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What is a 'failure' of bisphosphonate therapy for osteoporosis?

ABSTRACT

Assessing the effectiveness of bisphosphonate therapy is problematic. Bone mineral density and markers of bone turnover are often used, but the true measure is prevention of new fractures.

KEY POINTS

Certain oral bisphosphonates have been shown to reduce the incidence of vertebral, nonvertebral, and hip fractures, but only by about 50%.

Treatment may fail for several reasons, but particularly noncompliance. Significant loss of height or bone mineral density or little change in bone markers should be considered a possible sign of noncompliance or inappropriate therapy.

Although surrogate markers are useful, patients who take bisphosphonates reduce their risk of fracture even if their bone mineral density does not increase significantly or their biochemical markers of bone turnover do not decrease.

New fractures in compliant patients on therapy for 12 months or more should be considered possible therapeutic failures. However, there are currently no fracture data that support altering therapy in compliant patients who have fractures during therapy.

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WHEN WE PRESCRIBE a drug to prevent or treat osteoporosis, how can we tell if it is working?

The goal of treating osteoporosis is to prevent fractures, just as the goal of treating high blood pressure is to prevent stroke and heart disease. However, in clinical practice, the absolute risk of fracture may be hard to measure for an individual.

Surrogate markers of fracture risk have been developed, including height loss, bone mineral density, and biochemical markers of bone turnover.[1] But none of these markers tells the whole story. Fractures can be due to factors other than bone weakness, such as falling. Moreover, no drug can totally eliminate risk. And the best drug in the world won't work if the patient doesn't take it.

This article focuses on assessing the effectiveness of the bisphosphonates approved by the US Food and Drug Administration for treating osteoporosis, all currently available only in oral form in the United States. Several other medications are approved for treating osteoporosis, but they are not the subject of this discussion.

HISTORY OF BISPHOSPHONATES

Bisphosphonates were developed from pyrophosphates, compounds used to remove calcium carbonate scaling from industrial pipes and, later, plaque from teeth. In the early 1960s, investigators proposed that they might have similar actions on bone and could be used to treat diseases of the skeleton. Transformed into diphosphonates and later bisphosphonates, they are potent medications that decrease bone remodeling.

TABLE 1

Comparing the current bisphosphonates*

	ALENDRONATE (FOSAMAX)	RISEDRONATE (ACTONEL)	IBANDRONATE (BONIVA)
Available doses			
Daily	5, 10 mg	5 mg	2.5 mg
Weekly	35, 70 mg	35 mg	—
Monthly	—	—	150 mg
Prevents vertebral fractures	Yes	Yes	Yes
Prevents nonvertebral fractures	Yes	Yes	No data
Prevents hip fractures	Yes	Yes	No data
Indications			
Postmenopausal osteoporosis			
Prevention	Yes	Yes	Yes
Treatment	Yes	Yes	Yes
Glucocorticoid-induced osteoporosis			
Prevention	No	Yes	No
Treatment	Yes	Yes	No
Male osteoporosis treatment	Yes	No	No

*Second-generation and third-generation bisphosphonates approved for osteoporosis treatment in the United States

Bisphosphonates do not affect nonskeletal risk factors for fracture

Trials of first-generation bisphosphonates were promising,[2–4] but concerns over their narrow therapeutic index limited their use in the United States. Safer, more potent second-generation and third-generation bisphosphonates have fared better, and today, they are the most widely prescribed class of medications for treating a variety of skeletal disorders, most commonly osteoporosis.[5]

Currently, the oral bisphosphonates are the mainstays of osteoporosis treatment. Only drugs in this class are approved for preventing and treating involutional osteoporosis and glucocorticoid-induced osteoporosis in women and men and preventing hip fractures, and they are the only class shown to reduce all types of osteoporotic fractures, namely vertebral, nonvertebral, and hip.[6–17]

BISPHOSPHONATES REDUCE RISK BY ABOUT 50%

Although current bisphosphonates have some differences (TABLE 1), they are alike in several ways. They are all generally well tolerated. Though poorly absorbed, they all increase bone mineral density, reduce bone turnover, and decrease fracture risk by approximately 50%.[6–23]

For the patient this means that taking these medications reduces the risk of fracture, but does not eliminate it.

