REVIEW

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Western Osteoporosis Alliance Clinical Practice Series: Evaluating the Balance of Benefits and Risks of Long-Term Osteoporosis Therapies

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ABSTRACT

Osteoporosis is a chronic disease that requires life-long strategies to reduce fracture risk. Few trials have investigated the balance of benefits and risk with long-term use of osteoporosis therapies, and fewer still have investigated the consequences of treatment discontinuation. The best available evidence suggests that up to 10 years of treatment with an oral bisphosphonate maintains the degree of fracture risk reduction observed in the 3-year registration trials. With denosumab, 10 years of therapy appears to provide fracture risk reduction similar to or better than that observed in the 3-year registration trial. Available data suggest an increasing but low risk of fractures with atypical features with increasing duration of bisphosphonate therapy. Published data linking duration of therapy to osteonecrosis of the jaw are lacking for bisphosphonates and denosumab. Other side effects associated with denosumab or bisphosphonates do not appear to be related to therapy duration. The antifracture benefits of long-term therapy with bisphosphonates and denosumab in appropriately selected patients outweigh the low risk of serious side effects.
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The Western Osteoporosis Alliance, composed of clinical trial investigators and osteoporosis clinical practitioners from western Canada and the United States, is dedicated to translating the best available medical evidence into suggestions for osteoporosis management. Here we review the benefits and risks of long-term use of bisphosphonates and

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denosumab for treating osteoporosis, with consideration of the need for effective fracture prevention over a patient's remaining lifetime.

Long-term use of teriparatide will not be discussed, as treatment is limited to 18-24 months by regulatory guidelines, and discussion of side effects of long-term use of raloxifene and menopausal hormone therapy is beyond the scope of this paper. For a thorough review of the role of estrogen and progestin in osteoporosis management, refer to de Villiers.[1]

Osteoporosis is a chronic skeletal disease characterized by low bone strength and increased fracture risk. A wide range of pharmacologic agents reduce fracture risk. With nonbisphosphonate osteoporosis therapies, long-term therapy is required because discontinuation results in rapid loss of antifracture benefit.[2,3] With bisphosphonates, skeletal accumulation of the drug may offer persistence of antifracture benefit after drug discontinuation; thus, temporary interruption of bisphosphonate administration—a "drug holiday"—may be considered for low-risk patients who have been compliant with treatment for at least 3 to 5 years.[4]

CLINICAL SIGNIFICANCE

- Osteoporosis is a chronic disease that generally requires therapy and monitoring for the remainder of a patient's lifespan.
- Long-term bisphosphonate therapy is associated with a low risk for fractures with atypical features.
- The antifracture benefits of treatment with bisphosphonates or denosumab in appropriately selected patients far outweigh the small risks of osteonecrosis of the jaw and fractures with atypical features.
- Temporary interruption of bisphosphonate administration may be considered for low-risk patients who have been compliant with treatment for at least 3-5 years.

Regulatory requirements for licensure of osteoporosis treatments mandate placebo-controlled clinical trials focusing on antifracture efficacy over 3 years — long, logistically difficult, and costly trials. Few studies have evaluated safety or efficacy beyond 3 years, and fewer have assessed the consequences of treatment discontinuation. In the extensions of regulatory studies, the placebo groups have not been maintained beyond 5 years due to ethical concerns about leaving patients at risk for fracture untreated. Therefore, there is limited experience with continuous osteoporosis therapies extending to 10 years.[4-7]

Safety concerns have arisen surrounding long-term osteoporosis pharmacotherapy. In the view of many experts, there has been a disproportionate focus on rare adverse events in patients on long-term bisphosphonate or denosumab therapy, without balanced consideration of benefits, resulting in many patients discontinuing treatment and re-assuming their elevated fracture risk.

WHY DOES OSTEOPOROSIS REQUIRE LONG-TERM TREATMENT?

Osteoporosis is typified by bone loss that weakens the skeleton and predisposes individuals to fracture.[8] Osteoporosis therapies decrease the probability of a fracture,[9-17] with many providing rapid protection—within 6-12 months for vertebral fracture[18] and within 3 years for nonvertebral or hip fractures.[9,11,12,14,15] No therapy totally eliminates the risk of fracture, in part because of the notable role of trauma.

