PERSPECTIVE

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Postmenopausal Osteoporosis Treatment With Antiresorptives: Effects of Discontinuation or Long-Term Continuation on Bone Turnover and Fracture Risk—A Perspective

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ABSTRACT

Osteoporosis may be a lifelong condition. Robust data regarding the efficacy and safety of both long-term osteoporosis therapy and therapy discontinuation are therefore important. A paucity of clinical trial data regarding the long-term antifracture efficacy of osteoporosis therapies necessitates the use of surrogate endpoints in discussions surrounding long-term use and/or discontinuation. Long-term treatment (beyond 3–4 years) may produce further increases in bone mineral density (BMD) or BMD stability, depending on the specific treatment and the skeletal site. Bisphosphonates, when discontinued, are associated with a prolonged reduction in bone turnover markers (BTMs), with a very gradual increase to pretreatment levels within 3 to 60 months of treatment cessation, depending on the bisphosphonate used and the prior duration of therapy. In contrast, with nonbisphosphonate antiresorptive agents, such as estrogen and denosumab, BTMs rebound to above pretreatment values within months of discontinuation. The pattern of BTM change is generally mirrored by a more or less rapid decrease in BMD. Although the prolonged effect of some bisphosphonates on BTMs and BMD may contribute to residual benefit on bone strength, it may also raise safety concerns. Adequately powered postdiscontinuation fracture studies and conclusive evidence on maintenance or loss of fracture benefit is lacking for bisphosphonates. Similarly, the effects of rapid reversal of bone turnover upon discontinuation of denosumab on fracture risk remain unknown. Ideally, studies evaluating the effects of long-term treatment and treatment discontinuation should be designed to provide head-to-head "offset" data between bisphosphonates and nonbisphosphonate antiresorptive agents. In the absence of this, a clinical recommendation for physicians may be to periodically assess the benefits/risks of continuation versus discontinuation versus alternative management strategies. © 2012 American Society for Bone and Mineral Research.

KEY WORDS: OSTEOPOROSIS; LONG-TERM; DISCONTINUATION; FRACTURE; BONE MINERAL DENSITY; BONE TURNOVER MARKERS

Introduction

The efficacy of antiresorptive treatments in decreasing bone turnover, increasing bone mineral density (BMD), and reducing fracture risk in postmenopausal women with osteoporosis has been demonstrated in numerous clinical trials; however, these trials typically last only 3 years, a small proportion of the time for which most women need treatment. Thus, a number of important questions remain unanswered. Should lifelong treatment be provided for these women? If so, what are the implications for long-term safety? If not, what are the consequences of treatment discontinuation? And what is the target and optimal duration of treatment? This review summarizes the available data on these topics—with particular

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emphasis on bisphosphonates and denosumab—and suggests avenues for future research.

During antiresorptive therapy, the magnitude of bone turnover marker (BTM) suppression achieved differs depending on the marker being measured and the agent administered. BTM levels generally increase from their on-treatment level when treatment is discontinued, although the magnitude and speed of this offset differs among agents. The degree of offset that occurs following treatment discontinuation may fall into one of two categories: (1) BTM levels slowly increase toward pretreatment baseline levels but usually do not reach baseline levels at the end of follow-up (up to 5 years with bisphosphonates) or (2) BTM levels increase to above pretreatment baseline levels within 1 year after discontinuation. These scenarios also pertain to posttreatment changes in BMD. The magnitude and rate of BMD or BTM offset may be of clinical significance because, even in treated patients, bone density and bone remodeling may be determinants of bone strength and thus, fracture risk.[1]

Although fracture risk reduction remains the gold standard for the assessment of efficacy of pharmacological interventions, robust fracture data beyond 3 years of treatment are not available for most antiresorptives, and the few discontinuation studies have been underpowered to demonstrate the consequence of cessation of therapy on fracture risk. Thus, the effects of long-term continuation of treatment and its offset can generally only be assessed using BMD and BTM changes as surrogates for fracture risk. Although BMD is a strong predictor of fracture risk in the untreated state,[2] the relationship between pharmacologically-induced BMD increases and fracture reduction is unclear, and varies according to skeletal site and medication. The reduction in vertebral fracture incidence in women who lost BMD during alendronate treatment was similar to those who gained BMD,[3] with similar findings for nonvertebral fracture reduction in women taking risedronate.[4] In the Multiple Outcomes of Raloxifene Evaluation (MORE) study, only 4% of vertebral fracture reduction in raloxifene-treated women could be attributed to BMD changes.[5] However, some reports have demonstrated stronger correlations between BMD increases and fracture reduction; eg, vertebral fractures in women treated with alendronate or ibandronate,[6,7] and vertebral and nonvertebral fractures with denosumab.[8] Similarly for zoledronic acid, a large proportion of the antifracture effect is related to BMD accrual.[9]

Several factors contribute to the shortcomings of BMD as a surrogate for treatment-induced fracture reduction. First, changes in bone remodeling induced by therapy affect cortical and trabecular bone microarchitecture, the composition of bone matrix and mineral, and the extent and repair of microdamage, all of which may affect bone strength but are not captured by BMD measurements. Second, treatment effects in cortical and trabecular bone cannot be differentiated when dual-emission X-ray absorptiometry is used to assess BMD. These considerations are also relevant to BMD changes when treatment is stopped.

