OSTEOSCAN PARTNERS IN OSTEOPOROSIS MANAGEMENT

AUTUMN 2018

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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Welcome to our Autumn Newsletter. We have addressed ourselves to practical questions of managing osteoporosis. Firstly, and just to emphasise that treating osteoporosis wasn't meant to be too easy, we discuss the recently-recognised condition of **"rebound-associated vertebral fractures"** after denosumab discontinuation. We hope that the latter does not cause you too many sleepless nights! Secondly, **what constitutes a significant change in BMD?** Thirdly, we discuss **the new MBS item numbers for** BMD testing of the over 70s.

As always we thank you for your ongoing support of Osteoscan. Please remember that every referral is an opportunity for an endocrine consultation, all we ask is for the relevant information to be provided in the clinical notes.

Rebound-associated vertebral fractures after denosumab discontinuation

This topic was on everybody's lips who attended the session "The year in metabolic bone disease" at the recent American Endocrine meeting in Chicago. Reference was made to two papers appearing in 2017 which will be discussed. Lamy et al, JCEM, described 9 post-menopausal women who developed a total of 50, mean 5.5, rebound-associated vertebral fractures (RAVFs) after stopping denosumab. RAVFs occurred 9 to 16 months after last dose of denosumab. Initial (FRAX) fracture risk was low to moderate. RAVFs were not felt to reflect the underlying osteoporosis. It was hypothesised that severe bone turnover rebound was associated with damage to trabecular bone which caused RAVFs.

Anastasilakis et al, J Bone Min Res, described 24 patients with RAVFs after denosumab discontinuation. Total fractures 112, mean 4.7, most frequently at T12 and L1. All RAVFs occurred 8 to 16 months after the last denosumab injection. In 83 % of patients denosumab was the only antiresorptive with which they had been treated. In patients treated for less than 2 years the mean number of RAVFs was 3.2. In those treated for more than 2 years the mean number of RAVFs was 5.2. All vertebral fractures were painful. CrossLaps was measured in 4 cases after RAVF, mean 1147 (reference range 100 -800).

In this paper a further 32 women were identified who had ceased denosumab for at least 12 months but who had not suffered vertebral fracture. They were stratified according to previous bisphosphonate use.

Used bisphosphonate	No.	Median CrossLaps one year after last denosumab
Before denosumab only	8	577
After denosumab only	12	130
Before and after denosumab	6	202
No use of bisphosphonate	6	1190

These results suggest a plausible role for bisphosphonates before and/or after denosumab treatment in preventing severe bone turnover rebound as assessed by CrossLaps. However, it should be noted that CrossLaps is a surrogate marker only and it is not known if bisphosphonates can protect against RAVFs.

It was concluded that urgent studies were required to determine the pathophysiological process, clinical profile of RAVF patients, and to determine how pre and/or post bisphosphonate treatment might be best used to prevent this problem.

In our Spring 2017 newsletter the question "When to stop treatment with Prolia, or maybe you shouldn't" was addressed. This new information suggests that denosumab should not be ceased, or treatment intervals delayed beyond 6 months without covering the patient with a bisphosphonate to prevent severe bone turnover rebound.

This is clearly a very important development in the management of osteoporotic patients given the widespread use of denosumab in Australia. We will continue to follow this story in the next newsletter.

When is a change in BMD significant?

You may have noticed that Osteoscan reports compare the current BMD values with any previous value(s). Although we measure BMD with great care, the nature of DEXA technology is such that there is a minor amount of 'natural variability' between measurements. In order to make sense of this we calculate the Least Significant Change (LSC), and use an asterisk on the report itself to indicate whether or not any change which has taken place is significant. The level of significance uses the same standard that many of you will be familiar with from research papers, which is a 95% or greater chance that the change is not due to random variation (otherwise noted as $p < 0.05$).

The change in BMD required to reach significance varies according to the absolute BMD of the site being measured. Put simply, the higher the absolute BMD, the greater the degree of precision of the measurement, and therefore the smaller the percentage change required in order to pass the significance test. At low absolute BMD values the DEXA beams are passing through a smaller number of trabeculae and cortical bone, which leads to a greater degree of imprecision in the measurement. This means that a greater percentage change in BMD between any 2 measurements is required before the significance test is passed.

In practice, the change required for significance is usually of the order of 3 – 5%.

Statistical significance is not synonymous with clinical significance which is very dependent on underlying fracture risk. Osteoscan uses the Garvan Fracture Risk Algorithm (www.fracturerisk calculator.com) wherever possible as this uses data collected from the large Dubbo Osteoporosis Epidemiology Study (DOES). DOES takes into account an individual's age, gender, minimal trauma fractures since turning 50, number of falls in the past 12 months and BMD. It estimates 5- and 10-year risk of hip fracture, and of any major osteoporotic fracture.

If a patient starts with a high absolute BMD, is relatively young, and has no history of falls and fractures, they may experience a fall in BMD which is statistically significant as outlined above, but which does not affect clinical decision making. Equally, an older patient who starts with a low BMD, who has a previous fracture and has had several falls may find that a change which only just passes statistical significance is actually very meaningful in terms of its effect on clinical decision making. For this reason the Osteoscan report includes interpretive comments which highlight the **clinical significance** of any change in BMD.

The rate of change is also important, and is derived from the absolute change in BMD and the interval between two Osteoscans. A change of 10% in 3 years is quite different from a change of 10% over 15 years. Rapid bone loss is an independent predictor of fracture risk and can help identify those patients who require antiresorptive treatment. This information assists in determining the recommended interval before repeating the next Osteoscan.

As you can see, there is much more to significance than a least significant change calculation.

Change in BMD item numbers

As of November 1, 2017 the former item number 12323 ceased to exist. This had permitted patients > 70 years to have a MBS-reimbursed BMD with no regard to time elapsed since the previous scan and irrespective of previous BMD results. It has been replaced by two item numbers.

12320 Patients > 70 years	initial BMD or having previous BMD better than T score -1.5.	One BMD every 5 years.
12322 Patients > 70 years	previous BMD with T score -1.5 to -2.5.	One BMD every 2 years.