Antiresorptives such as bisphosphonates and denosumab primarily reduce osteoclastic bone resorption and rate of bone turnover, preserving, but not re-establishing, skeletal architecture. There is some evidence that denosumab may improve cortical strength through modeling-based bone formation and decreasing cortical porosity.[19]

The therapeutic effects of most drugs, including nonbisphosphonate therapies for osteoporosis, are lost quickly when treatment is stopped. When denosumab therapy is stopped, even after 8 years of therapy, bone mineral density declines as bone turnover rises to, or exceeds, pretreatment levels.[4,20,21]

The effects of bisphosphonate therapy on skeletal health also wane when treatment is stopped, albeit more slowly than with denosumab.[4,20] Thus, because osteoporosis, as with other chronic illnesses, is currently not curable, and the benefits of therapy dissipate when treatment is stopped, long-term treatment is generally required. Because of this, long-term safety needs to be weighed against benefits accrued by continuing therapy. Despite the chronic nature of osteoporosis and the risk of bone loss, discontinuation of therapy may be considered for a number of reasons.

WHY IS STOPPING OSTEOPOROSIS THERAPY CONSIDERED?

Possible Loss of Efficacy over Time

Most of the regulatory fracture prevention trials have had difficulty in retaining large numbers of patients for trial extensions. Further, there has been a lack of placebo groups in most studies over 3 years. Because of this, significant fracture endpoints, particularly for nonvertebral fracture, have been difficult to demonstrate over the long term. With long-term use of bisphosphonates there is no incremental fracture risk-reduction beyond that realized in the initial years of therapy.[12,22,23] Despite this, it has been repeatedly demonstrated that fracture protection occurs early and persists with long-term bisphosphonate and denosumab therapy.[5,14,18,22,24] This durable fracture risk reduction needs to be considered in the context of a progressive increase in fracture incidence expected in an untreated population, where fracture risk rises significantly with age.[25]

In the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) study, denosumab-treated patients experienced rapid fracture risk reduction after 1 year (61% reduction in vertebral fracture incidence), with significant vertebral, nonvertebral, and hip fracture protection after 3 years (68%, 20%, and 40% reduction vs placebo, respectively).[14] In the extension trial, denosumab treatment out to 7 years (10 years total exposure) was associated with a further reduction in the incidence of nonvertebral fractures, suggesting that longer-term denosumab therapy leads to accumulating nonvertebral fracture efficacy.[7] To summarize, while there is no evidence for further improvement in fracture protection after 5 years of bisphosphonate therapy (ie, fracture rates do not continue to decline), the concern that bisphosphonates and denosumab lose their efficacy with long-term therapy is unfounded.

Possible Increased Risk of Intolerance or Side Effects with Long-Term Therapy

A concern leading to therapy discontinuation is the possibility of duration-dependent risk of side effects. While bisphosphonates have been associated with chronic muscle and bone pain,[26] ocular effects,[27-29] upper gastrointestinal adverse events,[30,31] and atrial fibrillation,[12,23] causality has not been clearly established for any of these, and they have not been linked to duration of use.

Bisphosphonates adhere to bone and become increasingly concentrated with long-term exposure.[32] This retention in bone has raised concern of possible deleterious effects over time. Long-term use of bisphosphonates is associated with an increased risk of subtrochanteric fractures with atypical features.[33,34] Subtrochanteric fractures account for between 4% and 10% of all femoral fractures,[33,35] and approximately 0.3%-0.12% of all femoral fractures are fractures with atypical features.[36] It is important to note that fractures with atypical features also occur in people unexposed to antiresorptive therapy and that they can occur at sites other than the femur.[37-40] A Swedish population-based study reported that there was an increase in absolute risk of 5 cases of fractures with atypical features per 10,000 patient-years of bisphosphonate use (95% confidence interval [CI], 4-7).[33] A further analysis of this population found that the relative risk after at least 4 years of bisphosphonate therapy reached 126.0 (95% CI, 55.1-288.1), with an annual absolute risk of 11 fractures (95% CI, 7-14) per 10,000 person-years of use.[36] A treatment-duration-dependent increase in the risk of fractures with atypical features was found in a California Kaiser Permanente cohort: 0.178/10,000 patient-years in the first 2 years increased to 11.3/10,000 patient-years in years 8-9.9 of exposure.[41] The association of bisphosphonate therapy with fractures with atypical features may include some confounding by indication: they also occur in patients who have never been treated with bisphosphonates, but if they also had low bone mineral density, these patients would be more likely to be treated with bisphosphonates. Recently, a Danish nested case-control study demonstrated an overall benefit of long-term alendronate therapy.[42] They found no significant difference in risk of subtrochanteric or femoral shaft fracture (typical and atypical) in long-term (>10 years) or current users compared with past users. However, adherent (>80%) and long-term use (5+ years) of alendronate significantly decreased the probability of hip fracture (by 27% and 26%, respectively).

After discontinuation of bisphosphonates, the risk of fractures with atypical features appears to decrease rapidly. Schilcher et al[33,36] showed that the risk of fractures with atypical features diminished by 70% per year from last use (odds ratio 0.28; 95% CI, 0.21-0.38).