Elevated levels of biochemical BTMs in untreated patients have been reported to predict fracture[1,10–13] independent of BMD,[12,14–16] in part because they reflect stress risers in cancellous bone. A significant association between treatment-induced changes in BTMs at 3 to 6 months and subsequent fracture risk reduction has also been demonstrated,[17] suggesting that changes in bone turnover per se affect bone strength and fracture risk. This hypothesis is biologically plausible, because inhibition of new remodeling sites by antiresorptive drugs, in combination with ongoing bone formation in previously formed resorption cavities, reduces the number of stress risers in trabecular bone. It also reduces the risk of trabecular perforation and decreases cortical porosity.[18–20] These changes occur relatively early in the treatment course and may improve bone strength before BMD changes are detected. Furthermore, changes in matrix and mineral composition, as well as microdamage, are likely directly related to alterations in bone remodeling. However, associations between changes in BTMs and fracture risk reduction beyond 3 years of treatment have not been well studied, and the effect on fracture risk of the maintenance or the rapid increase in BTMs after cessation of some antiresorptive drugs is unknown. It should be noted that the rapidity and the magnitude of BTM change are dependent on the marker being measured (with C-telopeptide of type I collagen being the most dynamic and reliable marker among other commonly used BTMs).[21] However, with modern automated analytical techniques, the intra- and interassay variability of the various BTMs are small compared with the variability between patients.[22]

Effects of Long-Term Use and Discontinuation of Antiresorptive Agents on BMD, Remodeling, and Fracture Risk

Hormone therapy

Hormone therapy (HT) produces significant increases in BMD (Table 1),[23,24] and reductions in BTMs.[25,26] In the Women's Health Initiative (WHI) study of 16,608 women, at 5.2 years combination HT reduced hip and clinical vertebral fractures by 34% and all fractures by 24%.[27] Estrogen-only HT produced a similar reduction in fracture risk.[28] With discontinuation of HT, efficacy against hip fracture is lost after 3 to 5 years (compared with on-treatment values).[29–31] This loss of fracture protection is paralleled by a decrease in BMD and an increase in BTM levels that temporarily exceed baseline (Table 2; Fig. 1*A*).[26,32–34]

Safety of hormone therapy

Following the release of results from WHI studies[27] the benefit–risk of HT has been scrutinized. Long-term HT use was found to be associated with increased risk of stroke and venous thromboembolic disease. The overall risk of coronary heart disease was significantly increased in women taking combined HT, but in a secondary analysis of women taking combined or estrogen-only HT, those who started within 10 years of menopause showed a trend toward reduced risk.[35] Estrogen plus progestin HT was also associated with an increase in breast cancer diagnoses.[27] Consequently, the use of HT in management of osteoporosis was restricted to second-line by health authorities worldwide.

Table 1. Effect of Long-Term Antiresorptive Treatment on BMD in Postmenopausal Women

Reference (publication year)	Mean age at baseline (*n*)	Drug	Duration of treatment	Site	BMD % change from pretreatment baseline (*p* value)
Tremollieres et al.[23] (2001)	54 years ($n = 50$)	Estrogen-based HT	5 years (mean)	Lumbar spine	6.02% ($p < 0.05$)
Cauley et al.[24] (2003)	NR ($n = 194$)	Estrogen-based HT	6 years	Lumbar spine	7.5% (NR)
Siris et al.[38] (2005)	67 years ($n = 259$)	Raloxifene	7 years	Lumbar spine	4.3% (NR)
				Femoral neck	1.9% (NR)
Black et al.[52] (2006)	NR ($n = 643$)	Alendronate	10 years	Lumbar spine	14.80% (NR)
				Femoral neck	4.75% (NR)
				Trochanter	5.95% (NR)
				Total hip	2.41% (NR)
				Total body	3.6% (NR)
Sorenson et al.[55] (2003)	72 years ($n = 135$)	Risedronate	5 years	Lumbar spine	9.3% ($p < 0.05$)
				Femoral neck	2.2% ($p < 0.05$)
				Trochanter	5.7% (NR)
Black et al.[57] (2012)	76 years ($n = 616$)	Zoledronic acid	6 years	Lumbar spine	12.1% (NR)
				Femoral neck	4.5% (NR)
				Total hip	4.3% (NR)

BMD = bone mineral density; HT = hormone therapy; NR = pretreatment baseline comparison data was not reported. Value for *n* is the number of individuals.

