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NEWS

Long-term treatment of osteoporosis with bisphosphonates: clinical decision-making in an 'evidence-free zone'

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Osteoporosis experts react to recent FDA analysis, and put the focus on patients at high risk for fracture.

Introduction

Bisphosphonates, the bone field's mainstay of treatment for osteoporosis, have proven efficacy in decreasing the risk of fracture. Randomized, controlled clinical trials show that alendronate, risedronate, ibandronate and zoledronic acid decrease the relative risk of vertebral fracture by about 40–70%, with some agents also showing efficacy for hip and non-vertebral fractures. The trials, however, lasted only a few years, and although some additional information about long-term use comes from extensions to those studies even out to 10 years, overall there is a dearth of data to guide physicians who need answers to some key questions: Which patients merit treatment beyond the short-term time frame of the randomized trials? Which patients can safely stop? For those who stop, how long should they go without treatment, and how does one decide? Reports over the past several years of very rare, yet serious adverse consequences, particularly atypical femoral fractures, in bisphosphonate users have given urgency to those questions. Based on such safety concerns, the US Food and Drug Administration (FDA) undertook a systematic review of the data on long-term bisphosphonate efficacy. Their analysis, published recently in the *New England Journal of Medicine*,[1] determined that those who remain on treatment over the long-term have fracture rates similar to those who stop after 3–5 years. The FDA concluded that patients at low risk for fracture might be suitable candidates to discontinue bisphosphonates after 3–5 years, whereas those at high risk might benefit from further treatment, but did not make any specific recommendations to guide clinical decision-making.

Some experts in the United States are concerned that the media, as well as medical malpractice lawyers with their aggressively litigious mindset, will parse the FDA's analysis in a way that scares off even high-risk patients from using bisphosphonates, a troubling trend that leading osteoporosis physicians have been worried about ever since the first reports of atypical femoral fractures hit the press and reached the lay public a couple of years ago. 'That's what's happening out there, in the real world of medicine—and it's a real problem,' according to Paul Miller, MD, medical director of the Colorado Center for Bone Research in Lakewood, Colorado. Indeed, Dr Miller said that he already sees patients at very high risk for fracture who adamantly refuse to take bisphosphonates even though they would greatly benefit from the drugs, and he is even more struck by the number of patients who simply stop bisphosphonates without ever consulting a physician. However, despite their apprehensions, all the experts who spoke to *BoneKEy* generally agree with the substance of the FDA's analysis. They too believe that the end of 3–5 years of bisphosphonate treatment is the right time to have a legitimate discussion with patients about whether they should or should not continue therapy. Furthermore, they agree that high-risk individuals, who they say should be identified on the basis of older age, prior fracture and low bone mineral density (BMD), should continue treatment, whereas those at low risk can consider stopping. They also stress that because evidence-based medicine provides little guidance in this area, the physician's own clinical judgment is of paramount importance in making these significant decisions about long-term therapy. Finally, they are in universal agreement that the benefits of bisphosphonates in preventing fractures greatly outweigh the risks of serious yet very rare adverse events—that, above all else, is the most important message.

Reaching the Deadline—And Seeking an Extension

In making determinations about which patients merit long-term bisphosphonate treatment, one thing is clear: those decisions are not data-driven. 'We're entering an evidence-free zone,' said Juliet Compston, MD, a professor of bone medicine at the University of Cambridge School of Clinical Medicine in the United Kingdom. Indeed, there are only a handful of data points on this issue, and they come mainly from two extension studies to earlier randomized controlled trials of bisphosphonates.

The first is FLEX,[2] an extension of the Fracture Intervention Trial (FIT); the latter trial established the anti-fracture efficacy of alendronate in postmenopausal women with low bone mass

after 3–4 years of treatment. FLEX took 1099 subjects who had participated in FIT and randomized them to three groups: one group continued to take alendronate at 5 mg per day, another continued at 10 mg per day and the third received a placebo. Results after 10 years of continuous treatment showed that patients taking alendronate (pooled doses) exhibited a 55% decreased risk of clinical (symptomatic) vertebral fractures vs placebo (absolute risk of 2.4% vs 5.3%), but there was no difference in morphometric vertebral fractures, nor in non-vertebral fractures. A later *post-hoc* analysis of FLEX documented a 50% reduction in non-vertebral fractures for those without a prevalent vertebral fracture whose T score was $\leqslant -2.5$ at the beginning of FLEX.