Despite the concern about fractures with atypical features, the claim that long-term bisphosphonate therapy causes "brittle bones" is at odds with the observation that there are far fewer fractures in the aggregate in patients using bisphosphonates over the long term as compared with those patients not taking bisphosphonates.[4,23]

Recognizing the increased risk of fractures with atypical features with long-term bisphosphonate therapy provides clinical opportunities to minimize that risk. Risk factors for fractures with atypical features may include female sex, Asian ethnicity, hypophosphatasia, vitamin D deficiency, glucocorticoid use, and proton-pump inhibitor use.[36,43] Bisphosphonate exposure should be minimized in those patients and should clearly not be used in patients with hypophosphatasia or osteomalacia.

At least 70% of patients with femoral fractures with atypical features have prodromal thigh pain weeks to months before a complete fracture with atypical feature occurs, an important clinical symptom of its development.[43] A periosteal stress reaction in an asymptomatic patient's femur may be evident on radiograph or even dual X-ray absorptiometry.[44] About 50% of these patients have a similar abnormality in the contralateral femur. Imaging studies in patients on bisphosphonate therapy who experience thigh pain or who present with a fracture with atypical features, as well as long femur hip imaging by dual X-ray absorptiometry, allow identification of patients with incomplete fracture with atypical features in whom medical or surgical therapy might prevent a complete fracture.

Another concern with bisphosphonates is the development of osteonecrosis of the jaw with long-term therapy. In phase III clinical trials, there was an extremely low incidence of osteonecrosis of the jaw that did not seem to be an excess in treated patients compared with placebo patients.[45-47] The American Society for Bone and Mineral Research has reported an incidence of 1 in 10,000-250,000 patient-treatment years.[45]

In contrast to the risk of side effects, there have also been possible benefits associated with bisphosphonate therapy: decreased risk of breast,[48] colorectal,[49] and gastric[50] cancer; and decreased risk of stroke (hazard ratio 0.79; 95% CI, 0.66-0.99),[51] myocardial infarction (hazard ratio 0.35; 95% CI, 0.14-0.84),[52] and overall mortality (10%-28%)[12,53]. None of these putative benefits have been recognized as

such by regulatory authorities. A recent cohort study reported that in contrast to ordinary subtrochanteric fractures, atypical subtrochanteric fractures are not associated with an increase in mortality (age- and sex-standardized mortality ratios of 1.82; 95% CI, 1.69-1.99 and 0.92; 95% CI, 0.65-1.26, respectively).[54]

In summary, despite lack of clear mechanism, the main increasing risk associated with long-term bisphosphonate therapy is fracture with atypical features. However, in patients who are at high risk for fracture, benefits outweigh fracture with atypical features risk during first 10 years of treatment.[55,56] Consider 10,000 healthy women aged 67.8 years with femoral neck bone mineral density T-score values of −2.5 or lower, with 35% having a history of any fracture (but no vertebral fracture) since age 45 years: after 10 years of alendronate therapy, there would be 550 vertebral fractures prevented, 250 hip fractures prevented, 1620 clinical fractures prevented, and 100 deaths prevented as compared with an associated 11 fractures with atypical features.[11,56] While there is little debate that the benefits of therapy outweigh the risks from a public health perspective, the clinical decision to continue therapy is heavily influenced by the psychological overlay created by the persistent focus on the negative aspects of therapy by the media.

With denosumab, the incidence of adverse events, serious adverse events, fatal adverse events, skin rash or eczema, cellulitis, or erysipelas and serious infections were similar between placebo and denosumab groups at all time points up to 10 years of use.[7,24] Long-term use of denosumab may be associated with a very low incidence of fractures with atypical features, although the clinical trials do not show an increasing risk with dose duration.[6,57-63] Further, osteonecrosis of the jaw has been associated with denosumab at osteoporosis (60 mg/6 months) and oncology (120 mg/month) doses, with the incidence in oncology being far higher than in osteoporosis patients, suggesting a dose−response relationship.[64] It bears noting that oncology patients have many other comorbidities and are prescribed numerous drugs other than denosumab that may also play a role in osteonecrosis of the jaw development. Published data linking duration of therapy to osteonecrosis of the jaw are lacking for denosumab (or bisphosphonates), but the denosumab product label now suggests that this risk may increase with therapy duration.[65]

As long as patients are tolerating denosumab, there is no reason for discontinuation, because efficacy and safety both seem to be sustained.[6] Further, there are case reports of vertebral fractures occurring soon after stopping denosumab, raising the possibility that the increase in bone turnover to higher-than-pretreatment levels after stopping denosumab may result in increased bone fragility.[66,67] This has reinforced opinion that a "drug holiday" is not appropriate for patients receiving denosumab.[68] Another recent update to the product monograph for denosumab has included a statement regarding the risk of multiple vertebral fractures on denosumab discontinuation, particularly in patients with prior vertebral fractures.[65] If denosumab is discontinued, there is typically need for a replacement antiresorptive therapy to sustain antifracture efficacy.

