tolerability aspects of tibolone and raloxifene, although all were conducted with the higher 2.5 mg/day dose of tibolone. In this study neither tibolone nor raloxifene were associated with any significant changes in endometrial thickness or unscheduled bleeding/spotting confirming their favorable endometrial profile indicated in previous comparative studies. It must be emphasized that this study was not powered to identify the significance of less common serious AEs, such as VTE and stroke.

A strength of this study is that this is the first randomized controlled study comparing tibolone with raloxifene on various measures of menopausal health in elderly women. In addition we collected sexuality and quality of life data over a longer time period. Limitations of this study are that the actual number of subjects (310) was somewhat lower than the planned number of 325 and that for only one third of the women evaluable MFSQ data were available. For the primary efficacy parameter on bone the difference between groups was large enough to detect a statistical significant difference. However, for the secondary endpoints concerning behavioral science, the study population might not have been large enough to pick up clinically relevant differences especially because quality of life and sexuality are influenced by so many other factors than pharmaceutical treatment only. For the MFSQ analyses the two study groups were not entirely comparable at baseline. As only women who were sexually active completed the questionnaires a selection has taken place which might have prevented to measure more extreme changes in the MFSQ during the trial period. Moreover, the tibolone group had higher baseline scores on the MFSQ. In which way higher or lower scores at baseline influences treatment outcomes is a topic for further investigation.

In conclusion, tibolone showed benefits over raloxifene in certain aspects influencing quality of life which concern: depressed mood, presence of somatic symptoms, improvement of vasomotor symptoms, feelings of attractiveness, improvement of sexual function specifically due to improvement of vaginal lubrication, reduction of painful intercourse, presence of sexual thoughts and improvement of sexual arousal. In addition to the bone preserving effects of both treatments, the above aspects make tibolone an comprehensive treatment for postmenopausal with osteopenia.


33. Baracat EC, Barbosa IC, Giordano MG et.al. A randomized, open-label study of conjugated equine estrogens plus medroxyprogesterone acetate versus tibolone: effects on symptom control, bleeding pattern, lipid profile and tolerability. Climacteric 2002; 5: 60-69.

