A Model of BMD Changes After Alendronate Discontinuation to Guide Postalendronate BMD Monitoring

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Context: Women stopping alendronate are commonly monitored with serial bone mineral density (BMD) measurements, yet no information exists on how frequently or for whom these measurements should be performed.

Objective: The objective of the study was to develop a tool to guide post-alendronate BMD monitoring.

Design: A predictive model was constructed to estimate the time until a given percentage of women's BMD T-scores drop below a given threshold that indicates a management change (such as retreatment) would be considered. This model was then used to estimate the time it would take for groups of women defined by their baseline BMDs to drop below the given threshold.

Setting: Data were derived from the Fracture Intervention Trial Long Term Extension (FLEX), the largest multicenter clinical trial of its type to date.

Participants: Four hundred four women who had received an average of 5.1 years of alendronate during the Fracture Intervention Trial and were subsequently observed for 5 treatment-free years (on placebo) during the FLEX trial were used to estimate the change in BMD over time.

Results: If a management change such as alendronate reinitiation would be considered when BMD T-score drops below −2.5, the model shows that women with total hip BMD greater than −1.9 T-scores at the time of alendronate discontinuation have less than a 20% probability that at follow-up, monitoring BMD will be below the threshold within 5 years. The model performed similarly, and results are provided over a range of management change thresholds from −1.75 to −3 T-scores.

Conclusions: Using the tool developed in this analysis, it is possible to estimate when BMD repeat measurement after alendronate discontinuation could potentially be useful. Measuring BMD within 5 years after alendronate discontinuation is unlikely to change management for women with total hip BMD 0.6 T-scores above a prespecified retreatment threshold within the range of −1.75 to −3 T-scores. **(*J Clin Endocrinol Metab* 99: 4094–4100, 2014)**

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Abbreviations: ALN, alendronate; BMD, bone mineral density; BTM, bone turnover marker; DXA, dual-energy X-ray absorptiometry; FIT, Fracture Intervention Trial; FLEX, FIT Long Term Extension; FN, femoral neck; TH, total hip.

Bisphosphonates have been proven to reduce the risk of fractures and increase bone mineral density (BMD) for women with postmenopausal osteoporosis when used for durations of 3–5 years (1–7). Longer-term bisphosphonate use has been shown to increase or maintain BMD when compared with the use of placebo after the initial 3- to 5-year course (8–10). However, the ability of bisphosphonates to prevent fractures when used beyond 3–5 years is less certain, with mixed results being provided from trials not designed or powered to investigate fracture prevention (8–12). Additionally, there is growing concern for rare adverse effects of bisphosphonates including atypical fractures (13, 14) and osteonecrosis of the jaw (15, 16). The uncertainty surrounding bisphosphonate use beyond 3–5 years led the Food and Drug Administration (FDA) to assemble an Advisory Committee and perform a systematic review of the safety and efficacy of long-term bisphosphonate use (17, 18). The FDA concluded that there is no definitive benefit in favor of universal long-term bisphosphonate use and that many lower-risk women are candidates for therapy cessation after 3–5 years. The FDA also concluded that questions remain concerning for whom and when bisphosphonate therapy should be resumed after cessation.

Post hoc analyses of long-term bisphosphonate trials designed to study the effects on BMD suggest that women with the lowest BMD as measured by dual-energy X-ray absorptiometry (DXA) after the initial 3- to 5-year course of therapy derive vertebral fracture risk reduction from continued treatment (11, 12). It has also been found that age and BMD at the point of alendronate (ALN) discontinuation predict fractures over the subsequent 5 years, whereas changes in BMD made recently after ALN discontinuation only trend toward predicting fracture (19). However, a lack of power in this study keeps these conclusions from being definitive, and no attempt was made to find subgroups of women who may benefit from early BMD remeasurement. Some experts believe the appropriate approach is to continue bisphosphonates after 3–5 years in women deemed high risk for fracture (either by clinical risk factors or low BMD) and to consider therapy stoppage in women deemed to be at moderate or low risk (20–23). It has been further suggested by experts that women who stop therapy should be monitored with various strategies, usually involving the measurement of BMD, whereby therapy is to resume once BMD drops below a particular threshold, often −2.5 T-scores. Currently, no data exist to guide the frequency, timing, or for whom monitoring by DXA should occur to follow this strategy.