Selective estrogen receptor modulators

Like estrogen, selective estrogen receptor modulators (SERMs; also known as estrogen agonist/antagonists) such as raloxifene, bazedoxifene, and lasofoxifene act through the estrogen receptor and have an agonistic effect in some tissues (eg, bone) and an antagonistic effect in others (eg, breast).[36] SERMs may thus exert the beneficial effects of estrogen on bone, while limiting the risk of adverse events (AEs), and even reducing the risk of breast cancer.[36] Only raloxifene and bazedoxifene have long-term data, and treatment discontinuation has only been studied in raloxifene.[37–39] The magnitude of the effect of raloxifene on BMD and BTMs is generally lower than that of standard-dose HT,[40] and fracture protection appears confined to the spine.[41]

The Continuing Outcomes Relevant to Evista (CORE) study indicated that 7 years of raloxifene therapy maintained the initial increments seen in spine and hip BMD over 3 years, but showed no further gains (Table 1).[38] Long-term BTM data ($\geq$5 years) were not available. No effect on nonvertebral fracture incidence was seen in the MORE,[42] CORE,[38] or the Raloxifene Use for the Heart (RUTH) trial of over 10,000 women with documented or at high risk for coronary heart disease.[43]

Cessation of raloxifene results in a rapid decline of BMD values 1 year after treatment discontinuation (Table 2).[39] There are, however, no BTM data available following discontinuation of raloxifene treatment.

Safety of raloxifene

Raloxifene administration reduces the risk of estrogen receptor-positive breast cancer by 50% to 70%,[44,45] but increases the risk of venous thromboembolism by approximately twofold to threefold.[44,45] An increase in fatal stroke events with raloxifene treatment was reported in the RUTH trial.[46]

Bisphosphonates

Bisphosphonates bind to bone mineral and are deposited on the bone surfaces throughout the skeleton.[47] It has been hypothesized that during bone resorption, some of the bisphosphonate may be released and recirculated to bind again to nearby hydroxyapatite surfaces.[48,49] These phenomena, together with the long residence time of bisphosphonates on bone surfaces,[50] may explain why discontinuation of bisphosphonate administration generally results in a gradual reversion of BMD and BTM values toward pretreatment levels. This reversion is believed to be inversely proportional to the affinity of the bisphosphonate to the mineral content in bones.[51–53]

In the Fracture Intervention Trial (FIT) Long-Term Extension (FLEX), 1099 postmenopausal women who had received alendronate for 5 years in the FIT were rerandomized to continue therapy or receive placebo.[52] After over 10 years of alendronate treatment, BMD at the spine increased gradually but plateaued at other sites after approximately 3 years (Table 1). Serum BTM levels decreased substantially in the first 3 years, and were then sustained throughout the 10 years of active treatment.[52] Five years after treatment discontinuation, the spine BMD increase resulting from initial treatment was maintained, but BMD gradually declined at other sites, with levels remaining above the pretreatment baseline at most sites (Table 2). Discontinuation of alendronate was associated with gradual increases of BTMs, although at the end of 5 years, levels remained lower than prior to treatment.[52] When comparing patients who continued treatment with those who stopped, no

Table 2. Effect of Antiresorptive Treatment Discontinuation on BMD in Postmenopausal Women

Reference (publication year)	Mean age at baseline (*n*)	Drug	Duration of treatment	Duration of follow-up after discontinuation	Site	BMD change from pretreatment baseline (*p* value)[a]	
						End of treatment period	End of discontinuation period
Gallagher et al.[26] (2002)	72 years ($n = 121$)	Estrogen/HT	3 years	2 years	Lumbar spine	5.51% ($p < 0.0001$)	1.59% ($p = 0.091$)
					Femoral neck	3.72% ($p < 0.0001$)	0.99% ($p = 0.28$)
					Trochanter	3.43% ($p < 0.0001$)	−0.82% ($p = 0.66$)
					Total hip	3.64% ($p < 0.0001$)	−0.34% ($p = 0.94$)
					Total body	2.07% ($p < 0.0001$)	0.11% ($p = 0.86$)
Christiansen et al.[33] (1981)	50 years ($n = 19$)	Estrogen-based HT	2 years	1 year	Distal forearm		2.7%[b] (NR)
Greenspan et al.[34] (2002)	62 years ($n = 81$)	Estrogen	2 years	1 year	Lumbar spine		1.9% (NR)
					Total hip		2.6% (NR)
Neele et al.[39] (2002)	54 years ($n = 10$)	Raloxifene[c]	5 years	1 year	Lumbar spine	3.6% ($p = 0.045$)	−2.4% (NR)
					Femoral neck	0.2% ($p > 0.05$)	−3.0% (NR)
Black et al.[52] (2006)	NR ($n = 428$)	Alendronate	5 years	5 years	Lumbar spine		10.99% (NR)
					Femoral neck		2.50% (NR)
					Trochanter		2.62% (NR)
					Total hip		−0.16% (NR)
					Total body		2.48% (NR)
Black et al.[57] (2012)	76 years ($n = 617$)	Zoledronic acid	3 years	3 years	Lumbar spine		10.1% (NR)
					Femoral neck		3.1% (NR)
					Total hip		2.8% (NR)

BMD = bone mineral density; HT = hormone therapy; NR = pretreatment baseline comparison data was not reported. Value of *n* is the number of individuals.
[a]Values of *p* represent change from baseline.
[b]Endpoint: bone mineral content.
[c]Raloxifene 60 mg/d.

