CASE REPORT

A postmenopausal osteoporotic woman losing bone mineral density despite bisphosphonates

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Abstract

Bisphosphonates are pyrophosphate analogues, with a strong affinity for bones. They inhibit bone resorption and are currently the first choice of treatment for osteoporosis. Bisphosphonates should be taken in a specific manner and for at least one year to be effective in the maintenance and improvement of bone mineral density (BMD), as well as for protection against fractures. We report a case of a postmenospausal osteoporotic woman who lost BMD despite being on bisphosphonate therapy for eight years, highlighting issues that a primary care doctor needs to address before deciding on the next best option.

Introduction

Oral bisphosphonates are routinely prescribed for the treatment of postmenopausal osteoporosis. Bisphosphonates have been found to increase bone mineral density (BMD) and decrease fracture risk in majority of the treated population. However, not all patients experience significant increases in BMD. In clinical practice, a decrease in BMD greater than the calculated least significant change (LSC) is considered nonresponse to therapy.[3] It is important to determine whether patients with a decline in BMD may still benefit from bisphosphonate therapy (i.e. have a decrease risk of fracture), despite having suboptimal BMD response. This case report describes a postmenospausal osteoporotic woman who is a non-responder to bisphosphonate therapy. A discussion on the potential implications, medical and lifestyle management will be presented.

Case Report

Mrs. SW, a 68 years old Chinese woman, has been followed up by the Osteoporosis Clinic at a tertiary hospital since 2004. She presented at a university-based primary care clinic in June 2012 asking for an explanation as to why her most recent BMD scan showed no improvement. She also wanted an explanation on why her treatment with alendronate 70 mg weekly needed to be changed.

Mrs. SW (then aged 59 years) had an ultrasound scan of the heel at a shopping centre, which showed that it was in the osteoporotic range. She was then advised to go for a BMD scan, leading to her first visit to a primary care doctor in October 2003. A BMD scan was performed and the T- scores were -3.3 and -2.8 at the spine and the hip, respectively. Subsequently, she was referred to the Osteoporosis Clinic.

The medical history of Mrs. SW was not significant. She never had a fragility fracture. She had a lumpectomy performed at the age of 20 years (fibroadenoma of the breast). Her mother had an osteoporotic fracture. Mrs. SW does not like dairy products. She was on Progyluton for 10 years after an early menopause at the age of 45 years. She has never taken any over-the-counter (OTC)/traditional medicines or steroids. She is an ex-staff nurse, married, with two children, a non-smoker and does not consume any alcohol. Physical examination results showed that she was 146-cm tall, 46.8 kg by weight (body mass index: 22 kg/m2), with normal gait and no signs of kyphosis or signs suggestive of secondary causes of osteoporosis. Vitamin D adequacy was not assessed as this test was not available in our hospital. Mrs. SW was also not checked for hypercalciuria as she was on normal doses for calcium and vitamin D. Her complete blood count, renal profile, liver function tests, serum calcium, phosphate and alkaline phosphatase, and thyroid function tests from 2003 to 2011 were normal.

Risk factors for osteoporosis included female gender, Asian ethnicity, small body build, low body weight, early menopause, first degree relative with fracture, inadequate calcium/dairy/vitamin D intake, sedentary lifestyle and no sun exposure. Her BMD results and osteoporosis therapy are summarized in Tables 1 and 2, respectively.

Table 1. Bone mineral density results of Mrs. SW from 2003 to 2012

	2003	2005	2007	2009	2012
Age of the patient (years)	59	61	63	65	68
DXA machine used (manufacturer)	Lunar DPX IQ (Wisconsin, United States)				Lunar Prodigy (Wisconsin, United States)
	T- score (g/cm2)	T- score (g/cm2)	T- score (g/cm2)	T- score (g/cm2)	T- score (g/cm2)
Spine					
L1	-3.5 (0.707)	-3.2 (0.751)	-3.2 (0.746)	-3.4 (0.717)	-3.6 (0.692)
L2	-3.5 (0.785)	-3.5 (0.783)	-3.2 (0.817)	-3.6 (0.765)	-3.7 (0.751)
L3	-3.6 (0.763)	-3.2 (0.818)	-3.3 (0.800)	-3.1 (0.832)	-3.7 (0.761)
L4	-3.0 (0.838)	-2.1 (0.942)	-2.0 (0.963)	-2.0 (0.957)	-2.2 (0.932)
L2-L4	-3.3 (0.798)	-2.9 (0.855)	-2.8 (0.866)	-2.9 (0.853)	-3.2 (0.821)
Left femur					
Neck	-2.5 (0.674)	-2.5 (0.679)	-2.2 (0.715)	-2.4 (0.687)	-2.8 (0.646)
Wards	-3.6 (0.439)	-3.2 (0.506)	-3.2 (0.494)	-3.5 (0.459)	-3.3 (0.479)
Troch	-2.3 (0.538)	-1.8 (0.593)	-1.6 (0.618)	-1.7 (0.603)	-1.8 (0.595)
Total	-2.8 (0.664)	-2.5 (0.704)	-2.4 (0.717)	-2.5 (0.695)	-2.7 (0.676)

