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PERSPECTIVES

Is Monitoring Osteoporosis Therapy Worthwhile?

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Abstract

Bone mineral density (BMD) measurements are widely recommended for the routine monitoring of osteoporosis treatment. However, the evidence base to support this approach is weak, since treatment-induced changes in BMD take up to three years to detect and in any case do not predict the associated reduction in fracture risk. Biochemical markers have potential for monitoring since they change rapidly in response to treatment and are more predictive of fracture reduction, but issues related to the variability of their measurement greatly reduce their utility in clinical practice. Neither BMD nor bone turnover markers have been shown to improve adherence to therapy. In contrast, there is evidence that discussion with a healthcare professional improves treatment adherence, regardless of feedback about monitoring tests. At present, there is no scientific justification for the use of either BMD or bone turnover markers in the routine monitoring of therapy, but patients should be given adequate information about their treatment and routine follow-up should be provided to enable discussion of treatment-related issues. *IBMS BoneKEy*. 2009 March;6(3):99-106.

Introduction

Pharmacological therapy for osteoporosis does not produce obvious relief of signs and symptoms of the disease, and may cause side-effects. Treatment is usually given for many years and, understandably, both the patient and the physician may seek evidence that it is exerting the expected therapeutic effects. While few would disagree that patients who are started on bone protective therapy should have the opportunity to discuss treatment-related issues during follow-up, the question of whether routine monitoring of therapy using surrogate markers such as bone mineral density (BMD) or biochemical markers of bone turnover is more controversial.

The aim of monitoring treatment is to identify individuals who are not responding to treatment. The definition of a non-responder is, however, difficult; in the final analysis, it is someone who does not experience the expected reduction in fractures on treatment but since no treatment completely prevents fractures, detection of this is at best difficult and often impossible. The vast majority of apparent non-response can be attributed to failure to take the medication correctly and regularly for the prescribed period of time. A much less common cause of non-response is the emergence of diseases during treatment that cause bone loss, for example, hyperthyroidism, malabsorption or myeloma. If, however, secondary causes of osteoporosis are carefully excluded at the outset, such occurrences will be rare. Whether the true non-responder exists is uncertain: in theory lack of response might arise because of insufficient dose, genetic factors or other reasons but at present there is no evidence that this in fact occurs in clinical practice. Monitoring treatment is therefore primarily aimed at identifying individuals who fail to comply and persist with treatment.

Since the aim of treatment in osteoporosis is to reduce fracture, a monitoring test must be able to predict whether the treatment will decrease the risk of fracture in the individual patient. This essentially depends on two pre-requisites. First, the test that is used should reliably categorize a statistically and clinically significant change within an

appropriate time scale, i.e., one that allows appropriate changes in management to be put in place in time to influence the outcome of fracture. Second, such a change should be predictive of fracture reduction on treatment. If these two criteria are satisfied a third criterion is that if the test indicates lack of response, there are appropriate changes that can be made in management by the physician and/or, in the case of poor adherence to treatment, patient behavior can be modified. Finally, given limited healthcare resources, monitoring should be shown to be cost-effective.

BMD Measurements in Monitoring Osteoporosis Therapy

Both the International Society for Clinical Densitometry (ISCD) and the National Osteoporosis Foundation (NOF) advocate BMD measurements for the routine monitoring of treatment (1;2). The ISCD advocates that the first follow-up measurement should be performed after one year of treatment, with "longer intervals once the therapeutic effect is established," while the NOF suggests that repeat measurements should normally be made every two years.

Despite these recommendations, accurate characterization of changes in BMD at the spine and hip usually requires longer than one or even two years. In clinical practice, the method most widely used to categorize change in BMD during therapy is estimation of the least significant change (LSC), derived from the standard deviation of the precision error of the measurement (3-5). The ISCD states that the minimum acceptable LSC is 5-6.9%, depending on the site of measurement, and so the BMD change expected must equal or exceed this amount (1). This is extremely unlikely to be achieved in one year, at least for anti-resorptive therapy; indeed, changes of this magnitude are often not seen until after a treatment period of at least 3 years.

In clinical practice, *in vivo* precision is often established using same day measurements in the same individual because this is logistically the easiest approach. However, a recent study from the Manitoba Bone Density Program has demonstrated that when measurements are made on different days, as of course they will be when used for monitoring in clinical practice, the precision error and hence the LSC become substantially larger, even when the two measurements are made by the same technician (6). The larger the LSC, the lower the number of patients who will be categorized as showing a significant change in BMD while on treatment; hence if the LSC in a bone density unit is calculated using same day measurements, a substantial number of patients may be falsely categorized as showing a change. In the Manitoba study the rate of over-categorization of change was up to 19.3% for the lumbar spine and 18.3% for the total hip and the precision error limits stipulated by the ISCD were exceeded. For those individuals incorrectly classified as losing bone, this could lead to inappropriate changes in their management while others may be falsely reassured.