Why not? Bisphosphonates do not modify nonskeletal risk factors for fracture such as falls, genotype, comorbidity, and advanced age. They do not correct skeletal erosion that has occurred over many years. And they take some time to show an effect, although the reduction in risk is statistically significant within 6 to 12 months of starting therapy.[24] Data are currently limited on the impact of very early treatment on future risk reduction. Fractures that occur shortly after starting therapy may not be true therapeutic failures, as insufficient time may have elapsed for the drug to be effective.

HOW CAN I BE SURE THE DRUG IS WORKING?

In clinical practice we monitor and assess the success of therapy in two basic ways: through clinical follow-up and by measuring surrogate markers such as central bone mineral density

(in the lumbar spine and hip in most instances) and markers of bone turnover.

Clinical follow-up

An appropriate way to evaluate therapy and possibly to increase compliance is to follow up with patients in the office to discuss their medication use and concerns.[25] We cannot overemphasize how important it is to verify that the patient is:

- Actually taking the bisphosphonate
- Taking it correctly (first thing in the morning, at least 30 minutes before eating or drinking anything, with a full 8-ounce glass of water only, and staying upright at least 30 minutes afterward)
- Taking in adequate amounts of calcium and vitamin D. Current recommendations for calcium are 1,200 to 1,500 mg of elemental calcium per day, preferably through diet, or through supplementation. The recommended intake of vitamin D is 400 to 800 international units.

Modification of lifestyle and nonskeletal risk factors is important (**TABLE 2**).[26–30] A multidisciplinary approach to fall prevention can be very effective.[29]

New complaints of fractures should be verified if possible, and worrisome symptoms such as new back pain should be investigated with appropriate imaging techniques. Further loss of height or new or worsening kyphosis should arouse suspicion for new vertebral fractures and should prompt further evaluation.[7,14,15]

Siminoski et al[31] recently analyzed a nested cohort from a large bisphosphonate trial and found that progressive height loss correlated with new vertebral fractures and an increasing number of vertebral fractures. As a sign of new vertebral fractures, a loss in height of 2 cm or more within 3 years had a sensitivity of 35.5% and specificity of 93.6%.

Other studies showed that patients with new vertebral fractures lose significantly less height if they are on bisphosphonate therapy.[14,15]

Surrogate markers

Bone mineral density and biochemical markers of bone turnover are useful but imperfect surrogate markers of fracture risk.[1,18,20,32–34] Changes in these measures with therapy correlate with changes in fracture risk, especially when used in combination.

TABLE 2

Nonskeletal risk factors predisposing to falls

Chronic conditions
- Arthritis and other musculoskeletal disorders
- Visual impairment
- Hearing impairment
- Proprioceptive impairment
- Previous history of falls
- Poor gait
- Poor balance
- Dementia or confusion

Acute conditions
- Infections
- Strokes, cardiovascular events
- Medications: sedatives, psychotropic and other drugs, including alcohol
- Postural hypotension
- Stairs, restraints, lack of support rails
- Poor lighting
- Delirium
- Wet floors or uneven surfaces

Bone mineral density

Guidelines are available for monitoring bone mineral density during therapy.[34] A repeat scan should be done no sooner than 1 year after starting a bisphosphonate to increase the likelihood of seeing significant changes at the site of interest.

The effect on bone mineral density differs depending on the skeletal site, the bisphosphonate, and the length of time on therapy. Bisphosphonates generally increase bone mineral density more rapidly at sites of predominantly trabecular bone, so significant changes may occur in the lumbar spine within 1 to 2 years, but longer intervals may be needed to see significant changes at the hip or forearm.[6,7,12,14,15] Newer bisphosphonates such as alendronate, ibandronate, and risedronate increase bone mineral density at the lumbar spine by an average rate of 2% to 5% annually and at the femoral neck by 1% to 4%,[6,7,11,12,14,15,23,35] but using such criteria for individual patients is unwise: monitoring therapy using established guidelines is more appropriate.[34]