Alendronate started in 2004

DXA, dual-energy X-ray absorptiometry.

Table 2. Osteoporosis medications for Mrs. SW from 2003 to 2012

2003	2004 to May 2012	June 2012
Calcium carbonate 500 mg bd	Calcium carbonate 500 mg bd	Metocal D3 (elemental calcium 600 mg and vitamin D 400 IU) One tablet daily
Calcitriol 0.25 mcg bd	Calcitriol 0.25 mcg bd	
	Alendronate 70 mg once weekly	Advised to stop alendronate and to start teriparatide

Patient claims to be compliant to alendronate therapy, but does not take her calcium doses regularly.

Discussion

Ostoporosis is a systemic skeletal disorder characterised by compromised bone strength, predisposing an individual to an increased risk of fracture.[4] It can occur at any age or to any racial or ethnic group, but is more common in postmenopausal women. Osteoporosis is usually asymptomatic, especially in the early stages.[1] Risk factors for osteoporosis are shown in Table 3.[5]

Table 3. Risk factors for osteoporosis[(5)]

Non-modifiable risk factors	Potentially modifiable risk factors
Advanced age	Small body build or low body weight
Female	Inadequate intake of calcium or vitamin D
Early menopause	Use of medications (glucocorticoids, anti-convulsants or anti-neoplastics)
Race (Caucasian or Asian)	Oestrogen deficiency
First degree relative with fracture	Current cigarette smoking
Dementia	Excessive alcohol intake
Poor health	Sedentary lifestyle
Hormonal, neoplastic or connective tissue disorders	Environmental risks (loose rugs, dark stairs, etc.)
	Poor eye sight

Mrs. SW was initiated only on bisphosphonate therapy in 2004, as she was examined only by osteoporosis doctors then. From 2004 to 2007, her BMD improved both at the spine (L2-L4) and the hip (neck of femur) region. However, from 2007 to 2012, there was loss of BMD (5.1% at the lumbar spine and 5.7% at the hip) despite being on bisphosphonates (Table 1). The precision errors [i.e., least significant change (LSC)] for both DXA machines were 2% at the spine and 5% at the hip, indicating that Mrs. SW is a non responder to bisphosphonate therapy.

There are a few issues among patients with poor response to bisphosphonates. These issues can be (1) poor compliance to treatment, (2) possible secondary causes that might be missed in the initial diagnosis of primary osteoporosis, and (3) inadequate adjunct treatment with vitamin D, calcium supplements and life-style modification.

Bisphosphonates should be taken in a specific manner (with water in the fasting state followed by a meal 2 hours later).[(2)] If taken in the correct manner, the oral bioavailability of alendronate will range from 0.60% to 0.64% which is very low, but sufficient to provide therapeutic efficacy.[6] Bioavailability becomes negligible when alendronate is administered with or up to 2 hours after a standardized breakfast.[6] If non-compliance

to bisphosphonate regimen was suspected, a bone turnover marker (serum beta-crosslaps) can be measured.[7] Patients who experience a decline in BMD whilst on bisphosphonates still appear to receive some benefits compared with patients receiving placebo (fracture risk reduction, 38%-60%), but have a higher risk of fracture compared with patients whose BMD increases.[3] In the case of Mrs. SW, the loss of BMD does not mean failure of therapy because she did not fracture whilst on therapy, as the ultimate goal of osteoporosis treatment is fracture prevention, not an increase in BMD.[(1)] The estimated rate of non-response to bisphosphonate therapy can be as high as 15%.[8]

Calcium and vitamin D are essential for the prevention and treatment of osteoporosis.[9] Mrs. SW was prescribed calcium 500 mg bd and calcitriol 0.25 mcg bd, but she confessed that she has not taken the doses regularly. Vitamin D deficiency can result in secondary hyperparathyroidism and may partly contribute to the lack of improvement in BMD. Vitamin D3 (cholecalciferol) should be used instead of activated vitamin D because it is more cost effective and does not carry a high risk of hypercalcemia or hypercalciuria. Activated vitamin D should only be reserved for patients >65 years of age, with impaired renal function, persistently low calcium levels, who are intolerant to bisphosphonates/ selective oestrogen receptor modulators, on long-term steroid therapy, or have idiopathic or secondary deficiency of parathyroid or thyroid hormones.[10] As mentioned earlier, it was not possible to assess vitamin D levels in this patient.