We have previously reported the distribution of the rate of bone loss in women who have discontinued ALN through analysis of the placebo group from the Fracture Intervention Trial (FIT) Long Term Extension (FLEX) trial, the largest clinical trial to date studying long-term ALN use (24). Using those findings to model BMD changes over time, we aimed to generate an estimate of the time until BMD repeat measurement should occur after alendronate stoppage based on BMD at the point of alendronate discontinuation and the assumption that a particular BMD threshold defines where a management change should be considered.

Materials and Methods

Participants

The design and results of both the FIT and the FLEX trials from which our study group is derived have been previously reported (2, 3, 9, 25). The FIT, which began in May 1992, enrolled women with baseline BMD at or below −1.6 T-scores and randomized them to receive ALN 5 mg/d for 2 years and 10 mg/d thereafter (n = 3236) or placebo (n = 3223). Each participant was offered a daily supplement containing 500 mg of calcium and 250 IU of vitamin D3.

The FLEX trial enrolled postmenopausal women aged 61–86 years who had been randomized to ALN in FIT and rerandomized them to receive either 5 more years of ALN (n = 662) or placebo (n = 437). Women were excluded from the FLEX trial if total hip (TH) BMD was both less than −3.5 T-scores and lower than prior to ALN treatment, (26) or if they took ALN for less than a total of 3 years. On average, women randomized in FLEX had completed 5.1 years of ALN therapy. For the present study, we analyzed 404 women from the FLEX trial placebo group with qualified BMD data (92%) (Figure 1). Please see the section below for BMD qualification criteria.

BMD measurements

BMD was measured at the TH and femoral neck (FN) using DXA at the beginning of the treatment-free period (the FLEX trial baseline) and annually for 5 years. All measurements were made with the same Hologic QDR 2000 densitometers (Hologic Inc). If a participant experienced bone loss at the TH greater than 8% over 1 year, 10% over 2 years, 12% over 3 years, etc, or had three or more new fractures, the participant was deemed as having excessive bone loss, and the investigator was notified without disclosing treatment assignment. Risks and benefits associated with study continuation were discussed with the participant. Discontinuation from the study drug was required for women with excessive bone loss who also had any TH BMD measurement more than 5% below the FIT baseline value, a rare event (13 women). Due to the above-mentioned protocol, a common reason to discontinue study drug (placebo) during the FLEX trial was to switch to open-label osteoporosis therapy. The original trial protocol encouraged women discontinuing placebo to continue to contribute BMD data in an effort to perform an intention to treat analysis. In this analysis, measurements performed after placebo discontinuation were censored to avoid including data from women on open-label osteoporosis medication.