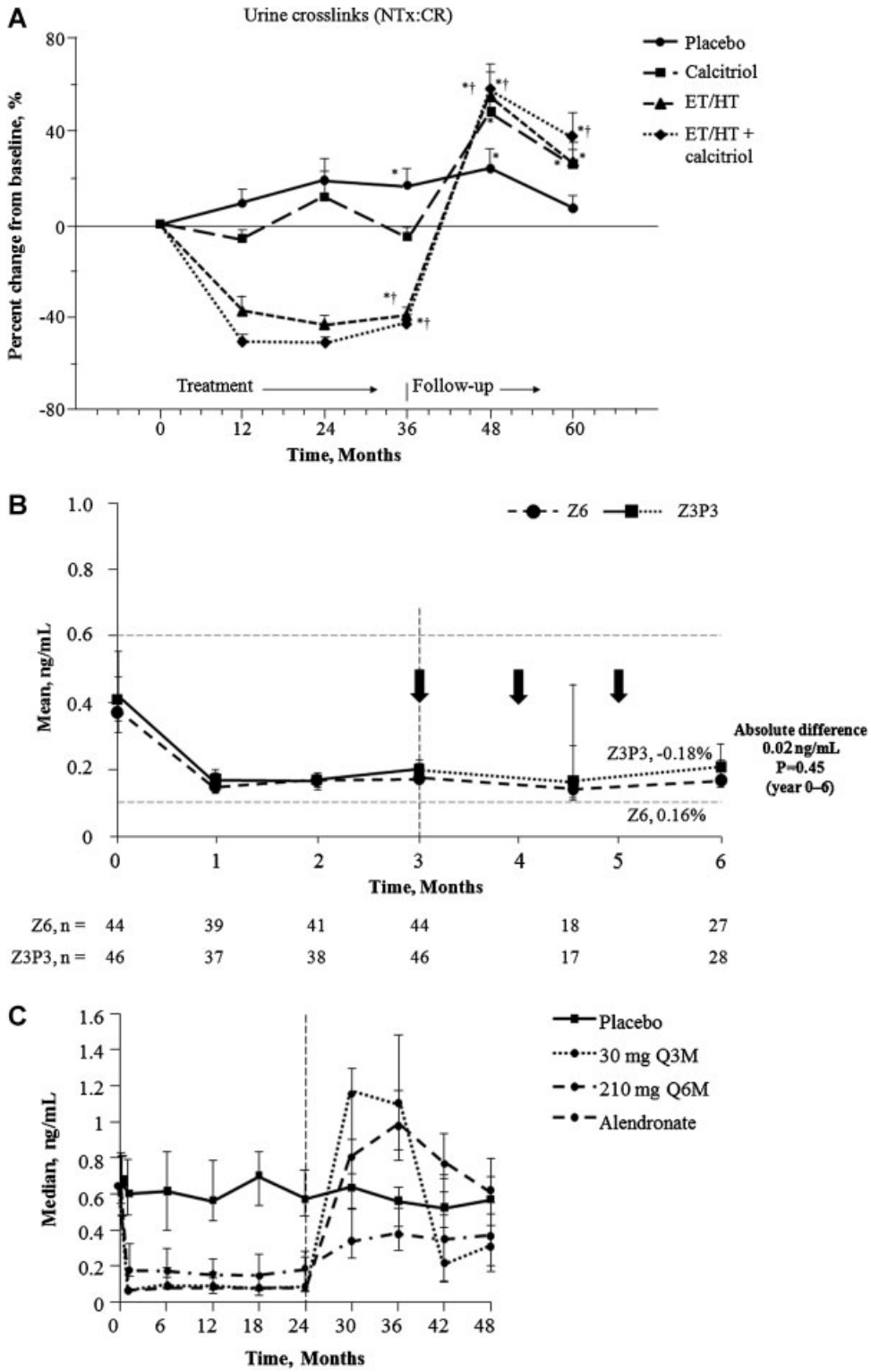

Fig. 1. Changes in bone turnover marker levels following discontinuation of (*A*) ET (urinary NTx [mean ± standard error change from baseline in NTx:creatinine ratio; %]),[26] (*B*) zoledronic acid treatment (serum CTx-I [geometric mean, ng/mL]),[57] and (*C*) denosumab treatment (serum CTx-1 [median ± interquartile range; ng/mL]).[70] In *A*, ET/HT treatment was discontinued at month 36. $^{*}p < 0.05$, compared with baseline measure; †$p < 0.05$, compared with placebo group. Figure adapted from Gallagher and colleagues.[26] In *B*, the gray, horizontal, long dashed lines indicate premenopausal reference ranges, the arrows indicate timing of infusions, and the vertical dash line indicates the end of HORIZON-PFT and the start of the extension study; the year 4.5 measurement was made 6 months after the most recent infusion whereas the year 6 measurement was 12 months after the most recent infusion. Z3P3 refers to the group of patients who received zoledronic acid in the HORIZON-PFT but placebo in the extension study; Z6 refers to the group of patients receiving zoledronic acid in both the HORIZON-PFT and the extension study. In *C*, the group receiving 30 mg denosumab every 3 months (30 mg Q3M) discontinued denosumab treatment at month 24 and then recommenced treatment at month 36 at a dose rate of 60 mg denosumab every 6 months; the groups receiving 210 mg denosumab every 6 months (210 mg Q6M) or alendronate discontinued treatment at month 24; the dashed line at month 24 indicates the time at which dosing was reallocated. CTx-I = C-telopeptide of type I collagen; ET = estrogen therapy; HT = hormone therapy; NTx = N-telopeptide of type I collagen; NTx:CR = NTx:creatinine ratio.

significant differences in morphometric vertebral, nonvertebral, or all clinical fractures were seen, although the study was underpowered for these endpoints.[52] The risk of clinical vertebral fracture was significantly reduced in those who received active treatment for 10 years. A post hoc analysis of the FLEX data indicated that among patients with no prevalent vertebral fracture, continued alendronate therapy provided protection from nonvertebral fractures in women with a femoral neck *T*-score of ≤ -2.5 but not those with a *T*-score > -2,[54] suggesting that BMD measurements after 5 years of therapy might therefore be useful in identifying those most likely to benefit from continued bisphosphonate therapy.

In the Vertebral Efficacy with Risedronate Therapy–North America (VERT-NA) study, BMD at the spine, femoral neck, and trochanter decreased 1 year after discontinuation of a 3-year course of risedronate, although BMD levels at the spine and trochanter were still above pretreatment baseline. Levels of urinary *N*-telopeptide of type I collagen (NTx) rose after discontinuation but remained significantly below the pretreatment baseline value at the end of the follow-up year.