CURRENT OSTEOPOROSIS MANAGEMENT

With a FOCUS on ideal length of treatment and considerations in the use of menopausal hormone therapy for fracture prevention

Introduction

This CPD Accredited report from the 16th congress of the National Osteoporosis Foundation of South Africa (NOFSA) held on 23-26 October 2014 at the Wanders Club, Sandton, South Africa, focusses on two review topics. Firstly, the ideal treatment time for Primary Osteoporosis that will ensure protection from fractures in the individual patient and secondly, clinical aspects concerning the use of Menopausal hormone therapy with regard to its use in osteoporosis.

These topics are directed at everyday clinical practice by Dr Tobie De Villiers, Specialist, Cape Town.

How long should we treat primary osteoporosis?

KEY MESSAGES

• In considering the length of treatment, the clinician must evaluate the efficacy, safety and pharmacokinetics of the specific drug in the context of the individual patient’s risk, response and adherence to therapy

• Menopausal hormone therapy prevents bone loss and fractures at any age, but benefit is more likely to outweigh risks when initiated in the first 10 years after menopause or before age 60 years

• Combination of estrogen and progestogen may be associated with the promotion of pre-existing breast cancer after 7 years and with estrogen alone therapy after 10 years

• Raloxifene has been shown to be effective for 3-5 years but has no specific limitation on duration of use

• Teriparatide use is restricted to a period of 18-24 months

• Strontium ranelate has been shown to be efficient in the prevention of fractures over 10 years. Although there is no specific limitation placed on duration of treatment, older patients may be at increased risk of cardiovascular risk. Strontium ranelate is contraindicated in the patient at increased cardiovascular risk

• Bisphosphonates used for periods longer than 3-5 years may be associated with ONJ and AFF, but the benefit to risk ratio is still very favorable. Bisphosphonates bind tightly to bone and have a residual effect when stopped. A drug holiday can be considered after 3-5 years in patients at low risk of fracture after treatment

• In all instances where therapy with a particular agent is discontinued and fracture risk remains significant, alternative therapies should be instituted.

“The question of the length of treatment with bone specific medications for the prevention of fractures in individuals with osteoporosis remains a much debated and controversial issue,” Dr Tobie de Villiers pointed out.

“There are however useful principles which can aid the clinician in his decision – making for an individual patient approach.”
Menopausal hormone therapy (HT)

HT is indicated for the prevention of bone loss and fractures in postmenopausal women at risk if initiated before the age of 60 years or within 10 years of menopause. The length of treatment is not subject to mandatory timelines but should be guided by the indication for treatment. The only safety issue related to duration of treatment is the promotion of preexisting breast cancer. When using estrogen alone therapy, this is not applicable in the first 10 years of therapy. When using combination of estrogen and progestogen, in the treatment naïve patient, this is not applicable in the first 7 years of treatment.

On discontinuation of HT, bone mineral density (BMD) reverts to baseline mostly within one year with the possibility of some degree of down-stream protection.

On stopping HT, other anti-osteoporotic agents should be used if the patient is still at risk of fractures.

Raloxifene

Raloxifene has been shown to be effective for 5 years without specific complications, but should be used with caution in patients at risk of stroke. Unlike HT, the risk of estrogen receptor positive breast cancer is decreased with the use of raloxifene. Cessation of this agent results in loss of BMD to baseline levels within 1 year and other agents should be considered for at-risk women.

Teriparatide for severe osteoporosis

“This recombinant human parathyroid hormone is the only pure bone anabolic agent presently available and is reserved for severe osteoporosis. It has a very narrow therapeutic window of 18-24 months. After this period an increase in bone resorption occurs and the anabolic effect is lost.” Termination of therapy with this agent must be followed by other anti-resorptive therapy.

Strontium ranelate

Fracture efficacy has been established over 10 years in a study and there were no specific safety issues during this period. Older patients are at greater risk for CVD and VTE’s and this aspect must be taken into consideration.