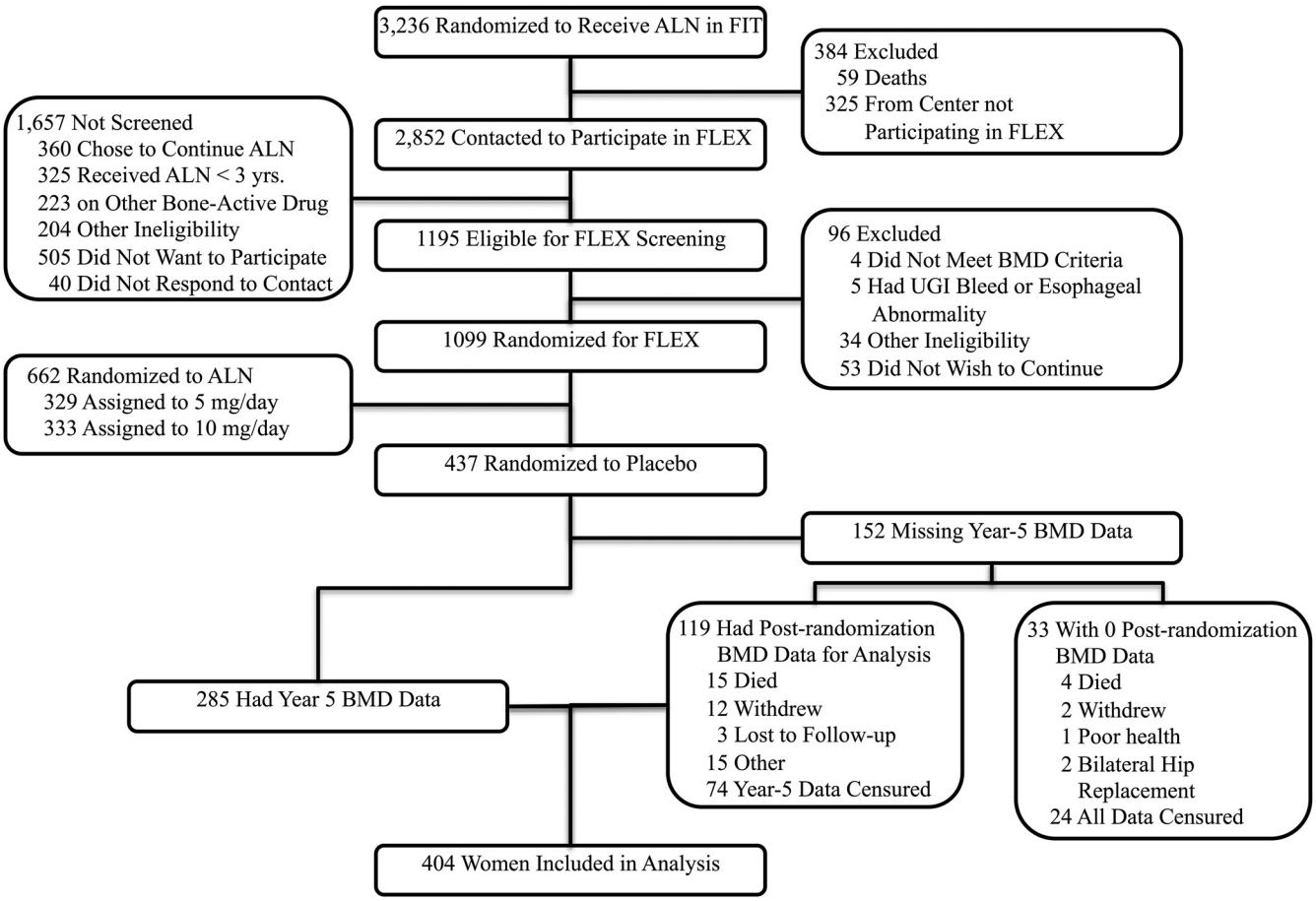

Figure 1. Above is the outline of the trials from which the study group was derived. FIT was 2.5–4.7 years in which all the participants from the study group took ALN 5 mg/d for the first 2 years and then 10 mg/d for the remainder of the trial time. There was a gap between FIT and FLEX of 1.1–3.2 years in which the participants were allowed to take open-label ALN. Participants randomized in FLEX took a mean of 5.1 year of ALN during FIT and the gap between FIT and FLEX. The FLEX trial was the post-ALN, treatment-free observation period in which the data were collected for this study. Participants were followed up for 1.4–5.4 years during FLEX, with a mean observation time of 4.9 years. UGI, upper gastrointestinal (GI).

Statistical methods

We estimated the time from the beginning of the treatment-free period until a range of critical percentages from 10% to 50% of women with varying baseline BMD T-scores would be expected to cross an array of BMD T-score retreatment thresholds ranging from −1.75 to −3. The array of retreatment thresholds near the most commonly used threshold in clinical practice (−2.5 T-scores) was selected as opposed to one specific threshold because we could not identify the ideal threshold that indicates retreatment should commence from these data or published results from other studies. Calculations were based on the conditional distribution of the follow-up BMD, given the baseline BMD, using standard results for bivariate, normally distributed outcomes. The required means, variances, and covariances were obtained using parameter estimates from linear mixed models. Confidence intervals were derived by bootstrapping with 100 repetitions for each iteration of the analysis.

Data for all participants who contributed at least one post-randomization BMD measurement were analyzed, including participants who dropped out or had later BMD measurements censored (27). This allowed inclusion of participants with incomplete data. To accommodate nonlinearity in the average trajectory of BMD, the models included linear, quadratic, and cubic terms in time as fixed effects (test for nonlinearity: $P = .0009$) and random intercepts and slopes to model subject-specific departures from the population trajectory. We found evidence for effect modification by baseline BMD (TH $P = .0001$, FN $P = .009$) that we accommodated by restriction: specifically, each iteration of the analysis for a specific baseline T-score was performed using the participants with baseline T-scores within 0.25 points of the specified value. We found no statistical evidence for effect modification by vertebral fracture status, so we analyzed women with and without vertebral fractures together.