[53] In a 2-year extension of a 3-year randomized, controlled trial (RCT) in which participants continued receiving placebo or risedronate according to their original randomization,[55] spine BMD of patients receiving risedronate increased gradually throughout the 5 years, while BMD at the hip (femoral neck and trochanter) increased during the first 3 years[56] and then plateaued (Table 1).[55] Urinary NTx levels decreased by 50% during the first 3 months of treatment and remained at this level for the 5 years of treatment (Fig. 1*A*). Levels of bone-specific alkaline phosphatase (BSAP) were also reduced within the first 6 months and increased slightly by the end of the extension trial.[55]

In an extension of the HORIZON–Pivotal Fracture Trial (PFT), in which women who had received 3 years of zoledronic acid treatment were randomized to receive zoledronic acid or placebo for a further 3 years, BMD (Table 1) and BTM levels remained constant in the group randomized to continue zoledronic acid.[57] In the discontinuation group, a small hip BMD decline (Table 2) and minimal BTM (Fig. 1*B*) increases were seen, though for both BMD and BTM, levels remained substantially above and below pretreatment baseline, respectively.[57] There were no differences in clinical vertebral or nonvertebral fracture rates between the continuation and discontinuation groups, and they remained well below placebo rates seen in the initial 3-year trial. New morphometric vertebral fractures were significantly less frequent in the continuation group, but the incidence in the discontinuation group was still below that seen in the placebo group in the initial trial.[57] These findings suggest that 3 years of annual treatment confers residual skeletal benefits for an additional 3 years. A post hoc analysis showed that predictors of fracture in the discontinuation group in years 3 to 6 were a hip BMD in the osteoporosis range at year 3, and the presence of incident morphometric vertebral fracture during the initial treatment period.[58] It is unknown how long BTMs remain reduced after zoledronic acid treatment and whether duration of offset is proportional to dose administered. However, in postmenopausal women with osteopenia administered a single 5-mg dose of zoledronic acid, antiresorptive effects are sustained for 2 to 3 years.[59–61]

It should be noted that the turnover estimates after bisphosphonate treatment based on histomorphometry are generally lower than those based on assessment of BTMs. The difference is probably related in part to the fact that histomorphometry studies are performed on iliac crest tissue, and the relationships between biochemical markers of bone formation and bone formation rate in the iliac crest by histomorphometry are weak.[62] Nevertheless, bone turnover estimates measured by histomorphometry and assessing BTMs are important to help understand the physiologic and pathologic skeletal processes and mechanisms of action of treatment.

