Full Length Article

Administration of teriparatide for four years cyclically compared to two years daily in treatment Naïve and alendronate treated women

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ABSTRACT

Purpose: We evaluated if equivalent doses of TPTD given cyclically over 4-years could increase BMD > 2-years of daily TPTD in 2 cohorts of women; previously untreated (Rx-Naïve) and women previously treated with ALN (ALN-Rx).
Methods: In Rx-Naïve, women were randomized to daily TPTD for 24 months (Daily; n = 23) or cyclic TPTD for 48 months (3 months on, 3 months off; Cyclic; n = 25). In ALN-Rx, women were randomized to continued ALN plus daily TPTD for 24 months, followed by ALN alone for 24 months (Daily; n = 21) or TPTD for 48 months (3 months on, 3 months off) while ALN was continued (Cyclic; n = 20). BMD (DXA) was measured at spine (LS), total hip (TH) and femoral neck (FN). The primary analysis compared 4 years of cyclic therapy to 2 years of daily therapy in RX-naïve and ALN-RX cohorts.
Results: In Rx-Naïve, BMD changes at 24 months after Daily TPTD vs. 48 months after Cyclic TPTD were: LS 8.6% vs. 6.9%; TH 2.5% vs. 2.6%, and FN 1.6% vs. 2.2%. None of the BMD changes differed significantly between groups but all changes were significant over time within each group (p < 0.01 except for FN where p = 0.17 Daily; p = 0.09 Cyclic). In ALN-Rx, BMD changes at 24 months after Daily TPTD vs. 48 months after Cyclic TPTD were: LS 7.5% vs. 7.2%; TH 3.8% vs. 4.1%, and FN 3.2% vs. 2.5%. There were no differences between groups but all changes were significant within each group (p < 0.01).
Conclusion: The same cumulative dose of TPTD given cyclically for 4-years, does not increase BMD more than standard daily TPTD over 2-years in either Rx-Naïve or ALN-Rx women.
Trial Registration: NCT00668941

1. Introduction

Parathyroid hormone 1-34 (teriparatide, TPTD) stimulates bone formation and bone remodeling, with positive net bone balance resulting in increased bone mass, improved bone architecture, increased bone strength and reduced risk of fracture [1–12]. The biochemical response to TPTD follows a consistent pattern, with a brisk increase in markers of bone formation upon initiating TPTD treatment [2,6,10,11], peak levels within the year and decline toward baseline thereafter [12]. Increases in serum markers of bone resorption are delayed, but also peak and decline toward baseline during the second year of TPTD [2,4,10,12]. The increase in spine bone density (BMD) following TPTD is also most rapid within the first 6 months of treatment [2–4,6,10,11]. Histomorphometric

analyses of iliac crest biopsies indicate dramatic direct stimulation of bone formation (modeling-based formation) and stimulation of bone remodeling (remodeling-based formation) at 1 to 6 months [8,13–15]. These effects are continued but somewhat dampened at 18–36 months [7,16–18]. Taken together, the biochemical turnover marker levels, BMD, and histomorphometric data suggest that there is a developing resistance to the effects of continued TPTD administration during the second year. This could be due to depletion of the osteoblast progenitor pool or the induction of bone formation inhibitors [19,20].

Considering the data summarized above, the concept of administering TPTD cyclically (in 3 month cycles) was based on two hypotheses. The first was that early direct stimulation of bone formation without prior resorption [21] might be more important to the ultimate

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accrual of BMD than later activation of bone remodeling. The second hypothesis was that repeated short cycles of TPTD might surmount the partial tachyphylaxis that develops after 6–15 months of continuous daily therapy. Short TPTD cycles could potentially dissociate the early modeling-based anabolic effect from the latter remodeling-based effect.

We previously published results from the first two years of this trial [22]. Cyclic TPTD over two years increased BMD similarly to daily treatment in women who remained on alendronate (ALN-Rx). However, in treatment naïve women (Rx-Naïve), BMD increments in the cyclic group were about half those in the standard daily group, consistent with the cumulative dose of TPTD administered. In the current study, we determine, in a group of Rx-Naïve women, if continued cyclic TPTD administration over four years increases BMD more than standard daily TPTD administration for two years (same cumulative dose of TPTD). Since both Rx-Naïve women and ALN-Rx women can be candidates for TPTD, we also tested equivalent cumulative doses of TPTD given cyclically vs. a 2-year standard daily TPTD regimen in the ALN-Rx.

To keep the time period equal in the 2 arms, a secondary analysis was also performed, comparing the daily group with the cyclic group at 4 years. Note that in the Rx-Naïve cohort, for the secondary 4-year analysis, the daily group received 2 years of ALN that the cyclic did not receive. In the ALN-Rx cohort, cumulative doses of TPTD and ALN were the same over 4 years.

2. Methods

This was a randomized, open label study in postmenopausal women with osteoporosis. Subjects were recruited concurrently into 2 parallel cohorts: women on ALN (70 mg/week) for at least one year (ALN-Rx; n = 64) and women with minimal or no prior osteoporosis therapy (Rx-Naïve; n = 86). In both cohorts, volunteers were randomized to daily TPTD (20 μg daily subcutaneously for 24 months) or cyclic TPTD given in 3 month cycles (3 months on TPTD 20 μg/day and 3 months off TPTD) [22]. After two years, women who completed the 2 year study and who had BMD t-scores ≤ − 2.0 at the lumbar spine (LS), total hip (TH) or femoral neck (FN) were offered enrollment in a two year extension study.