Results analyzing TH BMD are presented as the primary analysis due to superior precision over FN and the position of the International Society of Clinical Densitometry stating that the TH is the preferred region of interest when using BMD for monitoring (28). Results for the FN can be found in the Supplemental Materials.

Results

Participants

Of the 437 women from the placebo group, nine (2.1%) contributed no follow-up BMD measurements and 24 (5.5%) had all follow-up scans censured, leading to a

Table 1. Baseline Characteristics at Start of Treatment-Free Period After 5 Years of ALN

Baseline Characteristic (n = 404)	Mean (SD) or n (%)
Age, y	73.6 (5.9)
BMI, kg/m^2	25.8 (4.3)
White race	389 (96)
Self-reported general health	
Very good/excellent	235 (58)
Good	144 (36)
Fair/poor	24 (6)
Walk for exercise	225 (57)
Fall in last 12 mo	94 (24)
Prevalent vertebral fracture	134 (33)
Smoking	
Never	207 (51)
Former	168 (42)
Current	28 (7)
Drank alcohol in last 30 d	212 (53)
Dietary calcium baseline, mg/d	626 (383)
Years of ALN use	5.1 (0.7)
On ALN at baseline	319 (79)
Time since FIT baseline, y	5.7 (0.3)
Time since FIT closeout, y	1.8 (0.5)
BMD	
TH, g/cm^2	0.725 (0.089)
FN, g/cm^2	0.612 (0.073)
TH T-score	−1.94 (0.82)
≤−2.5	89 (22)
>−2.5 to ≤−2.0	95 (24)
>−2.0	220 (54)
FN T-score	−2.17 (0.67)
≤−2.5	120 (30)
>−2.5 to ≤−2.0	121 (30)
>−2.0	163 (40)
Change in BMD after 5 y of ALN, %	
TH	+3.53 (4.69)
FN	+4.20 (5.97)

Abbreviation: BMI, body mass index.

group of 404 women with analyzable data (Figure 1). Of these 404 women, 19 (4.3%) had all measurements after the first follow-up year censured, 19 (4.3%) had all measurements after the second follow-up year censured, 18 (4.1%) had all measurements after the third follow-up year censored, and 18 (4.1%) had only the last measurement censored. Baseline characteristics of the 404 women analyzed are summarized in Table 1. The average age at the treatment-free period baseline (FLEX baseline) was 73.6 years, the average BMI was 25.8 kg/m^2, and the average TH BMD was −1.94 T-scores. Duration of ALN use was an average of 5.1 years and was defined as the sum of the duration of treatment during participation in the parent trial and the duration of use of ALN in the time between closeout of the parent trial and baseline of the treatment-free period. Prevalent vertebral fracture was noted to be present in 134 women (33%).

The mean 5-year percentage change in BMD over the 5-year treatment-free period was −3.6% (−0.21 T-scores) at the TH and −1.7% (−0.08 T-scores) at the FN. Among the 93 (23%) women who experienced a clinical fracture, 83 had one or more nonspine fractures, and 23 had one or more vertebral fractures.

Years until 10%–50% of women cross prespecified retreatment BMD thresholds

Table 2 shows the suggested remeasurement times for each combination of retreatment thresholds from −1.75 to −3 T-scores, initial T-scores at ALN discontinuation, and critical percentages of women expected to cross the threshold from 10% to 50%. To highlight a specific example, assume a clinician wanted to reassess TH BMD when there was a 20% chance that the follow-up TH T-score would be less than −2.5. Focusing on the portion of Table 2 devoted to the threshold T-score of −2.5, the second BMD measurement should be obtained 4.8 years after ALN discontinuation for patients with baseline T-score of −2, 3.7 years for those with baseline T-score of −2.1, 2 years for those with a baseline T-score of −2.2, and 0.8 years for those with a baseline T-score of −2.3. Women with baseline T-scores of −1.9 or more have a low probability of crossing the threshold and need not be reassessed within 5 years. Greater than 20% of women with T-scores between −2.4 and −2.5 will have a second BMD measurement be below the threshold if measured immediately after the baseline scan due to the measurement error of DXA. Supplemental Table 1 provides analogous results for the FN and shows similar findings.