Safety of bisphosphonates

A recent review of AEs in bisphosphonate-treated patients showed that for the vast majority of patients, bisphosphonates are well tolerated. The most common AEs are gastrointestinal side effects (oral administration) and acute influenza-like symptoms (intravenous administration).[63]

Because of potential nephrotoxicity, the use of bisphosphonates in patients with estimated glomerular filtration rate below 35 mL/min is not recommended or contraindicated (for zoledronic acid). Intravenous administration of bisphosphonates has been implicated in a number of cases with renal toxicity,[64] possibly related to rapid infusion rates of high doses of bisphosphonates.[65] Adequate hydration prior to treatment and careful control of infusion rates are advocated, and under these circumstances renal toxicity is rare in patients with adequate renal function.[63]

Causality between bisphosphonate administration and atypical femur fractures, osteonecrosis of the jaw (ONJ), esophageal cancer, and atrial fibrillation have not been proven.[63] Although bisphosphonates in cumulative high doses for oncologic indications have clearly been associated with ONJ, the incidence of ONJ in patients with osteoporosis is much lower and may be similar to that seen in those with no prior bisphosphonate exposure.[63] Some studies suggest that the risk might increase with duration of bisphosphonate exposure.[66]

A potential association between prolonged bisphosphonate use and increased risk of atypical (subtrochanteric and femoral shaft) femur fractures has recently been identified and discussed by professional organizations and by health authorities.[64] A recent report by the European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation Working Group states that while long-term exposure to bisphosphonates (more than 5 years) may increase the risk of subtrochanteric femur fractures (typical and atypical) twofold, the number of atypical subtrochanteric fractures in association with bisphosphonates is small (an estimated 1 per 1000 per year).[67] Owing to the well-documented reduction of osteoporotic hip fractures in patients receiving treatment, the risk to benefit ratio remains favorable for use of bisphosphonates to prevent fractures.[67] Hence, the available evidence indicates that the benefit of preventing osteoporotic fractures in patients with osteoporosis over 3 to 5 years considerably outweighs the potential risk of atypical fractures.[67] However, there is insufficient information to fully evaluate the risks and benefits for longer-term therapy. It should

also be noted that the mortality rate has been found to be lower among bisphosphonate-treated osteoporotic women (and possibly men) compared with untreated patients.[68] Furthermore, a recent epidemiological study indicates that alendronate users have a lower risk of incident gastric cancer and no increased risk of esophageal cancer.[69]

Denosumab

Denosumab is a fully human monoclonal antibody that inhibits receptor activator of nuclear factor κB ligand (RANKL), a ligand required for osteoclast formation, function, and survival.[70] The 3-year Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 months (FREEDOM) RCT demonstrated that denosumab significantly reduced the risk of new radiographic vertebral fractures, hip fractures, and nonvertebral fractures in postmenopausal women with osteoporosis.[71] The FREEDOM trial is being extended for an additional 7 years[72] as an observational extension. Fracture rates (vertebral and nonvertebral) in the patients who received denosumab for up to 2 years in the extension study were low, and below that observed in the FREEDOM placebo group.[73]

Denosumab therapy is associated with BMD increases and BTM decreases, both of which continue with treatment beyond 3 years for up to 6 years (Phase II study).[72–74] Hip and spine BMD continue to increase throughout the initial 3 years and during the extension follow-up, in contrast to the plateau in BMD usually observed with bisphosphonates after 2 to 3 years. Also distinct from bisphosphonates is the decline in BMD and the rise in BTMs following discontinuation of denosumab that has been observed in both a Phase II multidose trial[74] and a Phase III osteoporosis prevention study.[75] In the Phase II trial, BMD gains were lost within 12 months of treatment discontinuation, and mean BMD at the total hip decreased to below the pretreatment baseline. In those who remained off treatment, BMD remained below baseline for a further 12 months, and then returned to baseline levels from month 36 to 48 without additional medication. In contrast, with 1 year of retreatment with denosumab (after 12 months of discontinuation), BMD increased again (more rapidly than the initial BMD effect) at both spine and hip to levels comparable with those achieved after the first 24 months of treatment.[70] A similar pattern of BMD change was documented in a 2-year follow-up to a Phase III prevention trial in which discontinuation of denosumab after 24 months of treatment was associated with a rapid decrease in spine and total hip BMD, both of which returned to the pretreatment baseline level within 12 months of discontinuation.[75]

The BMD decline that occurs after denosumab discontinuation is mirrored by an increase of BTM levels to above pretreatment baseline levels. In the Phase II multidose trial, discontinuation of denosumab 210 mg every 6 months after 24 months led to increases in serum C-telopeptide of type I collagen and BSAP levels to values substantially above the pretreatment baseline within 12 months of treatment cessation. Levels of both markers returned toward baseline in the second year of discontinuation even with no further therapy. In patients who were retreated after discontinuation, the BTMs returned close to baseline within 6 months of retreatment (Fig. 1*C*).[70] The rebound rise of BTMs above baseline after denosumab discontinuation is similar to the pattern seen after discontinuation of estrogen therapy (ET), although with denosumab, rebound occurs earlier. A similar pattern was also observed with odanacatib, a selective cathepsin K inhibitor, in a 2-year study in which a transient rise in BTMs above baseline after treatment discontinuation was seen.[76] The implication of this rebound effect on the clinical outcomes is not clear.