The second extension study[3] followed subjects who had participated in the 3-year Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly-Pivotal Fracture Trial (HORIZON-PFT). Findings indicated that in 1233 postmenopausal osteoporotic women from HORIZON-PFT who were randomized to receive 3 additional years of zoledronic acid or placebo, patients who stayed on the drug exhibited a 49% decreased risk of morphometric vertebral fractures vs placebo (absolute risk of 3.0% vs 6.2%), but there was no difference in clinical vertebral fractures, nor in non-vertebral fractures.

Overall, both FLEX and the extension to HORIZON-PFT point in a similar direction, according to Ian Reid, MD, an investigator on the latter extension trial and a professor of medicine and endocrinology at the University of Auckland in New Zealand. 'The consistent message that we get both from FLEX and from the extension to HORIZON-PFT is that people who are no longer osteoporotic on bone density measurement don't seem to accrue much further benefit from having prolonged treatment,' Dr Reid said. Instead, both extensions suggest that high-risk patients, particularly those at risk for vertebral fractures, might benefit from continued therapy.

An FDA Analysis Hits *The New England Journal of Medicine*

Based on concerns about adverse events like atypical fractures, and stressing the importance of fracture as the key endpoint in trials that assess bisphosphonate efficacy, the FDA undertook its own analysis[1] of FLEX and the HORIZON-PFT extension, highlighting three main findings from its examination. First, it pointed to what it said is an inconsistency in the vertebral fracture findings between FLEX—a decreased risk of clinical vertebral fractures, but no difference in morphometric vertebral fractures—and the extension to HORIZON-PFT, which found the converse—a decreased risk of morphometric vertebral fractures, but no difference in clinical vertebral fractures. Second, its analysis of FLEX concluded that subjects who received continuous alendronate for up to 10 years had similar rates of fracture as those who took placebo during the extension period (17.7% vs 16.9% in pooled data); it also found that fracture rates were similar in all three treatment groups (5 mg alendronate, 10 mg alendronate or placebo) and in all subgroups of BMD up to approximately 8 years of continuous treatment. Third, when the FDA pooled all the vertebral and non-vertebral osteoporotic fracture data from FLEX, the extension to HORIZON-PFT and a smaller extension[4] to the Vertebral Efficacy with Risedronate Therapy-Multinational Trial that included 164 postmenopausal women with osteoporosis, it found that fracture rates remained relatively constant over time. Finally, pooled data from those who had continuous bisphosphonates for 6 years or more indicated fracture rates of 9.3–10.6% vs 8.0–8.8% for those switched to placebo.

Based on those findings, the FDA concluded that '[t]he available data do suggest that bisphosphonates may be safely discontinued in some patients without compromising therapeutic gains, but no adequate clinical trials have yet delineated how long the drugs' benefits are maintained after cessation.' Furthermore, citing the limitations inherent to *post-hoc* analyses, they concluded that their *post-hoc* analysis of the fracture data did not allow for the identification of subgroups more likely to benefit from long-term treatment with bisphosphonates. As a result, the FDA made no clear recommendations on the matter, other than to address it in very general terms by stating that 'patients at low risk for fracture (e.g., younger patients without a fracture history and with a bone mineral density approaching normal) may prove to be good candidates for discontinuation of bisphosphonate therapy after 3–5 years, whereas patients at increased risk for fracture (e.g., older patients with a history of fracture and a bone mineral density remaining in the osteoporotic range) may benefit further from continued bisphosphonate therapy.'

Guidance for Clinicians

Osteoporosis specialists had been quite concerned that the FDA might set a limit on how long patients could take bisphosphonates, and so the new analysis provided a bit of relief. They worried, though, about the FDA's reluctance to illustrate for physicians how to make real-world decisions for their patients. 'Primary care doctors may come away from the analysis scratching their heads,' said Michael McClung, MD, founding director of the Oregon Osteoporosis Center in Portland and *BoneKEy* associate editor for clinical content. 'It would have been helpful to provide examples where it's clear that a patient should stay on therapy, examples when it's reasonable to discontinue, and then, if physicians stop treatment, examples of what to do then,' Dr McClung said.

In order to provide some direction to clinicians who need to know the best course of action for their patients, Dennis Black, PhD, a statistician and professor at the University of California, San Francisco, along with colleagues re-evaluated an earlier analysis that they did of FLEX and the extension to HORIZON-PFT, and published their findings in an article accompanying the FDA findings.[5] Although the FDA pointed to the inconsistency between the findings on vertebral fractures in FLEX and the HORIZON-PFT extension, Dr Black notes that those studies were not specifically designed to measure fracture endpoints, and so the likelihood of detecting statistically significant effects on fracture was low. 'The gestalt is that there is an effect on vertebral fractures,' Dr Black said.