BMD measurements therefore fail on the first requirement for monitoring, namely that the test should reliably categorize change within an appropriate timescale since the minimum period in which treatment effects may be accurately detected in the individual patient on anti-resorptive therapy is probably in the range of three years. Indeed, even a period of one year in which to detect treatment response would be inappropriately short given the high risk of recurrent fracture in the first year after an incident fracture (7). The case for using BMD measurements to evaluate the response to treatment is further damaged, however, by the poor ability of treatment-induced changes in BMD to predict fracture reduction. Whereas there is ample evidence from prospective studies that BMD is a reasonably good predictor of fracture risk in the untreated state (8), only a small proportion of fracture reduction in response to anti-resorptive therapy can be explained by changes in BMD (9-12). For example, Cummings *et al*. (11) showed that only 16% of the fracture reduction associated with alendronate was attributable to an increase in BMD and for the MORE study of raloxifene, the corresponding figure

was only 4% (12). Since reduction in bone turnover *per se* provides one of the main mechanisms by which anti-resorptive drugs reduce fracture risk, the poor predictive value of BMD changes for fracture reduction is not unexpected.

Further evidence for the lack of utility of BMD measurements in predicting treatment response comes from clinical trial data demonstrating similar reductions in fracture irrespective of BMD gain or loss. In postmenopausal women treated with risedronate in the VERT and HIP studies, the reduction in non-vertebral fractures after three years of treatment was very similar in women who lost BMD from the spine or proximal femur to that seen in women with a net gain in BMD (13). Similarly, in a *post hoc* analysis from the Fracture Intervention Trial, vertebral fracture reduction was similar regardless of the degree of BMD loss or gain (14). A reduction in fracture risk despite BMD loss on treatment is therefore well-documented and was also seen in the MORE study of raloxifene (Fig. 1) (12). It can be seen that there is a wide spectrum of BMD change during treatment in both the placebo and treatment groups and that, as expected, this is shifted to the left in the placebo group. Fracture incidence is lower in those who gain bone in either group than in those who lose bone, although the gradient is not steep. For any given rate of bone loss, the fracture incidence in raloxifene-treated patients is less than their placebo counterparts and this relationship remains quite stable throughout the spectrum of BMD change. However, a treated woman with 4% bone loss at the femoral neck still has a lower fracture risk than a placebo-treated woman with a BMD gain of 4%, in other words, women who lose BMD with raloxifene therapy will still have a lower vertebral fracture risk compared to placebo-treated women who gain BMD.

Even if BMD cannot reliably predict treatment response within an appropriate timeframe, it could be argued that regular measurements might provide reassurance for patients and improve their motivation to persist with treatment. However, this approach is fraught with difficulty, since it requires the healthcare professional to communicate to the patient judgments on BMD change that may be inaccurate and are irrelevant to the effectiveness of the treatment in reducing fracture. In any case, there is no robust evidence that BMD monitoring improves adherence to therapy, nor is there evidence that in an individual who is apparently not responding, switching to alternative therapies will improve the outcome. Adjustments of dose, which may be made when treating other diseases, are not relevant for osteoporosis therapies; not only are most approved at only one dose but evidence from clinical trials indicates that even where there is a dose-response for BMD, this is not seen for fracture reduction (15-17). Finally, where lack of adherence is due to real or perceived side effects, this is most appropriately addressed by talking to patients, not measuring their BMD.

The cost-effectiveness of monitoring treatment with BMD measurements has not been formally assessed but in view of the above considerations is unlikely to be favorable. Conversely, routine monitoring of therapy as advocated in some guidelines is costly and labor-intensive and diverts much needed healthcare resources away from more deserving needs.

Biochemical Markers in the Monitoring of Osteoporosis Treatment

Biochemical markers of bone turnover have potential as a means of monitoring treatment, since changes in response to treatment occur rapidly (18-21) and are more predictive of fracture risk reduction than are BMD measurements (22-26). However, they currently also have significant limitations, particularly with respect to their pre-analytical and analytical variability (27;28). The former is particularly important and includes both modifiable and non-modifiable factors. Of the former, circadian variability (29;30) and food intake (31;32) are particularly important for some markers, whereas non-modifiable factors include a number of skeletal and non-skeletal disease states, medications that affect the skeleton and the presence of a recent fracture (33;34). Although variability can be reduced