Safety of denosumab

Because denosumab has only been available to physicians since 2010, the overall safety experience is still relatively limited. In the FREEDOM trial, there were no significant differences between subjects who received denosumab and those who received placebo in the total incidence of AEs, serious AEs, or discontinuation of study treatment because of AEs. Similarly, there were no significant differences in the overall incidence of cancer or infections. A significantly higher incidence of serious AEs of cellulitis was observed in denosumab-treated patients,[71] but the incidence declined to placebo group levels during the first 2 years of the extension study.[73] Longer follow-up is currently underway,[72] but data from a 4-year extension of a 4-year phase II study found the long-term safety profile of denosumab was generally similar to that reported previously.[77] No neutralizing antibodies to denosumab have been reported. ONJ has been reported in patients in the extension study of FREEDOM. As with zoledronic acid, high-dose denosumab treatment for cancer was associated with higher rates of ONJ than that with osteoporosis doses.[78,79] No cases of atypical femur fractures have been reported, but data are limited to 5 years in the FREEDOM extension and are only a short time postmarketing.

Discussion

It is evident that there are differences among and within agent classes in the pharmacodynamic response to discontinuation of treatment for osteoporosis. These responses may have important clinical implications. Although the rapid reversibility of nonbisphosphonate agents could theoretically be beneficial in some clinical situations, the increase in bone remodeling and rapid decline in BMD may be detrimental to bone strength upon discontinuation. Conversely, for bisphosphonates, the delayed reversion of bone remodeling and slow decline in BMD may allow residual antifracture benefit upon discontinuation. It is unknown, however, whether the prolonged skeletal retention of bisphosphonates predisposes to adverse consequences.

It is important to note that neither the FLEX nor the HORIZON-PFT extension studies provide definitive information on fracture risk in patients who continue or discontinue treatment. In both studies the effect of continued treatment on fracture risk was an exploratory aim, and both trials had limited power to detect modest differences in fracture rates, reflected in wide confidence intervals for fracture outcomes. Both extension studies showed a reduction in vertebral fractures, but only for clinically-defined fractures in FLEX[52] and morphometric vertebral fractures in the HORIZON-PFT.[57] In both studies, if BMD remained in the

osteoporosis range after the initial 3- to 5-year treatment period, fracture risk in the subsequent years among those who discontinued therapy appear to be higher than those who continued treatment.[54,58] In such patients, some evidence of treatment efficacy was apparent for nonvertebral fractures in FLEX and vertebral fractures in both trials. The persistently low nonvertebral and clinical vertebral fracture rates in the discontinuation groups (similar to rates during treatment in the definitive trials), and the largely persistent effect on BMD and BTM after discontinuation, suggests for alendronate and zoledronic acid that most of the effect is retained for 3 to 5 years after discontinuation. At this time, there is little evidence to support the continued use of bisphosphonates beyond 5 years in patients without prior fragility fractures or persistent osteoporosis,[54] particularly at the hip.[58] In the absence of definitive benefit and possible adverse consequences related to prolonged use of bisphosphonate therapy (ONJ, atypical femur fractures) after 3 to 5 years of treatment, patients at high risk of fracture should be considered for continued therapy while others might discontinue for a number of years. In this context, a "proof-of-concept" study would be a fracture endpoint–powered discontinuation trial. More practical would be to establish a surrogate well-established strength endpoint for this type of trial, such as finite-element analysis of hip quantitative computed tomography.[80]

Regarding the potential mechanisms that operate following treatment with different classes of antiresorptives, clinical observations suggest two main differences between denosumab and bisphosphonate treatment.[81] With denosumab, there is both a continuous BMD gain for 3 to 6 years, which is observed both at the spine and hip, and a rebound of BTMs above baseline accompanied by a prominent BMD loss upon discontinuation. As the antibody is cleared, basic multicellular units (BMUs) are reactivated and bone remodeling recurs, a process that can only be stopped by re dosing. In contrast, the bone remodeling reduction with bisphosphonates is dictated by their adsorption, desorption, and re-adsorption to the bone surface (which varies according to the affinity of the individual bisphosphonate to the mineralized bone matrix), and eventually on their uptake into the mineralized bone matrix.[82] Hence, activation of new foci of bone remodeling may occur toward the end of the dosing period with denosumab, as suggested by the slight increase in BTMs (from their nadir). Upon new drug administration, that nascent remodeling space will again be refilled, and renewed inhibition of the osteoclasts will prevent more cavities from opening until the end of this next dose interval. It has been suggested that a positive imbalance might occur as a result of increases in endogenous parathyroid hormone (PTH) secretion with each dose of denosumab,[83,84] although this has not been proven by a detectable increase of bone forming indices at tissue level so far. If the cycle of reopening–refilling of the remodeling space is repeated with each new dose of denosumab, particularly if formation exceeds resorption within each remodeling unit, BMD could increase continuously. In contrast, frequent (weekly/monthly) administration of oral bisphosphonates and long-lasting inhibition of bone remodeling with intravenous bisphosphonates will not be accompanied by such a release of bone resorbing activity. Hence, reopening and refilling of the remodeling space is prevented, thereby limiting long-term BMD changes to the effects of secondary mineralization. Furthermore, endogenous PTH increments with bisphosphonate administration are limited to the first months of administration without suggestion of changes in the balance between formation and resorption within remodeling units. Alternatively, the difference between denosumab and bisphosphonates could be the result of the greater antiresorptive potency of denosumab, resulting in progressive increases in bone mineralization.

