Monitoring Osteoporosis Therapies

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Postmenopausal osteoporosis (PMO) is a progressive disease of bone loss, fractures, or both. The progression of osteoporosis leads to increased mortality and morbidity and impairs quality of life. There are effective treatments that prevent bone loss, increase bone strength, and reduce fracture risk. Improvement in persistence and adherence to therapy leads to better clinical outcomes. The management of PMO is facilitated by measuring surrogate markers of the efficacy of PMO treatments: 1) bone mineral density, 2) bone turnover markers, and 3) assessment of spinal integrity by vertebral fracture assessment by dual-energy x-ray absorptiometry. Appropriate use of markers measures the patient's baseline fracture risk and monitors response to treatments. Clinicians must interpret markers in the context of a patient's fracture risk and determine the effectiveness of therapy. Integrating these markers enhances overall patient care. The surrogate markers help the clinician to achieve the goal of managing PMO; attempting to manage PMO without markers reduces the clinical management to guesswork.

Introduction

Postmenopausal osteoporosis (PMO) is a chronic disease; once the process begins, it self-perpetuates unless it is treated. The high bone remodeling characteristic of PMO is not reversible with calcium or vitamin D alone because PMO is due not to calcium or vitamin D deficiency, but rather to estrogen deficiency [1]. Replacement of calcium and vitamin D are important adjuvant therapies, which can reduce the rate of bone loss and the number of fractures in patients who are deficient in calcium or vitamin D [2,3]. However, these essential elements are not as effective for the treatment of PMO as the pharmacologic interventions registered with the US Food and Drug Administration (FDA), which reduce bone remodeling more than do calcium and vitamin D. This observation is based on clinical trials whose end point is fracture risk reduction using hormone replacement therapy, raloxifene, calcitonin, the bisphosphonates, or teriparatide. Each study has shown a pharmacologic benefit beyond that achieved with calcium and vitamin D (placebo group) [4–8]. In order to have the maximal fracture-reduction benefit with the FDA-registered agents, however, patients with PMO must take their calcium and vitamin D supplements and the pharmacologic therapy in a persistent manner. Hence, the optimal treatment outcome that can be achieved can be witnessed only when patients follow the management plan. Herein lies the challenge for physicians treating all asymptomatic chronic diseases [9,10]. Thus, in clinical practice, there are reasons to monitor osteoporosis therapies with bone mineral density (BMD) measurements by dual-energy x-ray absorptiometry (DXA) and with biochemical bone turnover markers (BTMs) [11,12•,13]. In addition to assessing adherence and determining whether the patient is following the proper dosing instructions, monitoring also identifies treatment failures, defined as a loss of BMD beyond the least significant change (LSC) [14], fracturing despite treatment, or a consistently high resorption biomarker.

Monitoring and Adherence to Therapy

There is no direct evidence that monitoring alters adherence or persistence, but in clinical practice, discussing BMD or BTM results with the patient may uncover less-adherent patients who might not be identified by any other means. Since better adherence leads to better outcomes (eg, reduction of fracture risk), any means of improving adherence is worth the effort [15,16••].

It is far better in clinical practice to use surrogate markers that have strong correlations to improvements in bone strength when they change in the appropriate direction (BMD increases, BTM decreases with antiresorptive agents and increases with anabolic agents). These relationships are not perfect predictors of bone strength, but in the management of chronic disease, surrogate markers provide evidence to the physician and the patient that the medication is working. A dialog unique to the individual patient should be conducted based on trust and confidence that these surrogate marker changes have meaning for treatment decisions. Most recently, a randomized trial showed improved patient persistence with osteoporosis

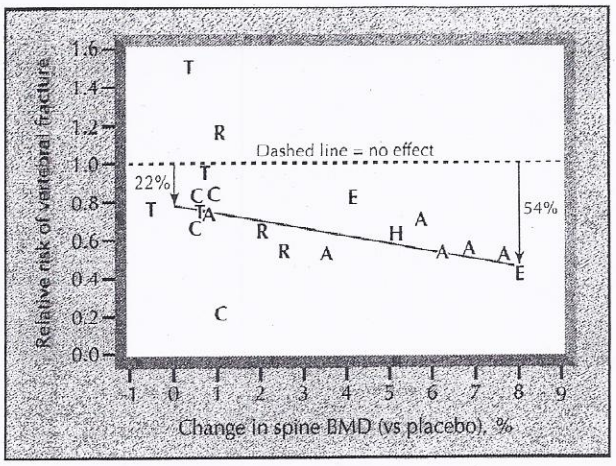

Figure 1. Relative risk of new vertebral fracture (vs placebo) relative to change in spine bone mineral density (BMD) in randomized, controlled trials of antiresorptive agents. The solid line represents the Poisson regression results. A—alendronate; C—calcitonin; E—etidronate; H—hormone replacement (estrogen); R—raloxifene; T—tiludronate. (*Adapted from* Wasnich and Miller [24], with permission.)

medications when the patient received a report explaining the meaning of the results [17].