Possible Persistent Benefit of Therapy After Discontinuation

An additional reason to consider discontinuation of therapy would be that a benefit of therapy persists following discontinuation. Again, this is applicable only to bisphosphonates, where the effects on skeletal metabolism wane gradually following discontinuation.[4,69,70] The persistence of antifracture efficacy appears to remain for at least 1 year after stopping risedronate[69] and 3 to 5 years after stopping alendronate[4] or zoledronic acid.[70] No data on discontinuation of ibandronate are available. Because of this persistence of antifracture benefit after stopping most bisphosphonates (based on small numbers of subjects in extensions of the major clinical trials), and the possible dose-duration-dependent risk of fractures with atypical features, the concept of a "drug holiday" has been proposed.[33,36]

After 3-5 years of bisphosphonate therapy, patients at low fracture risk can consider a "drug holiday," whereas patients at high risk (T-score <−2.5, prior vertebral fracture) should continue to be treated and followed to 10 years.[55] After 10 years of therapy there are no data, and it is unclear which patients may be candidates for a "drug holiday."[56]

Recommendations for duration of bisphosphonate drug holidays are not grounded on high-level evidence.[71] Neither repeated bone mineral density nor repeated bone turnover marker measurements were found to predict who would and would not fracture a year after discontinuation of bisphosphonates.[20] Bisphosphonate drug interruption might be appropriate for 1 year after risedronate therapy, up to 2 years after alendronate, and up to 3 years after zoledronic acid therapy in selected lower-risk patients.[56] Recommendations for temporarily discontinuing bisphosphonate therapy are truly relevant for only the relatively few patients at low-to-moderate risk for fracture who have been compliant with therapy for 3 to 5 years. At the end of the "drug holiday" the clinician should re-evaluate indications for therapy (bone mineral density, fracture, Fracture Risk Assessment Tool 10-year fracture-risk assessment) and, if the patient meets current criteria for therapy, re-start a treatment. A recent study demonstrated that bone mineral density, bone turnover markers, and Fracture Risk Assessment Tool status may help guide when it may be appropriate to resume treatment.[72] With all things considered, age and hip bone mineral density prior to initiation of therapy may be the most robust predictors of fracture once off therapy.[73]

The key message with discontinuation of osteoporosis medications is that the bone changes (bone mineral density, bone turnover markers) dissipate rapidly with all therapies except bisphosphonates, where resolution of effect wanes proportional to the duration of therapy and time since the last dose. Drug holidays should be more appropriately

termed "bisphosphonate drug interruptions," as the holiday concept does not apply to other antifracture medications.

CONCLUSIONS

There are effective clinical tools for diagnosing osteoporosis, assessing fracture risk, and identifying individuals most likely to benefit from pharmacological therapy to reduce fracture risk. There are many options for pharmacological therapy to reduce fracture risk; however, there remains a significant care gap in patients following fragility fracture.[74,75]

All therapies have risks, but in appropriately selected patients, risks of osteoporosis therapy are very low when compared with antifracture efficacy. Patients at high risk for fracture are most likely to benefit from therapy. High-risk patients who choose not to be treated must be informed on the potentially serious consequences of fractures and higher risk without treatment. The choice of therapy for an individual patient should take into consideration the clinical profile and risk for adverse effects. Long-term therapy is not appropriate for patients at low risk of fracture, while for high-risk patients, continuing therapy has potential for much more benefit than risk. All treatments should be individualized to match the patient's specific clinical characteristics and preferences. Lifestyle factors should be optimized as much as possible and include fitness, nutrition, and falls prevention, among others. Modalities to reduce the risk of falls are crucial in those at moderate or high risk of falling, as most nonvertebral fractures occur as a result of a fall.

Health care providers should strive for effective risk communication with patients so that the risk and consequences of fractures are understood, as well as the expected benefits and possible side effects of treatment.

In the near future, new drugs with novel mechanisms of action may become available, expanding our choices for treatment interventions and potentially providing greater opportunities for combination therapy. With these new drugs, monotherapy with antiremodeling agents will continue to be the primary therapy for most patients with osteoporosis. Repetitive sequential courses of therapy with anabolic followed by antiremodeling drugs may be used to treat patients with severe osteoporosis.

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