Small increases in bone density equal large reductions in fracture risk

Although the risk of fracture almost doubles with every standard deviation of decrease in bone mineral density, only very minor increases in bone mineral density are needed to see large associated reductions in fracture risk with treatment.[6,7,8,11–13]

Importantly, any change should exceed the least significant change for the testing center before definite conclusions can be drawn about either loss or gain of bone mineral density.[33,34,36] As in all scientific measurements there is a degree of variability between repeated readings, which can be calculated. This precision can be influenced by factors in the machine, patient, or technician—usually a combination of all three—and should be calculated for each testing center. While the details of calculation are provided elsewhere, the least significant change is in essence a measure of precision error for a site-specific bone mineral density scan.[33] This information allows you to decide whether changes in subsequent scans are significant. A change greater than the least significant change for that center and skeletal site is considered a clinically important difference.

Changes in bone density must exceed the least significant change for the testing center

Suppose, for example, the least significant change at your testing center is 3% for the total hip, and a patient has a repeat scan performed 2 years after starting therapy showing a 2.5% loss of bone mineral density. Although worrisome, the difference is not significant; however, a 3.5% loss would be. Care should be taken to repeat bone mineral density scans on the same machine, as the least significant change is specific for each machine, and changing from one to another will make any meaningful comparison between scans impossible in most instances.[33,34]

Biochemical markers of bone turnover

More recently, biochemical markers of bone turnover (of which there are two types: markers of bone formation and markers of bone resorption) have been shown to be useful for monitoring therapy. Although the tests are widely available, many physicians do not routinely use them yet, and knowledge of their individual intricacies is needed to use them optimally and to interpret the results correctly.

Monitoring these markers has several advantages compared with measuring bone mineral density.

Levels of bone turnover markers usually decline significantly within several weeks of starting bisphosphonate treatment, and the reductions with therapy correlate more closely with the reduction in fracture risk than do increases in bone mineral density.[18,20] Bisphosphonate therapy reduces the levels of these markers by about 40% to 50%, varying a little by dose, specific medication, and marker assay used.[18,20,23,37,38]

The tests are easy to do. Testing, particularly for resorption markers such as N-terminal telopeptide of type I collagen or C-terminal telopeptide of type I collagen, should be performed on either serum or a second morning urine sample, after an overnight fast, preferably at the same time of day, in patients not taking oral or intravenous corticosteroids.[32,39,40] A repeat test after 2 to 3 months of oral bisphosphonate therapy is usually sufficient to see a drug effect (changes become evident sooner with resorption markers than with markers of bone formation).

Moreover, the tests cost less than measuring bone mineral density, and they may increase compliance. On the other hand, they are significantly less precise than bone mineral density, that is, there is greater variability on repeated testing than with bone density. The least significant change is usually 2% to 3% for bone density but may be 20% to 30% for some bone marker assays. However, newer assays are much better and continue to be refined.[20,25,37–40]

WHAT IS TREATMENT 'SUCCESS'?

One can define treatment success in several ways, eg:

- Lack of definite fractures or symptoms or signs that suggest them. Preservation of height (< 1 cm of loss) has a negative predictive value approaching 97%.[31]
- No change or an increase in bone mineral density (greater than the least significant change for that site) measured by central dual energy x-ray absorptiometry[34]
- A reduction in serum or urine markers of bone resorption of 30% or more[9,18,20,41]
- Compliance with therapy. Although surrogate markers are useful, patients who take

bisphosphonates reduce their risk of fracture even if their bone mineral density does not increase significantly or their biochemical markers of bone turnover do not decrease, as shown in studies[6–9,11,13–17,20,35] and in clinical practice.[42] Thus, a prescription for and compliance with therapy indicate some measure of success in and of themselves.

WHAT IS THERAPEUTIC 'FAILURE'?