Bisphosphonates

The bisphosphonates are still the most widely used drugs for the prevention of post menopausal fractures. Bisphosphonates present different challenges when considering length of treatment;

1. Safety aspects related to duration of use

Osteonecrosis of the jaw (ONJ) is defined as exposed bone without healing after 8 weeks following a dental procedure. ONJ is extremely rare at the dosages of bisphosphonates used for fracture protection and is more commonly related to much higher dosages of bisphosphonates as used in oncology

Atypical fractures of the femur shaft (AFF)

Bisphosphonates reduce the risk of femur neck fractures. After 3-5 years of bisphosphonate therapy, a possible relationship with fractures of the femur shaft has been observed, although a direct causal effect has not been proven. If bisphosphonates are used for periods more that 3-5 years, the number of prevented femur neck fractures still far outnumbers the possible AFFs caused.

2. Unique pharmacokinetics of the bisphosphonates

Bisphosphonates are tightly bound to bone with residual efficacy up to 3 years or longer after cessation of therapy. “Zoledronic acid, (iv) is bound more tightly to bone than alendronate, which in turn is more highly bound than risedronate and ibandronate”, Dr de Villiers noted.

In terms of length of alendronate therapy, the FLEX trial suggested that alendronate may be discontinued after 5 years, except for those patients at high risk of vertebral fractures who should be continued for a further 5 years. The zoledronate extension trial suggested that after 3 years of treatment, a drug holiday of 3 years can be considered except in patients at risk of vertebral fracture.

NOFSA guidelines provide a useful approach to length of bisphosphonate therapy (Table 1).
Menopausal hormone therapy and bone in 2014: have we completed a full circle?*

Table 1. NOFSA Guidelines

We recommend that treatment with BPs should continue for at least 5 years. Following 5 years of therapy, we suggest that a drug holiday be considered in those who are not at high fracture risk. In subjects with fractures or BMD that is still in the osteoporosis range (T-score ≤ -2.5), in those with ongoing risk factors, and in those whose BMD responded poorly while on treatment (e.g. BMD decreased markedly), treatment with a non-BP like strontium ranelate or teriparatide should be considered.

- Estrogen and combined estrogen/progestogen therapies prevent the development of postmenopausal osteoporosis and osteoporosis-related fractures at both the spine and hip.
- Although the Women’s Health Initiative (WHI) investigators claimed that the risks of HT outweigh the benefits, these assertions were based on an illogical interpretation of the data and are unfounded.
- The timing of hormone therapy (HT) is very important. HT should be prescribed during the ‘therapeutic window of opportunity’, before the age of 60 years and within 10 years of menopause.
- Estrogen-only HT is not associated with an increased risk of breast cancer for at least 10 years.
- The increase in risk of breast cancer associated with combined HT is not clinically important if HT is used for less than 10 years and if started early after menopause.
- HT is associated with an increased risk of deep vein thrombosis, but this increased risk is limited predominantly to the first year of treatment.
- HT has additional benefits in postmenopausal women that are not shared by other bone-preserving treatments. These include fall prevention, reduction of vasomotor symptoms and prevention of urogenital atrophy.
- In the younger postmenopausal woman, in addition to its wide range of benefits for symptom relief, estrogen (alone or in combined HT) should be considered a first-line option for both treatment of osteoporosis and fracture prevention.

Overview of key developments in bone preservation
In 1984, estrogen was considered first-line therapy in treatment and prevention of postmenopausal osteoporosis. It was previously known that using estrogen after oophorectomy, even if it was initiated 3 or 6 years after surgical sterilization, could prevent bone loss. However, these results were based on metacarpal bone mineral content measurements using dual photon absorbiometry and they were not conclusively confirmed until the early 1990s, with the development of Dual-Energy X-Ray absorptiometry (DEXA), which allowed accurate measurement of bone mineral density (BMD). In 1996 the Postmenopausal Estrogen/Progestogen Intervention (PEPI) randomised trial showed that the use of hormone therapy (HT) with conjugated equine estrogen (CEE)/medroxyprogesterone acetate (MPA) at the time of menopause prevented menopause-related bone loss at both the spine and the hip. Although observational data suggested that HT would also reduce fractures, this had yet to be proven in a randomised controlled study.

In contrast, the efficacy of alendronate, a bisphosphonate, in reducing the incidence of postmenopausal vertebral fractures was conclusively demonstrated in postmenopausal women with and

*This presentation is based on the 8th Pieter van Keep memorial lecture delivered by Dr De Villiers in September 2014.

