Current knowledge of the effect of tibolone on the breast and uterus: an extract from the guidelines for the use of tibolone in South Africa

The South African Tibolone Advisory Board
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Background

Tibolone is an analogue of the progestin, norethynodrel. After ingestion, it is converted to three metabolites, namely 3 alpha and 3 beta hydroxytibolone which have oestrogenic effects, and delta 4 isomerase, which has progestogenic and androgenic properties. Both the oestrogenic metabolites bind to the alpha oestrogen receptor, but not the beta oestrogen receptor, whilst the delta 4 isomer binds to the alpha and beta oestrogen, the progestogen and the androgen receptors. Tibolone also is a sulphatase inhibiter, blocking conversion of oestrone sulphate to oestrone, as well as stimulating local sulphotransferase activity. In contrast to other forms of postmenopausal hormonal therapy, it decreases sex hormone binding globulin and hence increases circulating free testosterone, and thereby further adding to its androgenicity. Tibolone significantly decreases vasomotor symptoms, mood disorders, insomnia, bone loss, vaginal atrophy. It has a favourable impact on the cardiovascular system and minimal impact on the endometrium and on mammary tissue. It has been classified as a selective tissue oestrogenic activity regulator, a STEAR.[1-3]

Tibolone is an important treatment option in the management of the menopause and its specific properties not only relieve the general symptoms of the menopause, but have specific value amongst postmenopausal women with specific conditions. This would include, most notably, postmenopausal women with symptoms such as significant malaise and fatigue, marked insomnia, impaired sexual well being, labile moods, excessive breast tenderness or mastalgia.

Women with premature ovarian failure, and possibly even the young woman who has been rendered menopausal by surgical bilateral salpingo-oophorectomy, would benefit specifically from its use.

Tibolone and the breast

A particular attribute of tibolone is its impact on breast tissue. As stated previously, it inhibits the oestradiol sulphatase, but stimulates the sulphotransferase enzymes, which result in low levels of endogenous oestradiol in mammary tissue. The risk of mastalgia and breast density events which are fairly common with the other oestrogen containing preparations, particularly with oral preparations and the continuously combined preparations, are therefore minimised.

Increased breast density does decrease the sensitivity of the mammography and increases the frequency of recall for repeat mammographic studies. Mammographic density before use of tibolone, or other forms of oestrogen therapy, reflects the biological measure of the response of the breast to endogenous hormonal milieu and thus may be a surrogate marker for breast cancer development, whilst post treatment mammographic density is an indication of the ability of the breast tissue to metabolise additional exogenously prescribed oestrogen and may not be a surrogate marker. Nevertheless, tibolone will play an important role in both these scenarios – a woman who has increased breast density on mammographic examination whilst on hormonal therapy, needs to have the therapy stopped for about four weeks after which the examination is repeated. Provided the mammogram is clear, tibolone can then be reinstituted. In the woman who wishes to start postmenopausal hormone therapy and has a history of increased breast density, tibolone should be the drug of choice.[4,5]

Until about 2004, the risk of developing breast cancer in users of tibolone was not considered in the same light as had been the case for the other oestrogen/progestogen preparations. It has only been the Million Women Study that has suggested an increased risk (RR 1.45; 95% confidence interval 1.25–1.67) in tibolone users, even though within this study the RR was similar to that of oestrogen only users and significantly less than for the oestrogen/progestogen users.[6] This finding proved to be a surprise, and is in direct contrast to the LIFT study where there was a decreased risk for breast cancer as a secondary end point measure in women using 1.25 mg of tibolone daily compared to non users.[7] Unfortunately there are no randomised controlled trials which have primarily assessed

the risk of breast cancer in users of tibolone, so any further debate would in fact be speculative, although the consensus of the advisory board was that the Million Women Study was very likely to have overestimated the risk in light of some more recent data emanating from small prospective studies.

The very recent publication of the LIBERATE trial, wherein survival was assessed amongst breast cancer survivors who were using tamoxifen and tibolone as their adjuvant therapy, has proved to be most disappointing. Unfortunately women who were using this combination had a greater risk for developing breast cancer metastases compared to survivors who were using placebo only. In this study, approximately 3100 women with a history of breast cancer were randomised to tibolone or to placebo. The study cohort in both groups was about six years postmenopausal and on average about two years since their breast cancer surgery. Approximately 57% had axillary nodal metastases at the time of their surgery, 57% having had a mastectomy and 42.5% breast sparing surgery. About 71.5% of the breast tumours were oestrogen receptor positive.

The RR for breast cancer recurrence or metastases in the LIBERATE study was 1.4 (95% CI 1.14–1.70) in the women on tibolone. There was no significant difference in the sites of recurrence when comparing local recurrences versus recurrences in the contra lateral breast, although there was a non significant trend to support more likelihood of developing distant metastases in women using tibolone. The overall incidence of breast cancer recurrences was lower in lymph node negative women. Women with oestrogen receptor negative tumours had no increased risk of recurrence and surprisingly, users of aromatase inhibitors had a higher risk of developing a recurrence than women using tamoxifen. Even though the tibolone did significantly decrease vasomotor symptoms and increase bone mineral density (BMD) amongst the users, the study was terminated prematurely with the conclusion, and the recommendation, that tibolone was not safe in breast cancer survivors.[8]

This finding is obviously disappointing as breast cancer survivors commonly have menopausal symptoms, which can be most debilitating. The menopausal symptoms may arise as a result of the irradiation, the chemotherapy, the use of adjuvant tamoxifen or because of the natural age of the patient. Because of the specific properties of tibolone, it was hoped, and anticipated, that it could be an appropriate option in these patients. The increased incidence of breast cancer metastases did not increase the mortality amongst the patients. In fact tibolone was not different from placebo with regard to other safety outcomes, such as mortality, cardiovascular events or gynaecologic cancers. Vasomotor symptoms and bone mineral density improved significantly with tibolone compared to placebo.