Monitoring to Identify Nonresponders

Patients in clinical practice differ substantially from patients randomized into clinical trials [18]. In fact, these are two distinctly different populations. Clinic patients may have received glucocorticoids, may be vitamin D–deficient, or may have other conditions such as subclinical hyperthyroidism or hypercortisolism, secondary hyperparathyroidism, chronic kidney disease (even if their baseline serum creatinine concentration is below 2.0 mg/dL), or asymptomatic celiac disease. The potential for nonresponse to treatment in clinic patients, as opposed to patients in clinical trials, is thus so great that the so-called responder analysis examined in clinical trial data is applicable only to the preselected clinical trial population. It is simply common sense that one should expect to identify a greater proportion of treated clinic patients who are "nonresponders" *because* their BMD declined. Hence, monitoring BMD with DXA is as essential in the management of PMO as use of the sphygmomanometer is in the management of hypertension [19].

A decline in BMD beyond the LSC on treatment has been statistically related to regression to the mean. It has been shown that fewer fractures occur in treated patients even with a decline in BMD, compared with those who have a decline in BMD while not being treated [20–23]. However, these statistical analyses have no meaning in clinical practice. Regression to the mean is a group statistical phenomenon without applicability to an individual patient, and the comparison of a treated patient's fracture risk reduction to the risk for an untreated placebo group is a meaningless exercise in the clinical setting. Clinicians do not treat patients receiving placebo, nor do they treat groups of patients. Furthermore, in clinical trial datasets for many diseases, patients in placebo groups do better with regard to improvement in BMD and fracture risk reduction than patients who are not in clinical trials. An increase in BMD above the LSC with treatment is good and is associated with a greater fracture risk reduction than a stable BMD, whether that association is analyzed by meta-analysis or individual clinical trial data [24–26,27••] (Fig. 1). A stable BMD is an acceptable end point as long as the clinician reviews a specific checklist to ensure that the failure to see an increase in BMD with antiresorptive agents is not related to poor adherence, improper dosing, vitamin D deficiency, celiac disease, or other situations that may lead to poor therapeutic response. Antiresorptive agents increase bone mineral content (BMC) by slowing the remodeling rate and allowing a greater time for secondary mineralization. Hence, a decrease in BMD more than the LSC on therapy should not be acceptable in clinical practice. There must be a reason for the decline, which must be uncovered and resolved. The determination that a BMD decline is more than the LSC has been the focus of intense international educational processes by the International Society for Clinical Densitometry (ISCD) [28]. In vitro (phantom) precision studies are inadequate to calculate in vivo precision. Therefore, in vivo precision studies are required to calculate the LSC necessary for the competent interpretation of serial BMD changes [29]. A decline in BMD in a patient receiving treatment is usually due to a secondary condition mitigating the bone biologic response, a lack of bisphosphonate absorption, or end-organ pharmacologic resistance. Oral bisphosphonate absorption is fastidious and less than 1% of an oral dose is absorbed under the best conditions. There are many medical conditions (eg, celiac disease, gastrojejunostomies) in which oral absorption is doubtful and clinicians using oral bisphosphonates would find management decisions easier if a bisphosphonate blood level could be measured, but no commercial assays are available. Hence, clinicians must rely on the surrogate markers, BMD and BTMs, to assess whether a therapy is effective. Waiting for a fracture to occur is not a very appealing way to assess therapeutic response, and even the appearance of a fracture in a treated patient does not necessarily mean that the patient is not responding to treatment, because no treatment abolishes fracture risk. Nevertheless, when a new fracture occurs in a treated patient, the clinician must again review the checklist to determine if there are any reasons why the patient has not responded appropriately to therapy.