Discussion

We have developed a method that estimates the length of time a clinician should wait to measure BMD based on the difference between BMD at the time of ALN discontinuation and the threshold BMD that initiates retreatment. The number who drop below the threshold varies, depending on the initial BMD: for women closer to the threshold, they are much more likely to drop below it at any given time. By selecting a specific retreatment threshold, the proportion of women to cross said threshold determined to justify a management change, and knowing the distance from that threshold a patient stopping ALN is at the point of discontinuation, a clinician could use Table 2 to decide how long after ALN discontinuation a follow-up BMD measurement should be made. Selecting a lower critical percentage ensures more frequent use of DXA for monitoring, and we highlighted the example of 20% in *Results* to show a relatively aggressive use of post-ALN BMD monitoring.

Table 2. Time Until Critical Percentages of Womens' Total Hip BMDs Cross Retreatment Thresholds from −1.75 to −3 T-scores by T-score at Time of Stopping ALN

Threshold[a]	Critical Percentage[b]	Time (95% CI), y					
Starting T-scores →		**−1.15**	**−1.25**	**−1.35**	**−1.45**	**−1.55**	**−1.65**
−1.75	10	4.2 (3.5 to ≥5)	3.4 (2.8–4.4)	2.2 (1.6–3.2)	0.8 (0.6–1.3)	<0.1 (N/A to 0.3)	—
	20	≥5 (4.7 to N/A)	4.6 (3.9 to ≥5)	3.7 (2.7–4.5)	1.7 (1.1–2.7)	0.6 (0.5–0.9)	—
	30	—	≥5 (4.8 to N/A)	4.7 (3.8 to ≥5)	2.9 (1.9–4.1)	1.1 (0.8–1.6)	0.1 (0.1–0.3)
	40	—	—	≥5 (4.8 to N/A)	4.3 (3.1 to ≥5)	1.9 (1.3–3.3)	0.5 (0.3–0.8)
	50	—	—	—	>5 (4.6 to N/A)	3.9 (2 to ≥5)	0.9 (0.6–1.5)
Starting T-scores →		**−1.4**	**−1.5**	**−1.6**	**−1.7**	**−1.8**	**−1.9**
−2	10	4.2 (3.4–4.9)	3.1 (2.3–4.1)	2.2 (1.5–3)	1.1 (0.8–1.6)	0.2 (0.1–0.5)	—
	20	≥5 (4.5 to N/A)	4.6 (3.4 to ≥5)	3.7 (2.7–4.6)	2 (1.3–2.7)	0.8 (0.5–1.3)	—
	30	—	≥5 (4.8 to N/A)	≥5 (3.8 to N/A)	3.2 (2.1–4.1)	1.4 (0.9–2.2)	0.3 (0.2–0.6)
	40	—	—	—	4.5 (3.4 to ≥5)	2.5 (1.4–3.9)	0.8 (0.5–1.3)
	50	—	—	—	≥5 (4.8 to N/A)	4.8 (2.8 to ≥5)	1.4 (0.9–2.3)
Starting T-scores →		**−1.65**	**−1.75**	**−1.85**	**−1.95**	**−2.05**	**−2.15**
−2.25	10	4.6 (3.4 to ≥5)	3.9 (2.8–4.8)	2.4 (1.6–3.4)	1.3 (0.9–2.2)	<0.1 (N/A to 0.4)	—
	20	≥5 (4.6 to N/A)	≥5 (4.2 to N/A)	3.9 (2.5 to ≥5)	2.4 (1.6–3.3)	0.9 (0.6–1.4)	—
	30	—	—	≥5 (3.5 to N/A)	3.5 (2.3–4.8)	1.6 (1.1–2.5)	0.1 (<0.1–0.4)
	40	—	—	—	4.8 (3.4 to ≥5)	2.7 (1.7–3.9)	0.6 (0.4–1.1)
	50	—	—	—	≥5 (4.7 to N/A)	4.2 (3 to ≥5)	1.2 (0.7–2)
Starting T-scores →		**−1.9**	**−2**	**−2.1**	**−2.2**	**−2.3**	**−2.4**
−2.5	10	≥5 (3.5 to N/A)	3.6 (2.5–4.8)	2.5 (1.7–3.5)	1 (0.8–1.5)	<0.1 (N/A to 0.4)	—
	20	≥5 (4.9 to N/A)	4.8 (3.5 to ≥5)	3.7 (2.6 to ≥5)	2 (1.5–2.9)	0.8 (0.6–1.3)	—
	30	—	≥5 (4.5 to N/A)	4.9 (3.5 to ≥5)	3.1 (2.3–4.1)	1.6 (1.2–2.2)	0.2 (0.1–0.5)
	40	—	—	≥5 (4.6 to N/A)	4.4 (3.1 to ≥5)	2.6 (1.8–3.4)	0.6 (0.5–1.1)
	50	—	—	—	≥5 (4.4 to N/A)	3.8 (2.7–4.6)	1.2 (0.8–2.1)
Starting T-scores →		**−2.15**	**−2.25**	**−2.35**	**−2.45**	**−2.55**	**−2.65**
−2.75	10	≥5 (3.7 to N/A)	3.6 (2.7–4.2)	2.6 (1.7–3.6)	1.2 (0.8–2.1)	0.1 (<0.1–0.5)	—
	20	≥5 (4.9 to N/A)	4.8 (3.7 to ≥5)	4 (2.5–4.7)	2.5 (1.6–3.5)	0.7 (0.5–1.3)	—
	30	—	≥5 (4.8 to N/A)	4.9 (3.5 to ≥5)	3.8 (2.5–4.6)	1.4 (0.9–2.5)	0.3 (0.2–0.7)
	40	—	—	≥5 (4.5 to N/A)	4.8 (3.6 to ≥5)	2.7 (1.4–3.9)	0.7 (0.5–1.3)
	50	—	—	—	≥5 (4.7 to N/A)	4.1 (2.4–4.8)	1.3 (0.8–2.2)
Starting T-scores →		**−2.4**	**−2.5**	**−2.6**	**−2.7**	**−2.8**	**−2.9**
−3	10	≥5 (3.5 to N/A)	4.1 (2.6–4.7)	2.7 (1.6–3.5)	1.3 (0.7–1.9)	0.3 (0.1–0.7)	—
	20	≥5 (4.6 to N/A)	≥5 (3.7 to N/A)	4.2 (2.4–4.7)	2.4 (1.3–3.2)	0.9 (0.5–1.6)	<0.1 (N/A to 0.1)
	30	—	≥5 (4.6 to N/A)	≥5 (3.4 to N/A)	3.6 (1.8–4.1)	1.5 (0.9–3.2)	0.2 (<0.1–0.9)
	40	—	—	≥5 (4.4 to N/A)	4.6 (2.7 to ≥5)	2.6 (1.4–4.8)	0.7 (0.4–1.8)
	50	—	—	—	≥5 (3.8 to N/A)	4.4 (2.4 to ≥5)	1.4 (0.8–3.1)