These are the facts which must be used when counselling breast cancer survivors and it must ultimately, and unfortunately, be the patient who makes the final decision.

Quality of life must be weighed up against the small increase in relative risk of recurrence.

Tibolone and the uterus

From an endometrial point of view, tibolone has primarily a progestogenic effect and there is abundant evidence to support that it rarely induces endometrial hyperplasia or carcinoma in users. It has a very low propensity to induce endometrial proliferation. The occurrence of vaginal bleeding or spotting appears to be less common compared to users of continuously combined hormonal therapy. It also has a greater likelihood of resulting in amenorrhoea. The incidence of bleeding in the first 3–6 months, and up to three years after commencement, is lower in tibolone users compared to users of continuously combined hormonal therapy. In most studies these lesser occurrences of abnormal bleeding have led to better adherence to therapy with fewer patients stopping their medication.[9-11]

With view to endometrial cancer, the LIBERATE study did not show any increased risk in tibolone users versus users of placebo. It is only the Million Women Study that has suggested that tibolone may increase the risk of endometrial cancer in users. In this latter study, tibolone was associated with significant increases in the risk of endometrial cancer, namely a RR of 1.79 (1.43–2,25). An impact, that astonishingly, was similar to the use of continuous unopposed oestrogen therapy! Interestingly, tibolone was noted to substantially increase risk in normal and overweight women, in contradiction to the other continuous combined preparations and cyclical combined therapy being associated with reduced risk in obese women and having an adverse impact only in thin women.[6] The findings of this observational trial needs to be confirmed by trials with a different study design before a change in practice can be advised.

Should any bleeding occur during the first 3–6 months of usage, reassurance is all that may be needed, unless the bleeding is excessive. If the bleeding is excessive or it occurs after six months, the patient must have at least a transvaginal ultrasound examination of the pelvis, not only to determine the endometrial thickness, but also to exclude any other pelvic pathology. An endometrial thickness of < or = 5 mm, reflects an atrophic endometrium and the patient generally only requires reassurance. In cases such as these, if the bleeding does persist, however, tranexamic acid will be effective in decreasing or stopping the bleeding. If the endometrial thickness is > 5 mm, it is highly recommended an endometrial sampling is undertaken, using a Z-sampler, pipelle, etc. Should this not be possible or available, a formal diagnostic dilatation and curettage should be performed. In any woman with bleeding, it is always important to bear in mind that there may be an underlying endometrial polyp causing the problem, and this must always be excluded. Unless obvious pathology is found, tibolone should not be stopped, as in the vast majority of cases the bleeding ceases spontaneously or usually stops after the administration of tranexamic acid.

Summary of the guidelines

(a) Tibolone is as effective as other hormone therapy in managing the general symptoms of menopause.
(b) Specific groups of postmenopausal women who will benefit significantly from the use of tibolone after the menopause include postmenopausal women with:
    (i) Vasomotor symptoms who have significant mood swings or who are taking psychoactive medication at the time of the menopause.
    (ii) Poor sexual function, be it due to poor libido and/or because of dysparunia.
    (iii) Premature menopause as a result of a bilateral salpingo oophorectomy at a young age, including women who have had the surgery for endometriosis.
    (iv) A history of breast tenderness or increased mammographic density, or who were on other conventional hormonal therapy when their increased mammographic density was noted and who wish to continue with hormonal therapy.
    (v) Spontaneous premature ovarian failure.
    (vi) An increased risk for fracture or have had a fracture as a result of osteoporosis and are in the age group 50–60 years.
(c) Pre-, peri- and postmenopausal women on GNRH analogues who require "add-back therapy".

The Advisory Board

With the recent publication of the LIBERATE trial, it was felt appropriate and opportune to refocus on tibolone and re-evaluate its role as an option in postmenopausal therapy. An International Consensus Group has published its clinical recommendations and practical guidelines in 2005, and this is still the fundamental cornerstone of consensus.[1] The aim of the locally convened advisory board was not only to review the published data, but also to specifically provide its opinion with view to the use of tibolone in South Africa. The meeting of the advisory board took place at Fairlawns in Sandton, in November 2009, and had the cumulative input of ten national menopausal experts. There were a total of nine presentations from which ultimately the final consensus report emanated.

The members of the Advisory Board were:

Prof F Guidozzi (Chairman), Dr A Alperstein (Co-Chairman), Prof AB Koller, Dr T de Villiers, Dr J Coetzee, Dr M Davey, Dr R White, Dr P Koll, Dr T Kopenhager, Dr P Dalmeyer, Dr F Hayward.

Disclosure

All the members of the Advisory Board have spoken on behalf of a number of pharmaceutical companies about their products within South Africa for which they have received honoraria.

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Complete guidelines and references for complete guidelines available on request