Monitoring of Bisphosphonate Therapy

BTMs provide independent early evidence of the efficacy of antiresorptive agents. Antiresorptive agents cause the resorption markers (urinary N-telopeptide or serum

C-telopeptide) to decline soon after the initiation of therapy, so even though it requires 12 months to see a significant change in BMD with antiresorptive therapy, the BTM change can be seen within 1 to 3 months after the start of treatment. Thus, BMD and BTMs are complementary [30–32]. If a clinician does not see a significant decline in a BTM with antiresorptive therapy, then the clinician must again examine issues that might explain nonresponse. At times, a BTM will remain elevated or unchanged after the initiation of an oral bisphosphonate, and this may be evidence that the oral bisphosphonate is not being absorbed, a situation frequently observed in clinical practice. These clinical situations may be seen even if the patient is compliant with the strict dosing schedule necessary to optimize oral bisphosphonate absorption and has no underlying gastrointestinal disease that might preclude oral bisphosphonate absorption. In some cases, there is no obvious cause of oral bisphosphonate malabsorption, yet the intravenous administration of a bisphosphonate causes a rapid drop in the BTM. It should be pointed out that sustained elevation of a BTM might be due to a different disease, and a differential diagnosis must be completed to ensure that another cause of high bone turnover (eg, hyperthyroidism, hyperparathyroidism, myeloma, Paget's disease, metastatic cancer) is not present.

The decrease in bone turnover required to ensure a therapeutic effect of antiresorptive agents has been investigated with bisphosphonates. First, any decline in a BTM must exceed the LSC of that biomarker's assay. If the BTM decrease is more than the LSC, one can assume that the patient is taking the drug, the drug is being absorbed, and the drug is having a biologic effect on bone [31,32].

It is felt that the reduction in the BTM should fall into the normal premenopausal range, especially for the resorption markers, urinary N-telopeptide or serum C-telopeptide. High bone turnover in PMO is an independent risk factor for fracture [33]. Hence, treatment may be initiated earlier in life in a woman with PMO who has high bone turnover than for a woman with normal bone turnover. In addition, the magnitude of the decline in the BTM induced by an antiresorptive agent is correlated with the increase in BMD and the reduction in fracture risk [32,34–38]. This relationship has been linear in some studies and nonlinear in others. From the intermittent bisphosphonate studies, it appears that a threshold reduction in BTM is necessary to achieve fracture risk reduction; for intermittent dosing schedules, the BTM must be maintained within the normal premenopausal range. Otherwise, undersuppression of bone turnover has been shown to be associated with nonsignificant reduction of fracture risk [39].

Bisphosphonates reduce the BTM level and bone remodeling 50% to 80% from the pretreatment baseline within 3 to 6 months, but the BTM level does not continue to decline with continued treatment. Hence, there is no evidence that bisphosphonates "shut off" bone turnover or remodeling, nor that they induce adynamic or aplastic bone disease, which is observed in chronic renal failure. Long-term, quantitative, double-tetracycline–labeled bone histomorphometry completed in patients receiving bisphosphonates for 5, 7, or 10 years has never shown adynamic bone disease (the absence of single tetracycline labels) and has shown the presence of double tetracycline labels, indicating that mineralization is continuing and that the reduction in activation frequency (the birth of new bone remodeling units) is reduced in postmenopausal women to the normal premenopausal level [40,41]. Anecdotal case reports of unusual fragility fractures occurring in a few patients receiving long-term alendronate treatment, with bone biopsies showing little or no mineralization, are uncontrolled data. It should be remembered that unusual fractures accompanied by the absence of single labels can be seen in some younger persons who have never receive a bisphosphonate. Thus, more information will be required to determine whether there is a small subset of patients who develop oversuppression of bone turnover and fragility fractures while taking potent bisphosphonates.

Monitoring of Teriparatide Therapy

Monitoring patients receiving teriparatide therapy is different from monitoring patients receiving bisphosphonates [42,43]. Teriparatide increases bone strength by multiple mechanisms, one of which is increasing bone size through new periosteal apposition. As bone size increases, bone strength increases by the fourth power of the radius (cross-sectional moment of inertia). DXA, a two-dimensional measurement, does not measure true bone size, which is a three-dimensional volumetric measurement. DXA measures the two-dimensional area, and BMD is determined by DXA through a derived equation: BMD = BMC/area. Teriparatide increases BMC and also increases area [44,45]. There are circumstances in patients treated with teriparatide in which the area increases more than the BMC, so that the calculated BMD declines, yet the bone strength increases. This phenomenon has been shown in teriparatide-treated cynomolgus monkeys at the forearm (forearm BMD by DXA declined, yet forearm volumetric BMD increased and bone strength increased) [44]. Therefore, even though the pivotal clinical trial that led to the FDA approval of teriparatide showed that the axial BMD increased in most patients, there are some who show no change or a significant decrease in BMD. In these situations, the clinician needs to reassure the patient by explaining that her or his bone strength really is increasing, using diagrams of the cross-sectional bone area and describing how teriparatide works. In these patients, BTMs (especially bone formation markers) may be helpful. There are three bone formation markers that can provide evidence of osteoblast stimulation: 1) bone-specific alkaline phosphatase, 2) osteocalcin, and 3) procollagen I N propeptide (PINP) and procollagen I C propeptide (PICP). PINP, the most sensitive and responsive marker for teriparatide, has recently become