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In contrast, the efficacy of alendronate, a bisphosphonate, in reducing the incidence of postmenopausal vertebral fractures was conclusively demonstrated in postmenopausal women with and
without pre-existing vertebral fractures (Fracture Intervention Trial: FIT; 1996 and FIT2; 1998).\textsuperscript{1,6}

With this, interest in estrogen as a bone preserving agent began to wane.

In contrast, the interest in alternative prophylactic treatments was strengthened by publication of similar results for another bisphosphonate, risedronate (VERT study) and the selective estrogen receptor modulator (SERM), raloxifene, in the MORE study in 1999.\textsuperscript{7,8} Consequent to this, it was speculated that raloxifene might be a suitable replacement for postmenopausal estrogen. “However, raloxifene does not treat hot flushes, but rather increases their intensity, and suggestions that it may be suitable for recently postmenopausal women proved to be unfounded,” Dr de Villiers noted.

Recombinant parathyroid hormone (teriparatide) was introduced in 2001. It was the first available anabolic agent and also had evidence of fracture reduction efficacy.\textsuperscript{9} However, it is necessarily available only in injectable form, is expensive and efficacy is limited to 18-24 months of treatment. Consequently, it did not become a popular choice of therapy.

Evidence of the benefits of risedronate in reducing hip fracture published in 2001 strengthened the case for the use of bisphosphonates as the drugs of choice for prevention of postmenopausal fractures.\textsuperscript{10}

In 2002, the Women’s Health Initiative (WHI) showed that estrogen reduced both hip and vertebral fractures in postmenopausal women; even in women at low risk of fracture.\textsuperscript{11} This was important, because most other pharmacological agents do not have fracture-prevention data for both vertebral and non-vertebral fractures (including hip fractures). However, the WHI investigators further concluded that the positive effects of HT were outweighed by negative effects. Estrogen was downgraded to second-line therapy in the treatment of osteoporosis.\textsuperscript{12}

The introduction of strontium ranelate in 2004 was supported by robust vertebral fracture data in women with severe osteoporosis.\textsuperscript{13} Although it was initially positioned for use in osteopenia, recent data and concerns over its cardiovascular safety have resulted in its use being restricted to women with severe osteoporosis.

With the publication of the HORIZON study in 2007, the bisphosphonates were once again in the spotlight. In this 3-year trial, zoledronic acid was associated with a 70% reduction in risk of vertebral fractures and 41% reduction in risk of fractures at the hip.\textsuperscript{14} The was achieved with a convenient dosing schedule of once yearly intravenous infusion.

The benefits of postmenopausal estrogen were again confirmed in 2008 by the LIFT study showing that tibolone (a synthetic compound that is tissue-selectively metabolized to estrogen, progesterone and testosterone), reduced both vertebral and nonvertebral fractures.\textsuperscript{15} However, although it was also associated with a reduction in breast and colon cancer, concern was expressed over an apparent increase in fatal stroke (but not in total stroke).

“In reality, the absolute number of fatal strokes in this study was small and the women in which they occurred were at high risk before treatment, so the actual clinical significance of this finding is questionable,” Dr de Villiers pointed out.

In 2008, bazedoxifene (BZA), a SERM similar to raloxifene, was shown to significantly reduce the incidence of vertebral fractures in postmenopausal women with osteoporosis.\textsuperscript{16} It is also a potent inhibitor of endometrial proliferation, and studies were initiated to investigate its utility in combination with CEE for management of vaso-motor symptoms and bone preservation in postmenopausal women. These studies confirmed that this progestin-free combination provided effective symptom control, while improving BMD at both the spine and hip.\textsuperscript{17,18} It has recently become available in USA and is indicated for management of menopausal symptoms and prevention of osteoporosis.

Fracture data is not yet available.

The therapeutic options for osteoporotic women were further increased in 2009 with publication of favorable fracture data for denosumab.\textsuperscript{19} Denosumab is the first biological drug available for fracture prevention (human monoclonal antibody against RANK ligand).