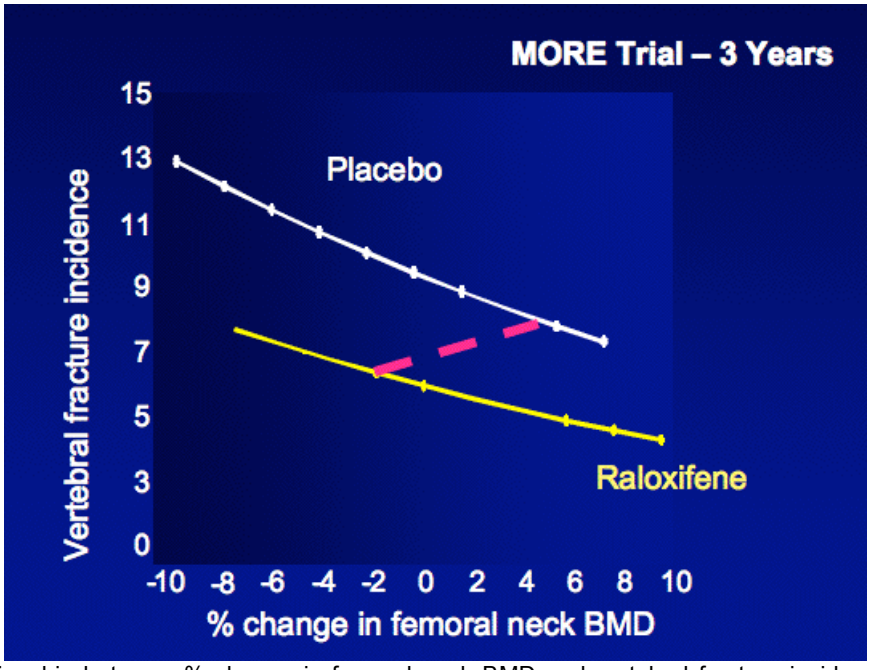

Fig. 1. Relationship between % change in femoral neck BMD and vertebral fracture incidence over three years in postmenopausal women treated with raloxifene. There is a wide range of BMD changes in both the placebo and treatment groups but for any given change, fracture incidence is always lower in the raloxifene-treated women. The dotted line shows that a raloxifene-treated woman with a 4% decrease in femoral neck BMD has a lower vertebral fracture incidence than a placebo-treated woman with 4% gain in BMD. Adapted from *J Bone Miner Res* 2002;17;1-10 with permission of the American Society for Bone and Mineral Research.

by obtaining paired, fasting samples at a standard time of day, this is often impracticable in everyday clinical practice and currently the use of bone turnover markers for monitoring is not recommended in official guidelines (28).

Two studies have been reported in which the effect of measurement of bone turnover markers on adherence or persistence with therapy has been examined. In a randomized controlled open label study in 75 postmenopausal women with osteopenia taking raloxifene, the effect of monitoring on adherence, defined as intake of ≥ 75% of the tablets, was investigated over a one-year treatment period (35). One group of women received no monitoring, a second group was interviewed by a nurse at 2, 24 and 36 weeks and given the opportunity to discuss their treatment, and the third group underwent measurement of urinary NTX at the same time points and was interviewed by a nurse and given feedback about their results. When data from the second and third groups were pooled, adherence was significantly better than in the non-monitored group. However, when the monitored groups were split into those who had marker feedback and those who were interviewed by a nurse but had no marker feedback, there was no significant difference, suggesting that it is the contact with a health professional rather than the feedback about the bone turnover marker per se that improved adherence. Interestingly, in this paper it is stated that the urinary NTX was not elevated at baseline in 37% of the women studied, highlighting the difficulty in defining a response in turnover markers if these are not elevated prior to treatment.

More recently the effect of feedback of changes in biochemical markers on persistence, defined as the number of days from the first dose to discontinuation, with treatment was examined in the IMPACT study (36). This was a randomized controlled trial in which postmenopausal women with osteoporosis taking risedronate

5 mg daily for one year underwent assessment of urinary NTX at weeks 10 and 22 and were subsequently either given feedback about the result or not: all women received information about the need to continue with treatment. No statistically or clinically meaningful difference in persistence at one year was seen between the two groups; indeed persistence at one year was surprisingly high in both groups (around 80%), perhaps reflecting the value of giving information to the patient. In women who had a good response, defined as a ≥ 30% decrease in urinary NTX, there was a small positive effect of feedback on persistence (hazard ratio (HR) for discontinuation 0.71, 95% confidence interval (CI) 0.53-0.95). However, in the non-responders, defined as those with an increase of ≥ 30% in urinary NTX, negative feedback actually had an adverse effect on persistence (HR 2.22, 95% CI 1.27-3.89), so it cannot be argued from these data that feedback about biochemical markers improves persistence in potential non-responders; in fact, the reverse was the case. Interestingly, in a sub-group analysis reinforcement using feedback about bone turnover measurements was associated with a decreased risk of vertebral fracture (1.2% vs 2.7% in the non-reinforcement group). Given the high persistence in both groups, this finding is hard to explain but might reflect positive effects of reinforcement on patient behavior. Overall these studies indicate that measurement of biochemical turnover markers does not significantly improve adherence to therapy in women with osteoporosis, although the opportunity for the patient to discuss therapy with a health professional has beneficial effects.

Currently, therefore, there is no scientific case for the routine monitoring of osteoporosis treatment by BMD or bone turnover measurements. BMD measurements during treatment provide information that comes too late, is unreliable in categorizing change and does not predict fracture outcomes. Bone turnover marker measurements have too high a variability for use in individuals in clinical practice and have not been shown to improve adherence with therapy. Conversely, there is some evidence that contact with a health professional in the early stages of treatment improves adherence to therapy and might therefore result in better fracture outcomes. Patients should receive adequate information at the start of therapy about their treatment and the need for it to be given long-term should be explained. They should be provided with the opportunity to discuss treatment-related issues with a health professional a few months later and at appropriate intervals thereafter. In the absence of a valid test for monitoring, this strategy provides the best approach to improving treatment outcomes.

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