Abbreviation: CI, confidence interval. Screening time estimate and upper and lower bounds are all 5 or greater or less than 0.1 for blank entries. This is a matrix of the number of years it would take for 10%–50% of women to have a second BMD measurement below an array of retreatment BMD thresholds from −1.75 to −3 T-scores by an array of baseline BMDs at the point of ALN discontinuation. The 95% CIs are provided in parentheses and were derived by bootstrapping with 100 repetitions.

[a] The threshold BMD where treatment is to be reinitiated. To be selected by the clinician determining BMD remeasuring time for a patient.

[b] The critical percentage of women to cross the retreatment threshold that justifies remeasuring BMD. To be selected by the clinician determining BMD remeasuring time for a patient. Note that selecting a lower percentage leads to shorter remeasuring times.

[c] The BMD at the start of the treatment-free period of the patient for whom BMD remeasurement time is being calculated.

We repeated this analysis for a range of retreatment thresholds because no data exist that tell us which retreatment threshold is most important. There is a recent analysis of the FLEX trial that suggests that the number needed to treat with longer-term ALN to prevent one vertebral fracture is sufficiently low for women with FN BMD T-scores of −2.5 or less (−2 with prevalent vertebral fracture) (12). Data for the TH were not presented, and benefits were found for vertebral fracture only. Nevertheless, it is probably reasonable to use these continuation thresholds as the retreatment thresholds until updated thresholds or algorithms for retreatment are available. This analysis is constructed to be flexible should new information that identifies a more appropriate retreatment threshold arise. Our results can be interpreted globally to imply that regardless of the threshold that identifies women for a management change, it is only those within 0.6 T-scores who have a significant chance of crossing the threshold within the first 5 years of ALN discontinuation. Monitoring women with TH BMD greater than 0.6 T-scores above a retreatment threshold within 5 years of ALN discontinuation is likely of no benefit.