Finally in 2013, the circle of trial evidence was completed, when 13-year data from the WHI was published, again renewing interest in the use of estrogen for bone health after menopause.

**Why did WHI lead to concerns about the safety of estrogen?**

The fracture data for estrogen in the WHI is actually very robust. In the combined CEE/MPA arm, the hazard ratios (HR)
(95% confidence intervals) for hip, clinical vertebral and non-vertebral fractures were 0.66 (0.45-0.98); 0.66 (0.44-0.98) and 0.77 (0.69-0.86), respectively. In the estrogen-only arm, they were 0.61 (0.41-0.91) for hip fracture, 0.62 (0.42-0.93) for clinical vertebral fracture and 0.79 (0.63-0.79) for total fractures. However, the investigators declared that these and other benefits were outweighed by adverse effects of HT.

The ensuing black box warning by the Federal Drug Administration (FDA) in the USA, confining HT to the treatment of vasomotor symptoms and the prevention of osteoporosis and the relegation of HT to second line treatment of osteoporosis, by the European regulatory agencies placed significant limitations on the use of HT, despite the positive data. It is notable that after 2002, in the USA, where most doctors stopped using HT for postmenopausal bone health, epidemiological studies demonstrated a significant increase in the incidence of fractures among perimenopausal and postmenopausal women. (Figure 1).²⁰

It is important to understand how the WHI investigators reached their conclusions on the risk/benefit ratio of HT. They based their estimation on a model called the global index (Table 2), where selected endpoints are grouped together as being of equal significance and judged on numerical occurrence, disregarding individual statistical significance of difference to placebo.²¹ “This approach, to combine HRs for a widely heterogeneous set of outcomes so that summation of ‘good effects’ may be subtracted from summation of ‘bad effects’ to produce a single HR that determines a risk to benefit ratio, is clearly irrational,” Dr de Villiers noted.

Furthermore, although vertebral fracture data and data for all non-vertebral fractures were reported in the study results,

| Table 2. Global Index: WHI²¹ More or less cases per 10000 patients |
|-----------------------------|------------------|------------------|
|                             | Combined CEE/MPA | CEE alone        |
| Coronary heart disease      | +6               | -3               |
| Stroke                      | +9               | +11              |
| Pulmonary embolus           | +9               | +4               |
| Breast cancer               | +9               | -7               |
| Endometrial cancer          | -1               | Not applicable   |
| Colorectal cancer           | -6               | +2               |
| Hip fracture                | -6               | -6               |
| All-cause mortality         | -1               | +3               |
| Total                       | +19              | +4               |
“We accept today that in the younger woman below the age of 60 years and within 10 years of menopause benefits of HT are more likely to outweigh any risk, irrespective of the indication.”

Table 3. Bone-centric Global Index: WHI More or less cases per 10 000 patients

<table>
<thead>
<tr>
<th></th>
<th>Combined CEE/MPA</th>
<th>CEE alone</th>
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</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>+6</td>
<td>-3</td>
</tr>
<tr>
<td>Stroke</td>
<td>+9</td>
<td>+11</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>+9</td>
<td>+4</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>+9</td>
<td>-7</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>-1</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>-6</td>
<td>+2</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>-6</td>
<td>-6</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>-1</td>
<td>+3</td>
</tr>
<tr>
<td>Total</td>
<td>+19</td>
<td>+4</td>
</tr>
<tr>
<td>All fractures</td>
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<td>-61</td>
</tr>
<tr>
<td>DVT</td>
<td>+12</td>
<td>+7</td>
</tr>
<tr>
<td>Total</td>
<td>-14</td>
<td>-44</td>
</tr>
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</table>
The age limitations as discussed before pertain only to the initiation of therapy. The global consensus statement does not place any mandatory limitation on the length of treatment. As a matter of fact most of the possible adverse events associated with use of HT actually decrease, the longer treatment is used, with the exception of breast cancer.

However, the effects of HT on breast cancer are poorly understood. In the estrogen-only arm of WHI the risk of breast cancer was reduced, even after 13 years of follow-up. Progestogens, on the other hand, have a cancer-promoting effect and use beyond 7 years may be associated with an increase in risk. This effect may be diluted by using the most natural progestogen (micronized progestogen) or by combining estrogen with bazedoxifene, which would probably eliminate the increased risk of breast cancer altogether.