Dr Black and his co-investigators focused their reanalysis on vertebral fractures. In particular, they looked back to FLEX and estimated the number needed to treat (NNT) for 5 additional years to prevent one clinical vertebral fracture in various subgroups defined by femoral neck BMD, as well as by prevalent vertebral fracture status when alendronate-treated patients from FIT entered FLEX. They found that clinical vertebral fracture rates were the highest in women with femoral neck BMD T scores $\leqslant -2.5$, and the NNTs in those subjects were lowest: for all women in the study, they found an NNT of 21 for

T scores ≤ –2.5, and an NNT of 17 for women with a prevalent vertebral fracture at the start of FLEX and T scores ≤ –2.5. They also found an NNT of 17 for women with prevalent vertebral fracture at the start of FLEX whose T score was > –2.5 and ≤ –2.0. Meanwhile, they saw the lowest fracture rates, and the highest NNTs, in patients with T scores >–2.0: an NNT of 81 for all women in the study and a T score >–2.0, an NNT of 102 for those with no prevalent vertebral fracture at the start of FLEX and a T score > –2.0, and an NNT of 51 for those with a prevalent vertebral fracture at the start of FLEX and a T score > –2.0. Based on those data, the authors concluded that after 3–5 years of bisphosphonate treatment, further therapy (with alendronate or zoledronic acid) will likely help individuals with T scores < –2.5, as well as those with T scores a bit higher who also have an existing vertebral fracture. Meanwhile, they wrote that those with T scores > –2.0, who have a low risk of vertebral fracture, likely won't benefit from further treatment.

Other experts who spoke to *BoneKEy* also advocate an approach to long-term bisphosphonate treatment that focuses on individuals at high risk for fracture. Patients who have suffered a fracture while on bisphosphonates certainly fall into that category, as do patients with low BMD after 3–5 years of initial treatment, particularly if they are older, because a T score of –2.5 in a 50-year-old is not the same thing as a T score of –2.5 in an 85-year-old. Age in and of itself is a key consideration in determining the need for further treatment. 'I would very rarely stop bisphosphonates in a patient in their 80s or older, because the risk of hip fracture becomes so high then,' according to Dr Compston, who also noted that patients who lose bone during treatment also merit long-term therapy. However, she stressed that such criteria are generic, and that each patient must be assessed individually, based on his or her own unique characteristics and circumstances.

Finally, the evidence does suggest that, for patients on alendronate who are deemed good candidates to continue therapy, reducing the dose is an attractive option. 'In FLEX, it didn't seem to matter whether patients took 5 mg or 10 mg a day of alendronate—the bone density, turnover and fracture data were the same,' Dr Reid said. 'An important message we can take from FLEX, then, is that if patients have been on alendronate for 5 years and it's felt that they need to continue therapy, going to a smaller dose of 5 mg a day is a perfectly acceptable way to proceed,' he said.

All Good Things—Including A Drug Holiday—Must Come to an End, but When, and for Whom?

If deciding which patients to treat with long-term bisphosphonates is to enter an 'evidence-free zone,' then determining which patients who have stopped should restart therapy, and when, is to enter a black hole—there is even less data to guide clinicians there. Consequently, as with decisions about continuing therapy, it is imperative for physicians to rely on their clinical experience and to assess each patient on his or her own terms. 'This is subject to judgment rather than to hard and fast rules because the trial data don't give us hard and fast rules,' Dr Reid said.

One of the themes to emerge from all of the debate about long-term treatment is that bisphosphonates are not all the same. In fact, Professor Black and colleagues underscored in their *NEJM* analysis that their recommendations for long-term treatment apply only to alendronate and zoledronic acid, because data show that stopping risedronate results in greater bone loss than does stopping alendronate or zoledronic acid, whereas there are no data in that regard for ibandronate. Thus, they concluded that bisphosphonates need to be considered on the basis of their unique strengths and weaknesses when determining the length of a drug holiday.

'One approach to deciding when to end a drug holiday would be to base it on the affinity of the bisphosphonate for bone, and they have a different rank order—zoledronic acid binds most strongly, and risedronate binds least strongly,' said Nelson Watts, MD, director of Mercy Health Osteoporosis and Bone Health Services in Cincinnati, Ohio. An alternative tactic is to base the decision on a change in bone turnover markers or bone density; Dr Watts, who has examined the effects of discontinuation of risedronate on fracture risk along with Dr McClung,[6] takes the latter approach. 'The way we approach this issue is to monitor bone density. For patients who are at lower risk, I would entertain stopping treatment after 3–5 years and maintain the holiday as long as bone density is not going down and the patient is not fracturing,' Dr Watts said. 'For higher risk patients at the end of 3–5 years, I would try to keep them on therapy somewhere in the 8–10-year time frame, and would not want them off therapy for more than 2 years, and if they are at high risk during the drug holiday, I would put them back on something.'