Differences in the pharmacokinetics/pharmacodynamics of denosumab and bisphosphonates could explain the differing profiles of BTMs and BMD after drug withdrawal. The rebound post-denosumab does not necessarily mean that bone resorption at any single site is more intense than at baseline; ie, that stress risers and trabecular perforations would be more pronounced than in the untreated subject. Indeed, a large increase in BTMs is expected to occur when bone turnover is turned back on synchronously; ie, when a large number of BMUs are activated at the same time, with discontinuation of denosumab or HT. This is distinct from the untreated situation when bone remodeling occurs asynchronously throughout the skeleton. Therefore, the area under the curve of BTMs post-denosumab (and HT) may reflect the overall amount of bone turnover that would normally occur over a longer period of time. Alternatively, the sharp increase in bone turnover post-denosumab could reflect targeted repair of microdamage, though this possibility is purely theoretical at this time. It would be of interest to analyze bone biopsies from an early time point post-withdrawal, in order to evaluate the rate and location of remodeling and effects on bone microstructure.

In most patients, treatment of osteoporosis is a long-term challenge. Currently, there are few data on the safety and efficacy of long-term treatment, to what extent intermittent therapy might provide continued fracture protection, and how different classes of agents can and should be integrated into the long-term management of individuals. These important clinical questions, which could take years to answer, should be addressed with some urgency by the research community. For example, the relationships among bone remodeling and fracture risk require better understanding. Is the higher fracture risk seen in treatment-naïve patients with higher bone turnover also seen in patients with increased bone turnover after pharmacological intervention? Conversely, is continued suppression of bone remodeling after discontinuation of treatment clinically relevant in terms of fracture protection? Moreover, despite the importance of bone remodeling as a determinant of bone strength and fracture risk, the clinical relevance of rates of change in bone turnover is currently unknown. The effects of rapid resolution of effect on BMD and BTM on fracture risk should be examined.

Other related topics that merit investigation include potential differences between treatment-naïve and previously treated patients and, within cohorts of treated patients, the use of BMD and fracture data to determine the advisability of continued treatment. An individual approach to treatment continuation is advised and will depend on the treatment and changes in BMD and BTMs (which may be difficult in individual patients) in

response to treatment. Overall, based on the long-term efficacy and safety data available, a hypothetical long-term treatment paradigm for the management of osteoporosis would be one that included changing osteoporosis treatments over time. However, the extent to which baseline and changes in BMD, BTM, and clinical determinants of fracture risk can be taken into account and guide long-term treatment, including potential "drug holidays," remains to be clarified. Furthermore, the approach to the patient who is stopping an agent (HT/ET and denosumab) with rapid resolution of BTM and BMD effects needs to be established. Additionally, it would be useful to have common terminology to define changes in BTMs or BMD following treatment discontinuation so as to set standards for future studies. Further characterization of antiresorptives should also include the assessment of the time to resolution of effect on BTMs and the time for BMD to return baseline. For medications in which BTM levels exceed baseline after drug discontinuation, assessment of the time to maximum increase, the magnitude of BTM change above baseline, and the reciprocal effects on BMD should be performed.

Conclusions

This review of clinical trial data has highlighted two major gaps in our knowledge regarding the use of osteoporosis therapies. First, conclusive efficacy and safety data describing the long-term use of these agents are lacking, and second, we do not know the clinical implications of differences among antiresorptive agents in the skeleton's response to drug discontinuation. There is, therefore, a clear need for studies of osteoporosis treatments that are designed to examine the effects of discontinuation on bone remodeling, microstructure, and fracture risk. Despite these uncertainties, some clinical recommendations can be made. First, there is extensive evidence from clinical trials that antiresorptive agents are effective in reducing fracture risk and are generally well tolerated in postmenopausal women with osteoporosis for over 3 to 5 years. Second, all therapies should be assessed periodically to determine the benefits/risks of continuation versus discontinuation versus alternative management strategies. With both alendronate and zoledronic acid, data indicate that a treatment holiday at about 5 years in those who are no longer osteoporotic does not increase fracture risk.[85] Usually, turnover markers are monitored during such a holiday and treatment is restarted when markers exceed the mid-point of the premenopausal normal range. Such holidays are unlikely to be appropriate with non-bisphosphonates, such as denosumab. Whereas current evidence suggests that the short- to medium-term benefits of osteoporosis treatments clearly outweigh the risks, we still have much to learn about the consequences of discontinuation and long-term continuation of osteoporosis treatments.

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