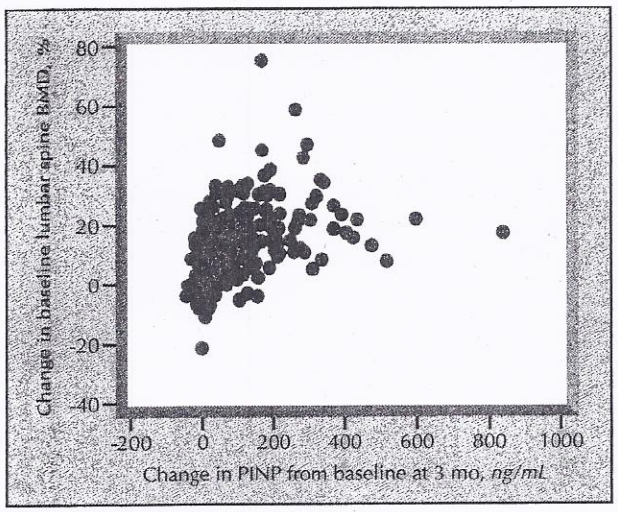

Figure 2. Relationship between absolute changes in serum procollagen I N propeptide (PINP) concentrations at 3 months and lumbar spine bone mineral density (BMD) responses after 18 months of treatment with teriparatide in postmenopausal women with osteoporosis. The relationship between changes in PINP and changes in lumbar spine BMD was evaluated by Spearman rank correlation analysis. Data represented are for all the groups (n = 602). (*Adapted from* Chen et al. [46], with permission.)

commercially available. It has been shown to increase from baseline within 3 months after initiation of teriparatide treatment and is correlated to an increase in lumbar spine BMD at 18 months (Fig. 2) [46]. It also has been shown to be correlated to the improvement in bone microarchitecture as assessed by histomorphometry [47]. Hence, in practice, if a PINP measurement 3 months after the start of treatment rises more than the LSC for the assay above a pretreatment baseline level, it can provide early feedback that the teriparatide is "working" and that BMD and bone microarchitecture should be improving as well. In teriparatide-treated patients whose BMD does not increase, an elevated bone formation marker can be reassuring.

Vertebral Fracture Assessment

A third tool for monitoring the treatment of PMO is vertebral fracture assessment (VFA). VFA (by DXA or by anteroposterior and lateral thoracic and lumbar spine x-ray) has advanced to become an accepted technology used to define prevalent as well as incident vertebral fractures [48••]. Prevalent vertebral fractures are common as humans age, are often asymptomatic, and are associated with a high risk for additional fractures at all skeletal sites in untreated patients. In multiethnic population studies, prevalent vertebral fractures are common, affecting 20% to 25% of whites, Hispanics, Asians, and American Indians or Alaska Natives by 70 years of age. Most vertebral fractures are not recognized and most are not managed correctly, perhaps because of a lack of appreciation of their role as a very strong risk factor for future systemic fragility fractures [49–51]. Vertebral fracture risk can be significantly reduced by pharmacologic treatment, and this reduction is associated with a significant positive effect on mortality, morbidity, and quality of life. Wider use of VFA should lead to the identification of a greater number of high-risk patients. In addition, serial VFA can be used as an additional monitoring tool to evaluate the efficacy of osteoporosis therapies. The development of a new vertebral compression fracture or the progression of such a fracture from one grade to a more severe grade during therapy should be viewed as a possible treatment failure and should be followed by additional assessment of the patient's medical condition. A clinician might consider changing therapy, using combination therapy, or staying the course, depending on the individual patient, even though a new or worsening vertebral fracture does not necessarily mean that any alternative approach would be better than the current treatment. However, without the knowledge of prior or new vertebral fractures obtained through VFA, the clinician may not consider the changes in fracture risk status that are associated with these VFA measurements [52].

Conclusions

Monitoring chronic diseases that require long-term therapy is of paramount importance in clinical practice. Persistence and adherence to chronic therapy in asymptomatic diseases is often inadequate and leads to poorer outcomes. Serial BMD, BTM, and VFA measurements, when appropriate, allow physicians to monitor the efficacy of therapy and improve compliance and persistence with therapy, thereby improving outcomes. It has been shown that discussions between physicians and patients regarding patient progress enhance medication persistence. In the field of osteoporosis, proper utilization of monitoring tools by clinicians provides feedback to patients. If these well-established monitoring tools are not used, the management of osteoporosis therapy is simply guesswork. In order to be useful, however, these tools require strict quality control and clinical interpretation, which is one of the missions of the International Society for Clinical Densitometry [53••].

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