

OCTOBER 2017

OSTEOSCAN

Osteoscan remains South Australian and doctor-owned... "of clinicians, by clinicians, for clinicians". We hope that this newsletter is of interest and welcome your feedback and support by way of referrals.

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Introduction

Spring is upon us at Osteoscan. We had planned a newsletter to welcome in the New Year but it is more a case of getting in early with Festive Greetings. The critical tasks of each newsletter are firstly to sincerely thank our referring doctors, and secondly to provide some informed commentary and entertainment on what can be a rather dry topic. We are awaiting a review of BMD test items on the MBS and will inform you of the relevant changes once they are to hand.

In this letter we present an educational case which demonstrates the holistic Osteoscan package of BMD, VFA, fracture risk and CrossLaps in action along with endocrinologist commentary. We also discuss the vexing question of when, if ever, it is appropriate to cease treatment with Prolia.

We welcome telephone enquiries from referring doctors and in particular any suggestions for future newsletters or criticisms of the *modus operandi*. Over the last 10 years this open dialogue has been incredibly helpful and we are very grateful to those who have contributed to it.

When to stop treatment with Prolia, or maybe you shouldn't

It is a common enough question from patients, when can I stop treatment with Prolia?

There is no definitive answer. Decision-making must be individualised. Two very bland and equivocating statements. Read on and I will explain the problem.

In July 2017 further data from the FREEDOM trial were released, now following a cohort of osteoporotic postmenopausal women through ten years of treatment with denosumab. BMD increased by 21.7% at the spine and 9.2% at the hip over the ten years. No plateau effect was observed. Put differently, after ten years of denosumab, BMD continues to rise and fracture rates remain low. Out of 2626 women completing 7 years of the extension study to FREEDOM there were 2 cases of atypical femoral fracture and 13 cases of osteonecrosis of the jaw.

Denosumab (Prolia) first became available in Australia on the PBS in December 2010. One now encounters patients who have been on treatment for at least 5 years.

It had been recommended to re-assess the need for ongoing bisphosphonate treatment after 3-5 years and to consider whether a "drug holiday" or "treatment cessation" might be appropriate. The hope of such a strategy, never proven in a scientific study, was to reduce the risk of osteonecrosis of the jaw and atypical femoral fractures.

Is this strategy also applicable to Prolia? The answer is a resounding no, as discussed by McLung et al in a paper titled "Observations following discontinuation of long-term denosumab therapy" and published in *Osteoporosis International* in January 2017.

This study looked at 52 patients treated with denosumab for 8 years, after which treatment was ceased. During the 8 years of active treatment BMD increased 16.8% at the spine and 6.2% at the hip. After one year of stopping denosumab, BMD had decreased 6.7% at the spine and 6.6% at the hip. If one looked at the 42 patients who did not use any other antiresorptives for the one year off denosumab then the respective decreases were even greater, 7.4% and 7.8%. There were 5 patients who were taking prescription medications for osteoporosis at the end of the observation period and for whom the respective decline in BMD was -2.9% and -2.2%. Therefore, while long-term treatment with denosumab results in large gains in BMD, it does not protect patients from bone loss when treatment is ceased. This phenomenon has been seen previously with estrogen which is also regarded as a rapidly reversible antiresorptive agent.

After stopping denosumab bone turn-over rebounds to exceed baseline levels. Does this result in an increase in fracture risk? Data in osteoporotic patients is scarce, but the answer is probably no.

The results of McClung's study make it clear that a "drug holiday" is not appropriate for patients with osteoporosis who have been on long-term denosumab treatment. The authors conclude that, in fact, there are few reasons to discontinue denosumab treatment. However, if denosumab treatment is discontinued in a patient at high risk for fracture it is prudent to substitute a long-acting bisphosphonate unless there is a compelling reason not to do so.

Alendronate has been shown to prevent bone loss after stopping estrogen, denosumab and parathyroid hormone (forteo).

Which brings us back to the original question, doc, when can I stop treatment with Prolia? I don't know, but you can now discuss the above data with your patient and individualise your approach.