Table 4. Secondary causes of low bone mineral density and laboratory tests to rule out these secondary causes

Secondary causes of bone loss	Tests to rule out secondary causes of bone loss
Hyperparathyroidism (primary or secondary)	• Complete blood count • Serum calcium • Albumin • Liver transaminases • Serum creatinine and calculated creatinine clearance • Alkaline phosphatase • Thyroid-stimulating hormone • Serum immunoelectrophoresis, calcium corrected for albumin Additional tests, as suggested by results of clinical evaluation: • Parathyroid hormone • Serum 25-hydroxyvitamin D • Celiac antibody testing: gliadin, endomyseal, tissue transflutaminase • 24-hour urine: calcium • 24-hour urine: free cortisol
Vitamin D inadequacy	
Calcium deficiency	
Malabsorption state (e.g., celiac disease, inflammatory bowel disease, and short gut syndrome)	
Chronic liver disease	
Hypercalciuria	
Hyperthyroidism	
Chronic lung disease	
Malignancy (e.g., myeloma and bony metastasis)	
Rheumatoid arthritis	
Hypogonadism	
Cushing's disease	
Osteogenesis imperfect	
Medications (e.g., glucocorticoids, heparin, and gonadotropin-releasing hormone agonists)	
Hepatic insufficiency	

Table 5. Comparison of costs of different osteoporosis therapies

Treatment	Cost per year (RM)#s
Alendronate 70 mg once weekly (Fosamax Plus)	1411
Alendronate 70 mg once weekly	480
Teriparateide 20 mcg subcutaneous daily (Forteo)	18,684

Lifestyle changes are also one of the foremost aims of disease prevention, and Mrs. SW did not amend her lifestyle to prevent further deterioration of her bones. Patients with osteoporosis need to consume adequate amounts of calcium (1200 mg/day) and vitamin D (800-1000 IU/day), have adequate sun exposure (20 min/day), perform weight-bearing exercises (e.g., walking 20-30 minutes three times a week), avoid cigarette smoking and excess alcohol consumption, and prevent falls.[11]

In addition, Mrs. SW needs to undergo re-evaluation tests to exclude new secondary causes of osteoporosis (Table 4), including the use of OTC or traditional medicines that may contain glucocorticoids.

Does the treatment prescribed to Mrs. SW need to be changed to teriparatide? Teriparatide, an anabolic agent, is indicated in high-risk postmenopausal women not responding to other treatments, such as on bisphosphonates, but still losing BMD, still having fractures, T-score less than -3.5 or intolerant to bisphosphonates.[12] Importantly, if Mrs. SW is commenced on teriparatide, it is essential that she is compliant to calcium and vitamin D supplement regimen as well. Bisphosphonate therapy should be discontinued once teriparatide therapy is initiated, and perhaps reinstituted when teriparatide is stopped.

An alternative anti-osteoporotic agent that may be used in this patient is strontium ranelate. Strontium ranelate has been shown to reduce both vertebral and non-vertebral fractures.[13] Whilst there have been no head-to-head trials comparing strontium directly with teriparatide, reduction in the incidence of fracture in women with postmenopausal osteoporosis treated with strontium appears to be lower (39% reduction in vertebral fractures and 16% in non-vertebral fractures)[13] than teriparatide (65% reduction of vertebral fractures and 53% in non-vertebral fractures).[14] Teriparatide is administered subcutaneously and treatment is limited to 24 months.[12] However, teriparatide therapy is about 18 times more expensive than proprietary alendronate (Table 5), and the issue of affordability needs to be discussed with the patient.

Conclusion

The ultimate end point of osteoporosis therapy is the prevention of fracture, not just an increase in BMD. In this case, teriparatide therapy may be warranted if Mrs. SW continues to lose BMD despite being on bisphosphonates. However, the patient needs to be counselled on lifestyle changes and compliance to calcium and vitamin D regimen to enhance the effectiveness of osteoporosis therapy.

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Conflict of interest

There is no conflict of interest among the authors

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