It should further be kept in mind that the risk of breast cancer is very small and is reversed after cessation of therapy.

Menopause treatment guidelines recommend that the dose and duration of HT should be consistent with goals of therapy and safety issues, and should be individualised.22

Comparison of HT to other available bone drugs

Although there are no head-to-head studies, the magnitude of fracture risk reduction with HT is comparable to that demonstrated in clinical studies of other bone-specific medications (Fig 2).23 However, in comparison to these other treatments, estrogen is the only agent with proven efficacy in primary analysis of a large randomised controlled clinical study to show protection against all types of osteoporotic fractures (Table 4). This is especially important in the osteopenic patient at risk of fracture.

All treatments are associated with the potential for side effects and, in addition to the effect on fracture risk, these need to be considered before choosing an appropriate therapy for the individual patient (Table 4).

HT has been shown to be associated with an increased risk of venous thromboembolic episodes in most studies. However, this is mostly limited to the first year of treatment, and is dependent on dose, age, body mass index and other risk factors.

Transdermal HT is not associated with an increased risk of DVT.

The effects of HT on stroke varies between different studies but was increased in the WHI study. This may be a specific effect of the dose of estrogen (not shown with lower dose in other studies) and/or the use of MPA.

In comparison to other drugs, estrogen is also associated with a number of additional benefits. These include fall prevention, reduction of vasomotor symptoms and prevention of urogenital atrophy. This

* with previous vertebral fracture(s)
** without previous vertebral fractures

RLX: raloxifene; ALN: alendronate; RIS: risendronate; CT: calcitonin

Figure 2. Comparison of the magnitude of fracture prevention with different bone-preserving agents.25
latter benefit is of considerable significance to improving the quality of life of the postmenopausal woman and on its own may justify the selection of estrogen as a first choice therapy in the symptomatic patient at risk of fracture.

**Have we completed the full circle?**

Thirty years after its recognition as a useful treatment to preserve bone in surgically sterilised and ageing women, a considerable volume of clinical trials bear testimony to the usefulness of estrogen after menopause. In 2014, in the younger postmenopausal woman, in addition to its wide range of benefits for symptom relief, estrogen should be considered a first-line option for both treatment of osteoporosis and fracture prevention.

In conclusion, Dr de Villiers noted that these recommendations remind us that: “New drugs are not better all of the time. Old drugs are better some of the time. Our treatment recommendations have indeed come full circle”.

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### Table 4. Comparison of fracture prevention and treatment-related side effects

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Fracture type</th>
<th>Potential side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Non-vertebral</td>
</tr>
<tr>
<td>Estrogen</td>
<td>yes</td>
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</tr>
<tr>
<td>Raloxifene</td>
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</tr>
<tr>
<td>Bazedoxifene</td>
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<td>no</td>
</tr>
<tr>
<td>Strontium ranelate</td>
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<td>yes</td>
</tr>
<tr>
<td>Bisphosphonate</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Denosumab</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>yes</td>
<td>No data</td>
</tr>
</tbody>
</table>

RCT: randomised controlled clinical trial; DRESS: drug reaction with eosinophilia and systemic symptoms; DVT: deep vein thrombosis

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**NEED FOR VIT D SUPPLEMENTATION IN SOUTH AFRICAN POPULATIONS**

- According to the US Institute of Medicine, Vit D deficiency is defined at serum 25- hydroxyvitamin D levels of <12ng/ml or <30nmol/l
- A recent study of Vit D deficiency in African-origin populations at varying latitudes has shown decreasing Vit D levels from the equator southwards/northwards\(^6\)
- In one study 30% of the US African adult population was Vit D deficient and 40% Vit D insufficient. Among Africans in Cape Town the prevalence of Vit D deficiency was 7% and Vit D insufficiency was 30%
- A study among black females in Johannesburg\(^7\) has shown Vit D deficiency in 5% of women (mean age 42 years). However almost one-third of the Asian females assessed were vitamin D deficient.
- Prof John Pettifor (Wits) noted that the level of Vit D deficiency in Indian females warrants universal Vit D supplementation in this group of women.
References: