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EXPERT PERSPECTIVES ON CLINICAL CHALLENGES

Expert Perspective: How, When, and Why to Potentially Stop Antiresorptive Drugs in Osteoporosis

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Osteoporosis is a chronic disease, and antiresorptive treatments are often continued for many years. Despite their established efficacy in reducing fracture risk, the most commonly used antiresorptive treatments, bisphosphonates and denosumab, have short- and long-term risks that, coupled with their benefits and other unique characteristics, influence consideration for at least periodic discontinuation. Bisphosphonates retain their effects even after discontinuation due to their prolonged skeletal retention, whereas denosumab discontinuation is associated with a rapid rebound in bone turnover and increased fracture risk. There is controversy about how, when, and why to potentially stop these agents. We discuss both permanent and temporary discontinuation of long-term treatment with bisphosphonates and denosumab. We focus on the reasons and timing for discontinuation as well as strategies to mitigate future fracture risk.

Clinical challenge

Two 70-year-old postmenopausal identical twins (Ms DMS and Ms BPS) were seen for a second opinion about their severe osteoporosis. Ms DMS had a vertebral fracture 12 years ago and experienced a wrist fracture in her fifties. She has been treated for nine years with denosumab at 60 mg subcutaneously every six months. Her twin sister has a history of two vertebral fractures 9 and 13 years ago, and she has been taking alendronate at 70 mg orally once a week for the past 15 years. Beyond age, menopausal status, and a family history of an early hip fracture in their mother, neither sister has additional major risk factors for fractures. They have both been reading about adverse effects related to long-term osteoporosis treatment and are concerned about continuing their medications.

Osteoporosis treatment considerations and why to consider stopping certain drugs. Effective management of osteoporosis is critical to reducing the risk of fractures, which significantly impact the quality of life in older adults. Several pharmacologic treatments are available for the management of osteoporosis, each with distinct mechanisms of action and long-term effects on bone metabolism. This perspective will be limited to issues surrounding the longer-term use of the two most commonly used types of antiresorptive osteoporosis drugs: bisphosphonates and denosumab.

Bisphosphonates and denosumab have been the cornerstone of osteoporosis management because of their wide availability and efficacy in reducing bone resorption by inhibiting osteoclast activity, leading to improved bone mineral density (BMD) and reduced fracture risk.[1–6] Bisphosphonates, such as alendronate, bind to hydroxyapatite crystals and are incorporated directly into the bone hydroxyapatite matrix. They inhibit osteoclast activity by targeting the enzyme farnesyl diphosphate synthase in the osteoclast mevalonate pathway and limit production of a ruffled border necessary for bone resorption. They have a very extended activity because as the bone is resorbed, they are progressively uncovered and become reactivated.[7] Based on this rather unique depot mechanism of action, bisphosphonates provide a prolonged antifracture benefit and have drug effects that may persist months or years even after their discontinuation. On the other hand, denosumab, a monoclonal antibody that inhibits the RANKL, a key factor in osteoclast activation differentiation, activation, and survival, has biologic effects that are sustained for only six months after a single subcutaneous dose. If denosumab is discontinued, there is a rapid "rebound" in bone turnover associated with an increased fracture risk.[8–12] Suppression of bone turnover is a key mechanism by which these drugs reduce fracture risk. However, prolonged suppression of bone turnover can cause the bone to become more highly mineralized and lose its ability to repair microdamage.[13,14] This can lead to bone fragility. Potential "oversuppression" of bone

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remodeling has been associated with rare adverse events with both classes of agents.

The most concerning adverse events associated with both bisphosphonates and denosumab are atypical femoral fractures (AFFs) and osteonecrosis of the jaw (ONJ). These adverse events are believed to stem, at least in part, from the profound and longer-term suppression of bone remodeling. Although both conditions share a common pathophysiology related to the suppression of bone turnover, each has unique characteristics and potential mechanisms.[15]

ONJ is characterized by exposed necrotic bone in the maxillofacial region, often following dental extractions or other invasive dental procedures. It is believed that prolonged suppression of bone turnover compromises the ability of the jawbone to repair microdamage and maintain vascularity, leading to localized necrosis. Additionally, factors such as local infection, reduced angiogenesis, and microbial biofilms play significant roles in the pathogenesis of ONJ.[16]

AFFs occur along the subtrochanteric or diaphyseal regions of the femur and occur with minimal trauma. The pathogenesis involves oversuppression of bone turnover leading to reduced bone remodeling capacity, accumulation of microdamage, and altered bone material properties.[17]

Both events are estimated to have an overall incidence of 1 of 1,000 to 1 of 10,000 in patients treated for osteoporosis.[18,19] Despite the overall rarity and the typical modest severity of most cases of ONJ in osteoporosis, it occasionally can be very serious and lead to morbidity and even death. Further establishing causality of these events with bisphosphonates, ONJ rates approach 1% to 10% when potent intravenous bisphosphonates are administered as frequently as every month in the setting of malignancy.[19] Because of the unusual depot effects of bisphosphonates, the risk of these longer-term adverse effects with both treatments, and/or achievement of successful bone health outcomes, some clinicians and patients, such as the twins, will consider stopping these treatments after variable periods of use.

In the complex clinical challenge we described, the approach to care for Ms DMS and Ms BPS varies greatly, based on their specific bone treatment history, even if the two sisters present with a somewhat similar health history and identical genetic background.

A detailed bone medication history is essential in evaluating and managing osteoporosis. For Ms DMS, questions should focus on her adherence to denosumab, including whether she has missed or delayed any doses, given the rebound risk. For Ms BPS, the medical history should explore her adherence to alendronate over the years. Indeed, oral bisphosphonates, although effective, are well known for poor long-term adherence due to their strict dosing requirements and potential gastrointestinal side effects. In addition to adherence, another challenge with oral bisphosphonates, particularly in older adult patients, is reduced gastrointestinal absorption. Bisphosphonates have inherently low bioavailability (~1%), and their absorption is further impaired by common factors in older adults, such as concurrent medication use (eg, proton pump inhibitors). Medical history should also include the evaluation of the need for future invasive dental procedures, particularly tooth extraction and intended dental implants, that might affect use and/or timing of antiresorptives due to risk of ONJ.

How and when to discontinue antiresorptives

Given their different mechanisms of action, we will discuss separately denosumab discontinuation and bisphosphonate drug holidays. The evidence supporting the decision-making in continuing or stopping these therapies is summarized in Tables 1 and 2.

Bisphosphonates. Bisphosphonates can be classified based on the route of administration and, more importantly, based on their relative osteoclast inhibition potency, mostly determined by their affinity to the bone. Among the commonly used bisphosphonates—alendronate, risedronate, zoledronic acid, and ibandronate—there are significant differences in their bone affinity, with zoledronic acid having the most affinity to bone and ibandronate and risedronate having the lowest.[20]

Long-term extension to the clinical trials of bisphosphonates, such as alendronate, have provided critical insights into their efficacy and the effects on treatment discontinuation. In the pivotal study of alendronate for postmenopausal participants with osteoporosis who continued alendronate treatment for up to 10 years showed significant and sustained increases in BMD. This was most notable at the lumbar spine, where after approximately five years of therapy, BMD essentially plateaued and persisted even after the drug was stopped for five years.[21] In contrast, BMD at

Table 1. Bisphosphonate discontinuation: benefits, risks, and competing evidence*

Benefits/rationale to discontinue	Risks to discontinue/ rationale to continue
Protracted efficacy even after discontinuation (especially with alendronate or zoledronic acid–prolonged skeletal retention)[21–23,26]	Residual fracture risk in high-risk patients[22,33]
Plateauing of BMD benefit after prolonged therapy (≈3–5 years) and similar fracture risk[21,22]	Refracture risk during drug holiday[23,32,36]
Risk of adverse effects related to treatment duration[18,32]	Secondary mineralization might offer benefit beyond BMD increase[76,77]
Reduced adverse effects upon stopping (ONJ, AFF)[18,19,33]	–
Temporary discontinuation (holiday)[23,33,36]	–

* AFF, atypical femoral fracture; BMD, bone mineral density; ONJ, osteonecrosis of the jaw.

Table 2. Denosumab discontinuation: benefits, risks, and competing evidence*

Benefits/rationale to discontinue	Risks to discontinue/rationale to continue
No further risk reduction after achieving T score greater than[78] −1.5/−2.0	Rebound in bone turnover markers and loss of BMD[8,10,12,40]
Successful exit strategies to attenuate rebound exist: transition to zoledronic acid or alendronate[41]	Increased risk of fractures and multiple vertebral fractures after discontinuation[40,42–44,50,54]
Adverse effects (eg, ONJ, AFF)[15,18,19]	Risk of fracture higher than expected from BMD loss[45,51]
–	Efficacy and safety tested through 10 years[39]
–	Bisphosphonates (especially with less potent bisphosphonates such as risedronate), SERMs, or romosozumab after discontinuation still associate with bone loss[52,53,55,70,79,80]

* AFF, atypical femoral fracture; BMD, bone mineral density; ONJ, osteonecrosis of the jaw; SERM, selective estrogen receptor modulator.

the hip and bone turnover returned toward baseline over approximately five years. The impact of alendronate discontinuation after five years on fracture risk is somewhat nuanced. Overall, there was no significant difference in the incidence of morphometric vertebral, nonvertebral, and hip fractures between those who continued treatment for 10 years and those who discontinued after only 5 years. However, there was a 55% reduction in the risk of clinical vertebral fractures in those who continued alendronate therapy for 10 years, and the subgroup of women who were at highest fracture risk also saw a preferential benefit to continuing therapy.[22] Notably, the study was considerably underpowered to detect differences in fracture risk among those who persisted with therapy and patients who remain in extensions to clinical trials have low generalizability to the general population.

Risedronate, another oral bisphosphonate given weekly or monthly, exhibits a comparatively much shorter "tail effect" than alendronate. Specifically, although bone turnover and BMD in patients treated with alendronate returns to baseline levels over approximately five years, those treated with risedronate revert to baseline within approximately one year after stopping the medication, regardless of the treatment duration.[23,24]

Zoledronic acid (also known as zoledronate), is another common bisphosphonate administered intravenously once a year. It also has an even longer tail effect, and participants who discontinued treatment after years still exhibited some residual benefits.[25] Notably, a single infusion of zoledronic acid can sustain BMD gains over baseline for up to 10 years and reduce clinical fracture risk,[26] supporting that its very prolonged effects may offer bone benefits even after discontinuation. Beyond its well-established role in fracture prevention, zoledronate has also been associated with a reduction in overall death in older adults with osteoporosis and after hip fractures. The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Recurrent Fracture Trial showed a 28% reduction in all-cause deaths in patients receiving zoledronate following a hip fracture.[27]

Although AFFs and ONJ have generated the greatest concerns, the most common bisphosphonate adverse events are gastrointestinal issues with oral administration and acute flu-like symptoms (acute-phase reaction) with intravenous administration.[15] However, gastrointestinal intolerance to oral bisphosphonates is usually rapidly reversible on discontinuation, not related to the duration of the treatment, and more likely to occur within weeks of the first dose. Acute-phase reactions (APR)s are usually limited to a few days and wane with subsequent administrations of bisphosphonates. Moreover, a short course of dexamethasone before the first infusion reduces APR severity.[28] Renal toxicity with zoledronic acid is also seen and primarily associated with rapid infusion rates in patients with impaired renal function.[29] Although concerns have been raised about esophageal cancer and atrial fibrillation being associated with bisphosphonates, causality has not been firmly established.[30,31]

The risk–benefit balance of bisphosphonates can be evaluated by the number needed to treat (NNT) and number needed to harm (NNH). Although the NNT for preventing typical osteoporosis fractures is largely favorable in the early years of treatment, the NNH for serious adverse events such as AFF increases with extended therapy. In White women, bisphosphonate use corresponded to a NNT for preventing a typical fragility hip fractures of approximately 350 and 170 at 5 and 10 years, respectively.[32] In contrast, in Asian women, the NNT was greater at 575 and 278 at 5 and 10 years, respectively. After five years of treatment, the NNH to cause an AFF was 12,500 for all women. However, The NNH decreased after 10 years of continuous treatment to 2,630. Of note, the NNH at 10 year was disproportionately lower among Asian women at only 424, thus indicating a higher rate of AFF compared to the overall population. The study also identified other risk factors for AFF, beside Asian ethnicity, including reduced height, weight, and glucocorticoid use. Importantly, the risk of AFF decreased rapidly after discontinuation of bisphosphonates, highlighting the importance of considering so called drug holidays. These therapy transitions to other types of medications are intended to mitigate long-term risks while maintaining the therapeutic benefits of fracture prevention. This balance in risk and benefit among different ethnic groups of women, in particular, necessitates careful consideration on the selective timing and duration of bisphosphonate therapy.

The 2016 American Society of Bone and Mineral Research (ASBMR) guidance on drug holidays for patients on long-term bisphosphonates offers emphasizes the balance between the benefits of fracture prevention with bisphosphonate and the need to reassess fracture risk over time[33] (see Figure 1). High-risk patients, such as persons age >70 years, those with a low hip T

score (less than –2.5), those who have had a major osteoporotic fracture, or those who continue to fracture while on therapy, may benefit from extended treatment for up to 10 years with oral bisphosphonates or 6 years with intravenous zoledronic acid. For patients deemed to be at low or moderate fracture risk after the initial treatment period, a drug holiday of two to three years may be considered. During this period, patients should undergo periodic reassessment of their fracture risk, including monitoring BMD and possibly bone turnover markers (BTMs). This reassessment helps determine the appropriate time to reinitiate therapy if the patient's fracture risk increases. A decrease in BMD of >3% (usually more than the least significant change on dual x-ray absorptiometry [DXA]) is considered significant at an individual patient level.[34]

BTMs, such as C-terminal telopeptide (CTX), also can be used in monitoring the effectiveness of osteoporosis therapy and guiding decisions about drug holidays or treatment reinitiation. CTX reflects the rate of bone resorption, and its levels typically decrease with effective antiresorptive treatment, such as bisphosphonates. A significant drop in CTX from pretreatment levels, defined as more than the least significant change of 30%, suggests that an antiresorptive therapy is effective in suppressing bone turnover. CTX levels also can be used to monitor drug holidays. A common approach involves comparing baseline (predrug holiday) levels with those during the drug holiday. Two potential thresholds for interpretation include a return to baseline levels (pretreatment) or an increase of more than 30% from the end-of-treatment levels. Our approach to these two thresholds can be summarized as follows: (1) a return to pretreatment baseline levels or higher (ie, before any bone active drug has been started), indicating complete loss of antiresorptive effect or (2) an increase of more than 30% (above the least significant change of most BTMs) from end-of-treatment levels, suggesting excessive bone loss. Measuring BTMs at 6 to 12 months after stopping bisphosphonates might allow clinicians to determine whether therapy should be restarted earlier than BMD alone would suggest, particularly in high-risk patients. Other BTMs, including urinary N-telopeptide, can be used in similar ways, albeit urinary turnover markers are more subject to diurnal variations.[35]

A corollary concern is that once bisphosphonates are discontinued for an extended period, fragility fractures may recur. US Medicare data were used to examine the fracture risk associated with various lengths of drug holidays among 81,427 women aged 65 years and older who had been adherent to

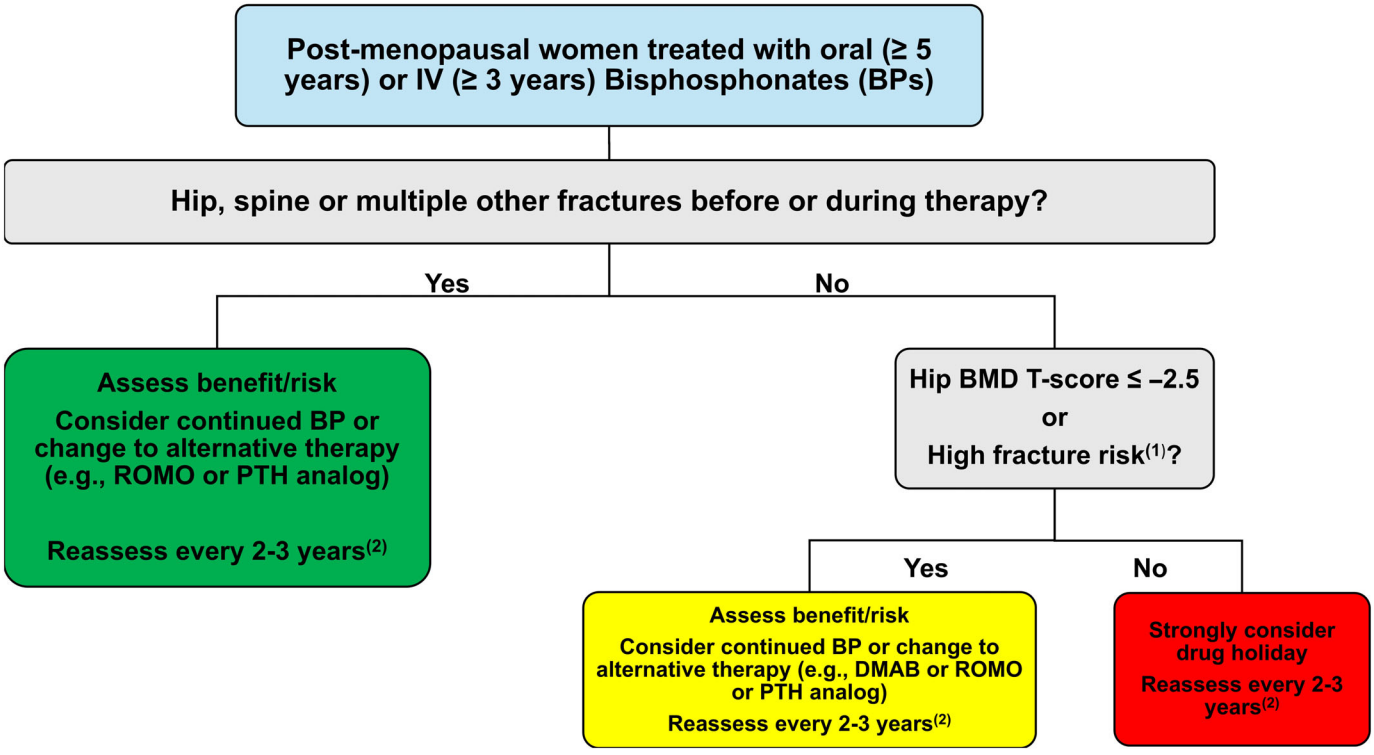

Figure 1. Approach to the management of postmenopausal women undergoing long-term bisphosphonate therapy (adapted from Adler et al[33]). (1) High fracture risk: defined by older age (70–75 years), other strong risk factors for fracture, or a validated fracture risk assessment tool fracture risk score above country specific thresholds. (2) Reassessment includes clinical evaluation and risk assessment including risk factors and may include bone density measurement by dual x-ray absorptiometry (DXA). The monitoring interval with DXA should be based on changes that are detectable and clinically significant. Reassessment may be necessary at <2 years in patients with a new fracture, or in light of anticipated accelerated bone loss (eg, institution of aromatase inhibitor or glucocorticoid therapy). BMD, bone mineral density; DMAB, denosumab; PTH, parathyroid hormone; ROMO, romosozumab.

bisphosphonate therapy (alendronate, risedronate, or zoledronate) for at least three years.[36] Discontinuing alendronate therapy for more than two years in more than a quarter of these women was associated with a significantly increased 30% greater risk of fractures compared to those who continued therapy (adjusted hazard ratio [HR] 1.3, 95% confidence interval [CI] 1.1–1.4). These findings suggest that extending the duration of a drug holiday beyond two years may significantly increase the risk of hip, humerus, and vertebral fractures. Among 25,000 matched pairs of older adults who had undergone long-term bisphosphonate therapy (either alendronate or risedronate) followed by a drug holiday (1.8 years on average), hip fracture rates were approximately 18% higher in the group of patients who discontinued risedronate compared to those who discontinued alendronate (12.4 vs 10.6 per 1,000 patient years, HR 1.18, 95% CI 1.04–1.34). Although risedronate and alendronate provide significant protection against fractures during active treatment, the shorter tail effect of risedronate may lead to a slightly higher risk of fractures, particularly hip fractures, during extended drug holidays.[36]

Many consider a slightly longer drug holiday duration for zoledronic acid (18–24 months) compared to oral bisphosphonates (no more than 12–24 months for alendronate and perhaps even less for risedronate).[23,24] Indeed, risedronate drug holidays may pose similar risk to alendronate drug holidays for most patients at up to two years, but over three years the risk was 18% higher. However, decisions should be individualized based on the patient's duration of bisphosphonates therapy, fracture risk profile, and overall health status. Regular monitoring and bone health reassessment are crucial to determining the appropriate time to resume therapy to balance the benefits of fracture prevention with the potential adverse event risks of continued bisphosphonate exposure.

Denosumab. Denosumab exhibits distinct effects on bone modeling and remodeling that may contribute to its unique safety profile. Unlike bisphosphonates, denosumab effects on bone remodeling are rapidly reversible, and a partial "escape" of remodeling occurs at the end of denosumab's pharmacologic effect, just before the next dose is due.[37] Moreover, denosumab's effect on BMD may not reach a plateau as seen with bisphosphonates, possibly due to an effect on modeling based bone formation.[38,39] These unique aspects of denosumab's action highlight the complexity of its impact on bone health and underscore the importance of careful timing and monitoring in its long-term use to optimize outcomes while minimizing potential adverse effects.

The problem of rebound following denosumab discontinuation is a significant concern in the management of osteoporosis. On denosumab discontinuation the beneficial effects of this agent are rapidly reversed, leading to a marked increase in bone turnover, that can surpass pretreatment levels. This corresponds to significant loss of BMD and a substantial increase in the risk of fractures, particularly multiple vertebral fractures.[8,40]

At six months after the last denosumab injection, CTX rises rapidly, often exceeding baseline values.[10–12] BMD typically returns to pretreatment levels within one to two years after stopping denosumab, and in some cases, the BMD can even drop below baseline, especially at the hip.[12,40] Those who took denosumab for three or more years and then discontinued had a heightened rate of fractures. The incidence of multiple vertebral fractures was as high as 10% to 15% within the first year after stopping denosumab, even in patients who are subsequently treated with oral bisphosphonates.[40–43] Beyond duration of previous denosumab use, other risk factors for developing vertebral fractures after denosumab discontinuation include a history of prevalent vertebral fractures, a greater gain in BMD during denosumab therapy, and a greater loss of hip BMD after stopping the drug.[41,44] Patients with chronic kidney disease are also at higher risk.[41] The rebound may be caused by an exaggerated hyperactivation of a pool of dormant preosteoclasts and osteomorphs that accumulate during the treatment.[45–48] Additional mechanisms have been proposed to explain this phenomenon, including the depletion of osteoprotegerin-producing osteoblasts and osteocytes, which leaves RANKL activity unopposed on denosumab cessation, leading to excessive osteoclast activation. Furthermore, the mechanostatic reset hypothesis suggests that bone mass accumulated during denosumab treatment exceeds mechanical strain demands, triggering a compensatory loss of bone on discontinuation.[45] Regardless of the risk factors that contribute to the overshoot, a different potent antiresorptive, such as an intravenous bisphosphonate, is recommended after the discontinuation of denosumab.[41] Previous treatment with bisphosphonates also offers some protection against the rebound effect observed on discontinuation of denosumab.[49,50] As noted, bisphosphonates, which remain embedded into the bone matrix for years, continue to inhibit osteoclast activity and very likely dampen the excessive bone resorption typically seen after stopping denosumab.

The rapid and profound rebound in bone turnover could lead to such excessive and uncoordinated remodeling that it results in the perforation of trabeculae, in addition to just their thinning.[51] This mechanism could help explain the observation that multiple vertebral fractures can occur within just a few months of the last denosumab dose, even in patients who had previously achieved substantial gains in BMD. The hypothesis that fracture risk is driven more by the quality of bone microarchitecture, specifically, the preservation of trabecular connectivity, rather than by BMD alone, underscores the importance of stabilizing bone turnover after discontinuing potent antiresorptive therapies such as denosumab. Monitoring BTMs may be as or more important than monitoring BMD in predicting and preventing fractures. If the rebound in turnover could be controlled or mitigated, it might be possible to prevent the catastrophic structural failures that lead to fractures, particularly multiple vertebral fractures. Bisphosphonate treatment before or after denosumab does not always reduce

the BMD loss over the time,[52,53] but it strongly reduces the incidence of multiple vertebral fractures by attenuating the rebound in BTMs.[54–56] Moreover, the Denosumab Adherence Preference Satisfaction trial demonstrated that switching to alendronate after one year of denosumab discontinuation successfully maintained bone mass in 80% to 90% of patients.[57] Furthermore, administering zoledronic acid after two years of denosumab can be effective in mitigating bone loss and maintaining bone density.[58]

The European Calcified Tissue Society (ECTS) provided guidance on managing the discontinuation of denosumab to mitigate the rebound effect.[41] The ECTS strongly recommended initiating an alternative antiresorptive treatment at the time the patient is due for the next denosumab injection. Moreover, in patients who have been taking denosumab for only one year, switching to alendronate has been demonstrated to be effective in preventing rebound bone loss.[57] The most commonly recommended approach is to administer a potent bisphosphonate such as zoledronate six months after the final dose of denosumab. This timing is crucial because it coincides with the period when denosumab's effects start to wane and the risk of rebound increases. The exact timing of bisphosphonate administration following denosumab discontinuation is still an open question.[49] For example, if bisphosphonates are administered too late (ie, more than nine months after the last denosumab injection), the maximum rebound in bone turnover might have already occurred, reducing the efficacy of bisphosphonates in preventing BMD loss and fractures.[52,59] Administration of a pulsatile bisphosphonate too early also might not be maximally effective. Indeed, six months after the last dose of denosumab, many patients still have a closed remodeling phase with less exposed bone available for binding by a bisphosphonate. In patients with prolonged denosumab use, the rebound effect is more pronounced,[40] and a single dose of bisphosphonate might not be sufficient, potentially necessitating additional doses or alternative strategies.

If clinically available, monitoring of BTMs after denosumab discontinuation can help tailor subsequent therapy more effectively. For patients showing significant increases in these markers, rapid BMD loss or not responding to a single dose of zoledronic acid, additional doses may be required. If BTMs are not available, then redosing as soon as three months or as late as six months after the first zoledronic acid dose is prudent. Moreover, the ECTS guidance on denosumab discontinuation may present challenges for implementation in the United States and other health systems due to payment concerns. Specifically, the recommendation for BMD assessment at six months after discontinuation, followed by a zoledronic acid infusion at the same time, is often not covered or reimbursed by some health plans. As an alternative approach, if BTMs remain elevated at 6 months, clinicians could consider adding alendronate for 6 months before administering a second dose of zoledronic acid 12 months after denosumab discontinuation.

An alternative preliminarily tested approach to managing denosumab discontinuation involves gradual dose reduction.[60] Tapering the dose of denosumab (to 30 mg and then 15 mg) could prevent the significant bone loss observed after stopping the standard 60-mg treatment. A combined approach with reduced dose of denosumab paralleled by the administration of a potent antiresorptive such as zoledronic acid could eventually be proven to attenuate rebound.

Beyond ONJ and AFF, denosumab potential adverse events include an increased risk of infections, seen in some but not all denosumab studies and in one metanalysis showing more mostly minor respiratory tract infections.[61,62] Although some studies have suggested a potential increased risk of infections with denosumab, other evidence provides more reassurance. In one population-based cohort, denosumab was not associated with higher rates of hospitalized infections in patients with rheumatoid arthritis receiving a biologic compared to those treated with zoledronic acid.[63]

There is an argument for continuing denosumab in patients who are responding well to treatment, particularly in terms of maintaining or improving BMD and reducing fracture risk. In contrast to bisphosphonates, there is no compelling evidence that denosumab becomes less effective or more dangerous with extended use. Therefore, continuing treatment can be a reasonable and effective strategy for long-term management of osteoporosis. The decision to discontinue denosumab can be considered particularly when the patient's clinical status changes. For example, if a patient experiences a new fracture or if their BMD does not improve despite ongoing denosumab therapy, this could indicate that the treatment is no longer effective. For cases in which denosumab is no longer sufficient to prevent fractures, the best strategy might not be discontinuation or switching but rather the addition of another treatment, such as an osteoanabolic medication, on top of denosumab to increase bone strength and reduce fracture risk.[64–66]

Adding romosozumab to ongoing denosumab treatment in postmenopausal women with severe osteoporosis led to a significant increase in lumbar spine BMD and the bone formation marker procollagen type 1 N-terminal propeptide, compared to continuing denosumab alone.[66] This approach is particularly relevant for patients who had a fracture despite being on long-term denosumab. However, this additive approach to managing osteoporosis in high-risk patients may be constrained in some health care systems by financial barriers to the concomitant use of two expensive antiosteoporotic drugs. The concept of adding treatment rather than discontinuing is further supported by findings showing that combining teriparatide (a parathyroid hormone analog) with denosumab in treatment-naïve patients led to greater increases in BMD than either treatment alone.[67] To date, no study has explored the combination of parathyroid hormone (PTH) analog in patients with ongoing long-term denosumab. A small observational study investigated the addition of teriparatide to ongoing denosumab; however, in that study, teriparatide was

introduced just three months after the initiation of denosumab. This time frame may be insufficient to ensure complete closure of the remodeling surface.[68] Nonetheless, a combination therapy approach could be effective in patients already receiving denosumab, especially those not responding adequately.

In contrast to adding, switching from denosumab to a PTH analog is not recommended. The rebound effect could be amplified by the stimulation of bone remodeling induced by bone anabolic agents, with negative effects on BTMs and BMD.[64] Although switching from denosumab to romosozumab has been shown to partially attenuate the rebound, there have been reports of vertebral fractures after this sequential treatment.[69–73] However, when the treatment duration with denosumab is limited, switching to romosozumab can increase lumbar spine BMD to a greater extent than continuing denosumab alone and CTX rebound was evident as soon as three months after the transition.[74] Figure 2 proposes an algorithm for osteoporosis management in patients on longer-term denosumab, adapted from the ECTS guidance.

Discussion

As the data on bisphosphonate and denosumab efficacy, adverse effects, and the risks and benefits of stopping indicate, the clinical management of Ms DMS and Ms BPS presents a nuanced challenge. It underscores the importance of individualized osteoporosis therapy, especially concerning long-term antiresorptive treatments.

For Ms DMS, who has been on denosumab for more than eight years, the primary concern revolves around the potential rebound she will experience on discontinuation. A complete clinical evaluation should also assess for any signs of new fractures, height loss, or kyphosis, which may indicate undiagnosed vertebral fractures. Diagnostic testing should include a current BMD assessment via DXA, with comparisons to previous results to evaluate BMD trends. Additionally, measuring bone turnover makers can provide insights into her bone resorption status and treatment adherence. For many patients, particularly those at a higher risk of future fracture, denosumab discontinuation is not encouraged in patients with long-term treatment (>2 years) given the potential for bone loss and the risk of multiple vertebral fractures.

Given her history of vertebral and wrist fractures, and assuming her fracture risk remains high by DXA, the continuation of denosumab may be the most prudent course. If discontinuation is chosen, likely due to her strong preference, transitioning to a potent bisphosphonate such as zoledronic acid is recommended

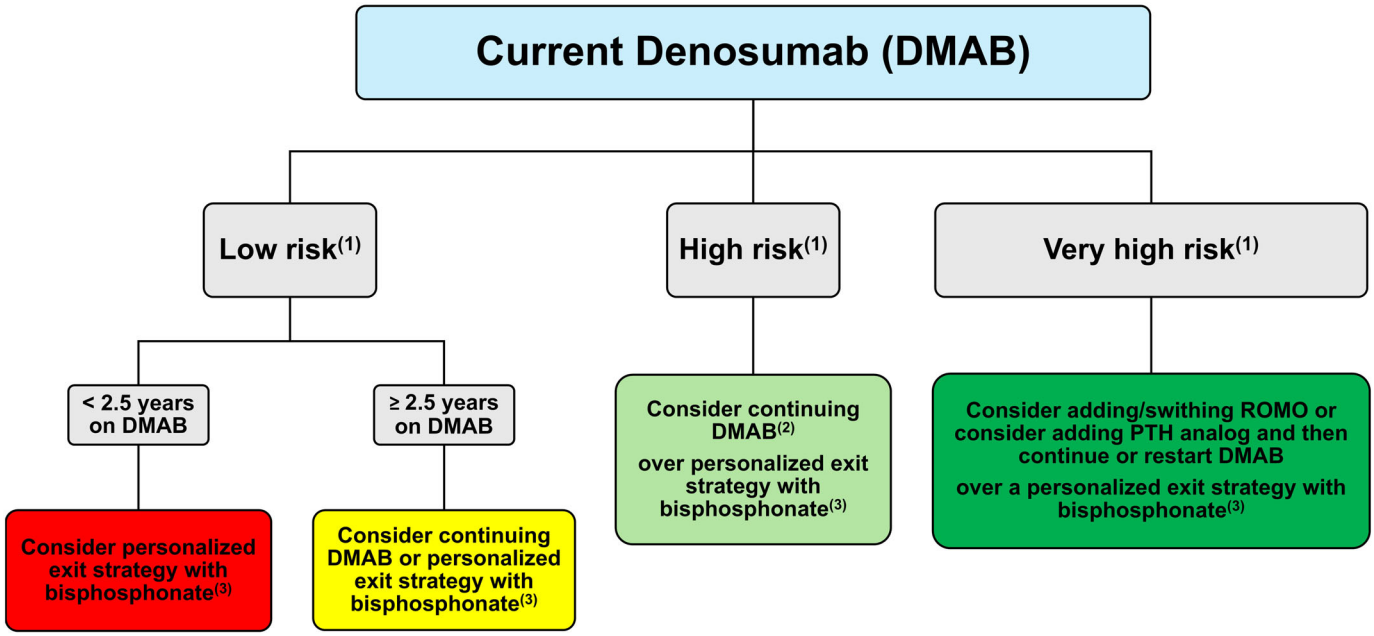

Figure 2. Approach to considering DMAB discontinuation (adapted from Tsourdi et al[41]). (1) Risk–benefit balance should account for the risk for rebound multiple vertebral fractures on DMAB discontinuation. High fracture risk: defined by older age (70–75 years), other strong risk factors for fracture, or validated fracture risk assessment tool fracture risk score that is above country specific thresholds. Very high or imminent fracture risk: defined by recent (within two years) fracture while taking DMAB. (2) DMAB can be used indefinitely but only has been studied for up to 10 years. (3) Exit strategy: usually a potent intravenous bisphosphonate (eg, zoledronic acid) administered when the next dose of DMAB would have been due. A pulsatile bisphosphonate can be repeated based on bone turnover markers or if there is a high risk of rebound associated vertebral fractures. Other exit strategies include oral bisphosphonates or DMAB dose reduction ± bisphosphonates. Combination could be considered based on the results of the Denosumab and Teriparatide Administration study and other observational studies.[64,66,68] DMAB, denosumab; PTH, parathyroid hormone; ROMO, romosozumab. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.43179/abstract.

to prevent postdenosumab rebound bone loss. Zoledronic acid should initially be administered at the time she is due for her next dose of denosumab. She should optimally have monitoring of BTMs three to six months after this first dose of zoledronic to guide the timing of the need for additional doses. If her BTMs remain elevated or if BTMs are not clinically available, it is reasonable to administer a second dose of zoledronic acid three to six months after her first dose. However, the effectiveness of even this potent bisphosphonate to fully prevent the rebound phenomenon is variable, and she should be counseled about these residual risks. Lastly, an alternative, but arguably minimally tested, approach might be to reduce the dosage of denosumab to 30 mg every 6 months and continue this dosage indefinitely of further reducing the dose to 15 mg and combining with zoledronic acid and then stopping the treatment within 18 months. However, little is known about potential adverse effects of reduced doses and their ability to control the rebound overshoot.

Ms BPS has been taking alendronate for 15 years, a duration of treatment that should be generally discouraged due to the cumulative efficacy of bisphosphonates and concern of rare adverse effects, albeit ones that are more strongly associated with very prolonged bisphosphonate use. A detailed history should explore any previous drug holidays or temporary discontinuation (prescribed or self-administered). This could help to tailor the length of a new, possible drug holiday. Clinical evaluation should include assessment for thigh or groin pain indicative of prodromal symptoms of AFF and oral examination for dental health status that might affect ONJ risk.

Diagnostic evaluation should include a current DXA scan to assess BMD changes over time. If her BMD has remained stable or improved, and her fracture risk is now moderate to low, initiating a drug holiday might be considered. In addition, DXA images sometimes (if the window of interest is slightly lowered) can be used to screen for AFF and may add value. During her drug holiday, she should be under regular monitoring of BMD and BTMs. A significant decline in BMD or a significant increase in BTMs toward baseline levels may indicate the need to resume therapy. The duration of her drug holiday might vary but is typically less than one year.

However, given her history of two vertebral fractures, Ms BPS would be considered by the ASBMR task force to be at higher risk for future fractures. Moreover, the ASBMR guidance suggests that all patients aged >70 to 75 years should be considered at high risk, independently from T score improvement. Thus, continuing bisphosphonate or switching to an alternate bone therapy could be justified despite her very prolonged duration of bisphosphonates. If she is agreeable to transitioning to a nonbisphosphonate therapy, options would include osteoanabolic agents such as teriparatide, abaloparatide, or romosozumab. Romosozumab, in particular, demonstrated significantly greater increases in bone mass and bone strength, as assessed by finite element analysis, compared to teriparatide.[75] We would not generally favor a selective estrogen receptor modulator in this circumstance after alendronate. If a PTH analog is chosen, she should know that there may be a period of slight and temporary bone loss at cortical sites such as the hip. Of note, an antiresorptive agent would again be recommended at the end of any anabolic treatment. It is important to note that osteoanabolic agents may be less effective after 15 years of bisphosphonate therapy compared to a treatment-naïve patient. Long-term bisphosphonate use significantly suppresses bone turnover and leads to reduced remodeling surfaces, which are necessary for an optimal anabolic response.

Both patients require comprehensive fracture risk assessments incorporating clinical factors, BMD results, and using validated fracture risk calculators or algorithms. This assessment should consider the limitations of these expert panel generated recommendations for drug holidays and should be heavily guided by shared decision-making. It is critical to discuss with these sisters the known benefits of fracture prevention against the risks of longer-term risks of therapy with alendronate and the rebound risk when discontinuing denosumab. The sisters' preferences are paramount, especially when concerns about adverse effects influence their willingness to continue treatment and when the evidence available is not of the highest level.

Conclusions

In conclusion, the management of Ms DMS and Ms BPS should be individualized. The treating clinician must consider their fracture histories, treatment responses, and individual concerns to devise a personalized treatment plan informed by the best available evidence and understanding of the biology of these two effective therapies that, like all drugs and biologics, are not without risk. Close monitoring through clinical evaluations, imaging, and laboratory tests are essential in optimizing osteoporosis care and minimizing the risks associated with osteoporosis therapy modifications.

AUTHOR CONTRIBUTIONS

. All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Saag confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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