There are some patients, Dr Watts said, who merit another drug during their bisphosphonate holiday. An example of the latter, he said, is a patient he saw who still had very low BMD despite years of alendronate treatment, and for whom he then prescribed 2 years of teriparatide. Dr Miller follows a similar practice. 'For high-risk individuals, including those with fractures, and older people with a femoral neck T score of –2.5 or lower, I feel uncomfortable leaving them treatment-naive,' Dr Miller said. 'In those cases I tend to use teriparatide for a year, and for those who can't take that drug, I would try denosumab,' he said.

Whether denosumab might be a safer option than bisphosphonates for long-term treatment of osteoporosis remains unclear. The chief concern regarding long-term anti-resorptive therapy, with bisphosphonates or with drugs like denosumab that work via a different mechanism, is atypical femoral fractures, however rare those fractures may be; the experts who spoke to *BoneKEy* say that there is no good evidence to support a link between esophageal cancer and long-term bisphosphonate use, nor are they concerned about osteonecrosis of the jaw in typical osteoporosis patients, who take much lower doses of bisphosphonates than those who are treated for cancer-induced bone disease. Thus, they say that the ultimate place of denosumab in long-term treatment of osteoporosis will depend on the mechanism of atypical fractures. Denosumab suppresses bone turnover more strongly than bisphosphonates, and if suppression of bone turnover is a culprit resulting in atypical fractures, then denosumab might pose more of a problem than bisphosphonates. On the other hand, if atypical fractures are bisphosphonate-specific, then denosumab might indeed be a safer choice for therapy over the long-term. There does not appear to be a major safety signal in this regard for denosumab thus far, but the bone field is looking forward to seeing more long-term data to feel completely reassured; in the extension to the Fracture Reduction Evaluation of Denosumab

in Osteoporosis Every 6 Months (FREEDOM) trial, two cases of atypical femoral fractures have recently surfaced in subjects taking denosumab for 6 years.

Randomized Controlled Trials Are *Not* the Answer

Physicians would like better data to guide decisions about long-term treatment, but that information is unlikely to ever come from randomized, placebo-controlled trials, the gold-standard of evidence-based medicine, because of ethical concerns about leaving subjects on placebo for long periods of time. In addition, because atypical fractures are driving the concern about long-term bisphosphonate treatment but are so rare, randomized controlled trials are unlikely to ever illuminate them, because of the large numbers of subjects that would be required for those trials. In short, everyone wants fracture data from randomized controlled trials, but to ask for it is, in practical terms, to ask for the impossible.

What, then, is the way forward? Experts say that observational studies relying on large databases from health maintenance organizations or government programs like Medicare will be quite helpful, by providing information about bisphosphonate use, bone density, risk factors for fracture and fracture rates. Another promising route is to develop the ability to pinpoint those at risk of atypical fractures, said Dr McClung. 'I suspect that, within the next few years, we'll be able to identify, using genetic or metabolic testing, the subgroup or subgroups of patients who are uniquely susceptible to suppression of bone turnover with bisphosphonates or likely with other potent anti-resorptives,' he said. With that data in hand, physicians could avoid overtreating those at high risk of atypical fractures, and feel more confident that long-term treatment in others would not be problematic.

The next generation of osteoporosis therapies also offers an opportunity to move ahead. 'The arrival of new drugs like cathepsin K inhibitors that work in a totally different way than bisphosphonates could change the whole paradigm' for long-term treatment, Dr McClung said. Indeed, he said that patients on alendronate for 5 years, for instance, could for a time then switch to odanacatib, a cathepsin K inhibitor in phase 3 clinical trials for postmenopausal osteoporosis and that does not inhibit resorption as strongly as bisphosphonates and has little effect on bone formation. 'That might provide a strategy that protects patients from fracture without permanently reducing their bone turnover to low levels,' he said.

In the meantime, doctors making long-term treatment decisions will need to rely heavily on their clinical judgment, and simply make the most out of very limited data. 'What we were trying to do in our analysis,' Dr Black said, 'is say as much as we could out of the data we've got, because this is probably the best data we're ever going to have on this particular topic.'

Conflict of Interest

The author declares no conflict of interest.

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