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Bone Density & Fracture Risk Assessment

Clinical Notes: PH vertebral crush fracture in a 72 year old woman

Densitometry

Site	BMD (g/cm ²)	T-score (cf young adults)	Z-score (Age Matched)
Lumbar Spine	0.623	-3.9	-1.7
Proximal Femur	0.646	-2.4	-0.8

Vertebral Fracture Assessment

Fracture(s) are present at L2 and T10
New fracture(s) found at T10

Bone Turnover

Serum CrossLaps: 633 ng/L
Normal bone turnover: <350 ng/L
Increased bone turnover: >450 ng/L

Estimated Absolute Fracture Risk

Hip		All Fractures	
5 Year (%)	10 Year (%)	5 Year (%)	10 Year (%)
34.3	56.9	66.7	90.6

Source: Garvan or WHO*

* WHO regards treatment as cost effective if the 5 yr risk of hip fracture is > 3% or 10yr risk of any fracture >20%

Comments and Recommendations

Fractures are present at L2 and T10. The fracture at T10 is "new" since the previous assessment. Osteoporosis of the neck of femur. Osteoporosis of the lumbar spine. Fracture risk estimates are high. Note that fracture risk estimates are calculated as though the patient were not taking an antiresorptive. BMD has fallen since last measurement. The fall in BMD of more than 4%, combined with high bone turnover, suggests that the medication is either not being taken, not being absorbed (if oral) or that there is an underlying cause of secondary low BMD. Continue to encourage adequate vitamin D (1000 units daily) together with dietary or supplemental calcium. I suggest another BMD measurement, vertebral fracture assessment & measurement of fasting serum CrossLaps in 2 years. Consider changing to a better-absorbed oral antiresorptive, or a parenteral antiresorptive.

Dr Osteoscan

Factors that might increase fracture risk

Fracture(s) since age 50 (1 reported).

Patient-Reported Medication

Actonel.

Densitometry Results Detail

Comparative Lumbar Spine				BMD Change (%)	
Scan Date	Age	BMD	T	vs Baseline	vs Previous
19 May 2017	71	0.623	-3.9	-15.0	-13.2
01 May 2015	69	0.718	-3.0	-2.0	22.3
Comparative Proximal Femur				BMD Change (%)	
Scan Date	Age	BMD	T	vs Baseline	vs Previous
19 May 2017	71	0.646	-2.4	-9.9	-12.6
01 May 2015	69	0.739	-1.7	3.1	20.9

Commentary on case report

In a nutshell, this patient has continued to lose bone at an accelerated rate and to sustain an additional vertebral fracture despite treatment with risedronate (Actonel).

This may reflect poor compliance (representing at least 50% of patients prescribed oral bisphosphonates), poor absorption (at best 1% of oral bisphosphonates are absorbed) which may be contributed to by a failure to comply with the protocol for administration (fasting, 30 minutes before food, swallow with a glass of water, remain upright for 30 minutes, no calcium for at least one hour) or use in patients with active upper G.I. disease.

There may also be a secondary cause of osteoporosis which has developed since the patient was first assessed and treated. A poor response to treatment may also indicate a failure of the patient (surprisingly common) to comply with calcium and vitamin D supplementation.

The case illustrates the value of vertebral fracture assessment (VFA) in patients at high risk of future vertebral fracture, risk factors here being previous vertebral fracture and spine T score < -2.5.

The finding of a new vertebral fracture would make one consider a change of treatment, most likely to denosumab, but this patient would also qualify on the PBS for teriparatide (forteo). Indications to perform VFA were discussed in the previous newsletter and are available on the Osteoscan website.

The case illustrates the potential role of the bone turnover marker CrossLaps in assessing compliance with or efficacy of oral antiresorptive treatment. One could test as early as 3 months after initiating oral antiresorptive treatment, rather than waiting 2 years to survey the above disaster. One is looking for an absolute decrease to below 350 or > 40% decrease from the baseline level.

The calculation of baseline fracture risk adds nothing to this case, but is useful in less extreme scenarios when one is contemplating whether or not to invoke antiresorptive treatment (may be cost effective if 10 year all fracture risk >20%).

The endocrinologist comment hopefully rounds off this holistic approach. We hope you think the effort is worthwhile.