A new fracture despite treatment for a sufficient time (> 1 year) is a possible sign that the drug isn't working. Previous fractures are the biggest risk factor for future fractures and may be the most significant risk factor for fractures on bisphosphonate therapy.[43]

For an individual patient, it is hard to prove whether treatment has reduced the number or severity of new fractures. Studies show patients with new vertebral fractures on therapy experience less loss of height or deformity.[7,14,15] Loss of 2 cm or more of height may warrant further investigation for vertebral fractures.[31]

Like fractures, significant loss of bone mineral density on follow-up scans after 12 to 24 months of therapy is generally considered treatment failure.[1,33,34,42–44]

However, several other questions need to be considered when fractures or loss of bone mineral density occurs during therapy[1,34,42–44]:

Does the patient really have primary osteoporosis? Other diseases such as hypercalciuria, vitamin D deficiency, and malignancy can affect the skeleton and result in secondary osteoporosis.[45] Appropriate evaluations should be performed in all patients before starting bisphosphonate therapy. Indeed, these medications may be contraindicated in certain conditions, such as severe renal insufficiency or vitamin D deficiency.[46–48]

Is the patient taking the drug? Noncompliance often results in treatment failure and should not be overlooked. Many patients do not fill their prescriptions for osteoporosis medications, and of those who do, many stop taking them within the first year, limiting the effectiveness of therapy.[25,42,44] Many patients readily admit not taking their medications for fear of side effects or due to their cost ($70–$100 per month), so compliance should be addressed at a follow-up visit soon after starting therapy.

Regular follow-up coupled with testing of biochemical markers of bone turnover may help improve adherence.[25] Though testing of biochemical markers is imperfect, failure to reduce levels of these markers should raise concern, particularly if noncompliance is suspected.[25]

Is the drug truly failing? Bisphosphonates do not prevent all fractures, and they do not modify nonskeletal risk factors for fracture. Other diseases or medications that can exacerbate bone loss may need to be addressed.

If a patient has a marked reduction (≥ 30%) in biochemical markers of bone turnover or an increase in bone mineral density while undergoing long-term therapy, but still has a new fracture, he or she is probably taking the drug, and it is working in a biochemical sense, but it has failed in a practical sense.[20]

However, don't be fooled if the bone mineral density of the lumbar spine increases with incident spine fractures, as compression fractures can falsely elevate bone mineral density (the bone area is usually smaller in such circumstances). Although therapy may slow the rate of bone mineral density loss in "rapid losers," this is not usually considered a treatment success.

Compression fractures can falsely elevate bone mineral density

Lastly, there is more going on in the skeleton than can be assessed by bone mineral density and biochemical markers of bone turnover, and recent studies suggest that mineralization and other skeletal microarchitectural improvements result in better bone quality and fracture risk reduction.[49,50] Newer technologies that will allow accurate and precise measurement of these changes may be important monitoring tools in the future.

I THINK TREATMENT HAS FAILED: NOW WHAT?

The first step is to try to establish whether the drug truly failed—or whether the patient stopped taking it, or is taking it incorrectly, or has some other disorder of bone metabolism for which this is the wrong treatment to use.[1,34,44]

Unfortunately, at this time no one can say what to do if a bisphosphonate truly fails.

Although different agents may affect bone mineral density and biochemical markers of bone turnover to different degrees,[23] and these measures may change more with certain treatment combinations,[37] currently there are no fracture data to support use of one of the approved medications over another (with the exception of prevention of nonvertebral fractures) or for using combinations of compounds.

If a patient has a fracture while taking an oral bisphosphonate, it may be appropriate in some circumstances to consider switching to an anabolic agent (ie, teriparatide [Forteo], a recombinant form of parathyroid hormone). However, currently there are no fracture data to support this strategy. Indeed, switching to an alternative compound such as an anabolic agent may not have quite the expected impact.[51] Large studies using fractures as the primary outcome are needed to establish whether there is truly a benefit to such practice. Individual treatment decisions should be left to the physician caring for the patient until such data are available.

When patients do experience fractures while on therapy, appropriate management with analgesia, physical therapy, bracing, casting, or surgery is needed. Modification of nonskeletal risk factors for falls is appropriate and has been shown to be effective. One should also reassure the patient and encourage him or her to continue treatment.

Further study is needed to address these issues so we can prevent most, if not all, osteoporotic fractures and make evidence-based recommendations to alter therapy when fractures occur during bisphosphonate therapy.

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