The recommendation that women at lower risk of vertebral fracture can discontinue ALN is based on a relatively high number needed to treat to prevent one vertebral fracture, and the lack of a demonstrated benefit with regards to the risk of nonvertebral fracture (12). However, the risk of fracture in these women is still substantial, with

11.9% of such women experiencing a clinical nonvertebral fracture within 5 years of ALN discontinuation (11). This makes the lack of utility for BMD monitoring after ALN discontinuation particularly disappointing because early follow-up BMD measurements are unlikely to capture who will go on to fracture among women discontinuing ALN. In fact, follow-up BMD measurements may underestimate fracture risk when found to remain above a retreatment threshold. Alternative monitoring strategies such as the measurement of bone turnover markers (BTMs) are potentially important. It has recently been shown that BTMs measured after ALN discontinuation do not predict fracture (19). However, a small sample size keeps this conclusion from being definitive, and the relationship between BTMs and future BMD changes has yet to be explored.

Although our tool can be used to generate specific numbers of years until 10%–50% of women will drop below a retreatment threshold, it is likely more practical to consider all of the women who could potentially benefit from DXA monitoring within 5 years as a single group. For example, if we would consider retreatment when 20% of women cross the threshold of −2.5 T-scores, then we could remeasure BMD at the same time (perhaps 3 y after discontinuation) for all women with TH BMD above −2.5 T-scores and below −1.9 T-scores.

The implications of our longitudinal approach in deriving the distribution of follow-up BMD measurements and our censorship decisions of those measurements merit a brief discussion. The censorship process had the potential of introducing selection bias as the FLEX protocol made women who lost the most bone be the most likely to discontinue placebo in favor of open-label ALN. Because data were analyzed with longitudinal methods, women with year 5 data missing or censored were analyzed as if they continued in the trial for the full 5 years, such that only 24 (5.5%) and nine (2.1%) women had all follow-up data censored or missing, respectively. This reduced the possibility of underestimating bone loss after ALN discontinuation. However, this benefit came at a cost. Generating unbiased estimates by this method depends on the assumption that the data were missing at random (27), an unlikely scenario, given the reasons for censorship. Knowing that the censored measurements were necessarily low, if those participants had contributed additional measurements beyond the point of censorship, they would likely have continued to lose less bone than estimated due to regression towards the mean. Therefore, we may have slightly overestimated the rate of bone loss, meaning we produced, if anything, a conservative tool that advocates more use of DXA after ALN discontinuation. Moreover, the statistical technique used to derive our estimates is robust to minor violations of the above assumption, and we believe this issue has little if any impact on our results.

Incorporating more than two measurements per participant reduces the influence of measurement error by DXA on the distribution of follow-up BMD measurements. Because we felt that measurement error of DXA is something clinicians must deal with, we estimated the distribution of a follow-up BMD measurement dependent only on the value of the baseline measurement, effectively disallowing the reduction of error afforded by multiple measurements. This is why a significant percentage of women drop below a selected retreatment threshold immediately after ALN discontinuation.

There are a number of limitations of our analysis. The FIT included some women who had no history of vertebral fracture and whose BMD was above −2.5 T-scores. Many of those women would not currently be treated with ALN. We showed in this and previous analyses (24) that BMD changes after ALN discontinuation occur in a similar pattern for both nonosteoporotic and osteoporotic women. Thus, we feel justified in including the data of nonosteoporotic women for the purposes of calculating BMD rates of change after ALN discontinuation. The population studied consisted of women aged 61–86 years, which was mostly Caucasian. It may not be appropriate to extrapolate these results to men, younger women, or other racial groups. Also, the participants exclusively took ALN prior to therapy cessation. It is likely not appropriate to generalize these results to other bisphosphonates because it has been shown that different bisphosphonates have different long-term kinetics (20, 29, 30). This analysis was performed using data from participants in a clinical trial. Because of known greater adherence to treatment among trial participants and potential healthy volunteer bias, these results should be viewed as a best-case scenario for clinical practice. Finally, these results are based on a single group of patients. Ideally, this tool's performance should be evaluated in other studies of different cohorts of patients who have discontinued bisphosphonates.

Conclusion

We have provided a tool to estimate the amount of time to wait until remeasuring BMD for the purpose of monitoring women discontinuing ALN. Applying this tool shows that measuring BMD within the first 5 years of ALN discontinuation is unlikely to affect management for women with TH BMD 0.6 T-scores above a specified retreatment threshold within the range of −1.75 to −3 T-scores.

Acknowledgments

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B.M. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. B.M. and E.V. performed all data analysis.

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