GUIDELINE

Guideline for the use of tibolone in South Africa

Tibolone Advisory Board

Following 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 published its clinical recommendations and practical guidelines in 2005, and this is still the fundamental cornerstone of consensus. A locally convened advisory board has reviewed the published data on tibolone and presented an expert opinion on its use in South Africa.

With the recent publication of the Liberate Trial, it was felt appropriate to re-evaluate the role of tibolone as an option in postmenopausal therapy. An International Consensus Group 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 specifically to give its opinion on the use of tibolone in South Africa. The meeting of the South African advisory board had cumulative input from 10 national experts on menopause. There were a total of 9 presentations from which the final consensus report ultimately emanated. The meeting was sponsored by an unconditional grant provided by Adcock Ingram. The meeting of the advisory board took place at Fairlawns, Sandton, in November 2009 and had cumulative input from 10 national experts on menopause.

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, while the delta-4 isomer binds to the alpha- and beta-oestrogen, progestogen and androgen receptors. Tibolone is also a sulphatase inhibitor, 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, thereby further adding to its androgenicity. Tibolone significantly decreases vasomotor symptoms, mood disorders, insomnia, bone loss and 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 (STEAR).[2-4]

Advisory Board members: Professor F Guidozzi (Chairman), Dr A Alperstein (Co-Chairman), Professor A B 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.

There was general consensus that tibolone is an important treatment option in the management of the menopause and that its specific properties not only relieve the general symptoms of the menopause but have particular value for postmenopausal women with specific conditions. Most notably these include significant malaise and fatigue, marked insomnia, impaired sexual wellbeing, labile mood, and excessive breast tenderness or mastalgia.

Women with premature ovarian failure, and possibly even young women who have been rendered menopausal by surgical bilateral salpingo-oophorectomy, would obtain particular benefit from its use.

1. Menopausal symptoms

Tibolone has been shown in a number of placebo-controlled studies to eliminate or decrease hot flushes, night sweats, insomnia, headaches and fatigue as effectively as other oestrogen-containing products. There is, however, some evidence that it may be more effective than 17-beta-oestradiol in controlling symptoms in women with surgically induced menopause, also bringing about an improvement in somatic symptoms and sexual desire. It appears to be particularly effective in highly symptomatic women, and it should always be considered

as an alternative option if menopausal symptoms persist despite other forms of oestrogenic supplementation and a change of medication for control of menopausal symptoms is being considered.[5-8] Alpha- and beta-oestrogen receptors are found throughout the brain and there are androgen receptors in the hypothalamus. Tibolone has a favourable impact on moods, somatic symptoms and the 'feeling of wellbeing'. This may be attributed to the increase of beta-endorphin levels in the pituitary gland and plasma that occurs with its use, the androgenic impact of the delta-4-isomer metabolite on the brain, or the greater availability of testosterone because of lowered sex hormone binding globulin.[4,5] All these specific features not only have a positive effect on mood and wellbeing, including fatigue and malaise, but have a beneficial effect on sexual wellbeing, including sexual desire, frequency of orgasm, sexual responsiveness, arousability and fantasies. It also improves vaginal pulse amplitude, a measure of vaginal blood flow, in postmenopausal women, normalises the vaginal maturation index, increases vaginal lubrication, and generally decreases the symptoms of vaginal atrophy.[9-13]

2. Bone mass

Tibolone has been shown to be as effective as other oestrogen-containing preparations in increasing bone mass, although the increase appears to be dose dependent. In recently menopausal women it produces a highly significant improvement at both hip and spine, and it is as effective as other agents used in treating bone loss, including alendronate, raloxifene and risedronate. In older postmenopausal women, the increase in spine and hip bone mineral density (BMD) is substantial after 2 years. An improvement in BMD has also been shown to occur in older osteoporotic women with previous fractures. The benefits are seen with 1.25 and 2.5 mg, but not with 0.3 mg. The beneficial effect is equal to that of 2 mg oestradiol. It may be prudent to decrease the dose of tibolone to 1.25 mg in older postmenopausal women with a history of stroke or who are at high risk of stroke, because of the possible higher risk of stroke in women taking tibolone compared with placebo.[14-16]

3. Breast tissue

A particular attribute of tibolone is its impact on breast tissue. As stated previously, it inhibits 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 oral preparations and continuously combined preparations, is therefore minimised.

Increased breast density does decrease the sensitivity of 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 the endogenous hormonal milieu and may therefore be a surrogate marker for breast cancer development, while 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 while on hormonal therapy needs to have the therapy stopped for about 4 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.[17,18]

Until about 2004, the risk of developing breast cancer in users of tibolone was not considered as high as for the other oestrogen/progestogen preparations. It has only been the Million Women Study that has suggested an increased risk (relative risk (RR) 1.45; 95% confidence interval (CI) 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 oestrogen/progestogen users.[19] This finding was a surprise and is in direct contrast to the Lift Study, which found a decreased risk for breast cancer as a secondary end-point in women using 1.25 mg tibolone daily compared with non-users.[14] Unfortunately no randomised controlled trials 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 the light of some more recent data emanating from small prospective studies.

The very recently published findings of the Liberate Trial, which assessed survival among breast cancer survivors who were using tamoxifen and tibolone as their adjuvant therapy, have proved to be most disappointing. Women who were using this combination were found to have a greater risk of developing breast cancer metastases than survivors who were using placebo only. Even though tibolone did significantly decrease vasomotor symptoms and increase BMD in the users, the study was terminated prematurely with the conclusion and recommendation that tibolone was not safe in breast cancer survivors. This finding is disappointing, as breast cancer survivors commonly have menopausal symptoms, which can be very debilitating. The menopausal symptoms may arise as a result of the irradiation, the chemotherapy, the use of adjuvant tamoxifem, or the 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 RR for breast cancer recurrence/metastases in the Liberate Study was 1.4 (95% CI 1.14 - 1.70), even though the increased incidence of breast cancer metastases did not increase mortality.

In fact tibolone was not different from placebo with regard to other safety outcomes, such as mortality, cardiovascular events or gynaecological cancers. Vasomotor symptoms and BMD improved significantly with tibolone compared with placebo.

These are the facts that must be taken into consideration when counselling breast cancer survivors, and it must ultimately, and unfortunately, be the patient who makes the final decision[20] regarding quality of life versus the small increase in RR of recurrence.

4. Cardiovascular

Tibolone improves insulin insensitivity in postmenopausal women who are insulin resistant, does not have an adverse effect on blood pressure, including in women with hypertension, has a minimal impact on various haemostatic factors with a trend towards increased fibrinolysis, and lowers plasma levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides and lipoprotein(a). Tibolone does, however, reduce circulating levels of high-density lipoprotein (HDL) cholesterol, a putative cardioprotective lipoprotein. Despite this significant 20 - 30% decrease in plasma HDL cholesterol, however, it is unlikely to increase the risk of atherosclerosis, as shown by findings in the OPAL study of women taking tibolone who did not have an increase in carotid artery intima-medial thickness or an increase in the number of atheromatous plaques after 7.5 years of follow-up.[21] Of importance, tibolone has also been shown to increase C-reactive protein levels, although it has a mixed effect on venous thrombosis. On the one hand, it does not have an impact on activated protein C resistance or protein C, fibrinogen, factor VII, plasminogen activator inhibitor (PAI)-1 or plasmin/plasmin inhibitor (PAP) complex levels, whereas on the other hand it increases levels of prothrombin fragment 1+2 (F 1+2) and D-dimers. These surrogate markers for venous and arterial disease are inconclusive with regard to benefits or risks and require further research. Nevertheless the consensus is that provided it is commenced during the window of opportunity, as with all hormonal therapy, it does not increase the risk of cardiac disease.[21-23]

5. The endometrium

From an endometrial point of view, tibolone primarily has a progestogenic effect and there is abundant evidence that it rarely induces endometrial hyperplasia or carcinoma in users. It has a very low propensity to induce endometrial proliferation. Vaginal bleeding or spotting appears to be less common than in 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 after commencement, and up to 3 years, is lower in tibolone users than in users of continuously combined hormonal therapy. In most studies this decrease in the occurrence of abnormal bleeding has led to better adherence to therapy, with fewer patients stopping their medication.[24-26]

6. Conclusion

Taking into account all the beneficial effects on vasomotor symptoms, mood, sleep patterns, sexual desire and enjoyment, the atrophic vagina, the likelihood of breast tenderness and the favourable impact on the endometrium, most studies that have used quality-of-life measures concur that tibolone is well tolerated and has a very positive impact on quality of life and general wellbeing in postmenopausal women.[27,28]

Furthermore, there is accumulating evidence that it will also decrease body fat and significantly increase fat-free mass and total body water, leading to the conclusion that weight gain should not be a major concern among users.[29,30]

In order to minimise the likelihood of abnormal vaginal bleeding, it is best to only initiate use of tibolone 1 year after the menopause. Should any bleeding occur during the first 3 - 6 months of use, reassurance is all that will be needed unless the bleeding is excessive. If the bleeding is excessive or occurs after 6 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 ≤5 mm reflects an atrophic endometrium and the patient generally only requires reassurance. If the bleeding persists in such cases, tranexamic acid will be effective in decreasing or stopping it. If the endometrial thickness is >5 mm, it is highly recommended that an endometrial sample be taken, using a Z-sampler, pipelle, etc. Should this not be possible or available, hysteroscopic assessment of the endometrial cavity with a directed biopsy should be performed, and if this is not possible, formal diagnostic dilatation and curettage should be considered. In any woman with bleeding, it is always important to bear in mind that an underlying endometrial polyp may be 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 stops after the administration of tranexamic acid.

In summary

6.1. The advisory board felt that tibolone is as effective as other hormone therapy in managing the general symptoms of menopause.

6.2 In addition, there are specific groups of postmenopausal women who will benefit significantly from use of tibolone after the menopause. These include postmenopausal women with:

6.2.1 vasomotor symptoms or significant mood swings, or who are taking psychoactive medication at the time of the menopause

6.2.2 poor sexual function, whether due to poor libido and/or dysparunia

6.2.3 premature menopause as a result of a bilateral salpingo-oophorectomy at a young age, including women who have had surgery for endometriosis

6.2.4 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

6.2.5 spontaneous premature ovarian failure

6.2.6 an increased risk for fracture or who have had a fracture as a result of osteoporosis, and are in the age group 50 - 60 years

6.2.7 Pre-, peri- and postmenopausal women on gonadotrophin-releasing hormone (GNRH) analogues who require 'add-back therapy'.

7. Acknowledgement

The consensus report was prepared by Professor Franco Guidozzi, Chief Specialist, Professor and Academic Head of the Department of Obstetrics and Gynaecology at the University of the Witwatersrand, Johannesburg

8. Disclosure

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

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