In the Rx-Naïve cohort, the Cyclic group continued to receive cyclic TPTD for 2 additional years whereas the Daily group was followed while on alendronate for 2 years after TPTD. The primary comparison (*equal TPTD dose*) was BMD change over 4 years in the cyclic group vs. BMD change over 2 years with standard daily TPTD therapy. A secondary analysis (*equal time period*) was performed comparing the Cyclic group over 4 years to the Daily group after 4 years, reflecting equivalent periods of time, but with 2 years of additional ALN in the latter arm. Similar comparisons for equal TPTD dose (*primary analysis*) and equal time (*secondary analysis*) were made between cyclic and daily groups who remained on ALN for the 4 years.

This study was approved by the Helen Hayes Hospital Institutional Review Board and a DSMB appointed by NIAMS had oversight for the safety of participants in this clinical trial.

2.1. Patient population

This study was approved by the Helen Hayes Hospital Institutional Review Board and all women provided informed consent. Volunteers were recruited from referrals to our Osteoporosis Clinic and Bone Density Screening Program and from the community by advertisement and public speaking at educational programs and support groups. After completion of the 2 year study in 2013 [22], participants were asked to enroll in an extension study where follow-up continued for an additional 2 years. Seventy-seven% of eligible women agreed to participate.

2.1a. Inclusion criteria

All women who completed the original study [22] were eligible for entry into the extension study unless exclusions (below) were found.

2.1b. Exclusion criteria

Women (n = 24) were excluded for the following reasons: if all BMD T-scores were > − 2.0, the paricipant was unwilling to take bisphosphonates, new diagnosis of renal stone, hypercalcemia, elevated serum levels of parathyroid hormone (PTH) or bone specific alkaline phosphatase (BSAP), clinically significant elevation of serum uric acid level, or new diagnosis of cancer. A few women with contraindications to oral bisphosphonates were given annual infusions of zoledronic acid (n = 6; 5 in daily naïve; one in cyclic ALN).

2.2. Protocol

2.2a. Treatment assignment

For the orignal study, volunteers within each cohort (Rx-Naïve and ALN-Rx) were randomly assigned to cyclic vs. daily TPTD treatment (treatment assignment was not blinded). Randomization was computer generated using SAS. In the Rx-Naive cohort, women who had 2 years of daily TPTD were given ALN for the next two years and those on the cyclic regimen continued for 4 years. In the ALN-Rx cohort, ALN was continued during and after daily TPTD treatment and throughout cyclic TPTD. Volunteers presented to the Clinical Research Center every 3 months for assessment of compliance, side effects, and lab assessment. BMD measurements were made every 6 months and thoracic and lumbar spine radiographs were performed at 24 and 48 months.

2.2b. Biochemical Bone Turnover Marker (BTM) determinations

Fasting blood samples were obtained in the morning at baseline, and every 3 months during the 48 months of study. Samples were batched for each individual and analyzed in our laboratory for Osteocalcin (OC), Propeptide of Type I Procollagen (PINP), and Crosslinked C-telopeptide (CTX) (Elecsys cobas, Roche Diagnostics Corporation, Indianapolis, USA). Reagents for these biochemical markers were also generously provided by Roche Diagnostics Corporation. The ranges of intra and inter-assay coefficients of variation, based on the analysis of control samples with high, medium and low concentrations were: OC (0.5–1.1% and 2.4–4%), PINP (1.6–2.5% and 1.9–3%), and CTX (1.0–1.6% and 2.9–4.2%).

2.2c. Bone density determinations

BMD of the LS, TH, TR (trochanter), FN, and RAD (proximal third radius) was evaluated by DXA at baseline and at 7, 15, 24, 30, 36, 42 and 48 months (GE/Lunar Prodigy, Madison, WI). Coefficients of variation for DXA performed in our laboratory on that machine were as follows: LS 1.1%, TH 1.5%, TR 1.5%, FN 2.0%, and RAD 2.2%.

2.2d. Clinical fractures

Clinical fractures excluded fractures of the hands, feet, face or skull and fractures associated with major trauma (more than a fall from standing height). Historical clinical fractures were recorded by medical history at baseline. Subsequent fractures were recorded at each visit as adverse events (AEs) or serious adverse events (SAEs).

2.2e. Assessment of radiographic vertebral fractures

Prevalent and incident radiographic vertebral fractures were assessed by lateral thoracic and lumbar spine radiographs at baseline, 2 and 4 years. Optasia Medical software (Cheadle, UK) was used to obtain a 6 point vertebral fracture assessment with vertebral body contouring which places markers on anterior, middle and posterior sections of each vertebral body to determine heights (PG). These heights were used to determine the presence and degree of vertebral deformity (mild, moderate or severe) and all were counted as fractures (after review and confirmation by FC). All assessments were made while blinded to treatment assignment.

2.2f. Compliance

Compliance was assessed by review of subject injection diaries and by measuring returned TPTD pens.

2.2g. Safety assessments

Total serum calcium level was assessed at every visit via standard automated chemistry. A preplanned algorithm for hypercalcemia (defined as any value above the upper limit for our laboratory, 10.1 mg/dl) required stopping calcium supplements and repeating the measurement within 2 weeks (as previously described) [22]. If hypercalemia persisted, TPTD was to be withheld. BMD was assessed for excessive loss (> 7.5% at the LS or TH) at each follow up as compared to any prior measurement. The protocol planned for repeat BMD measurement and subject withdrawal if excessive bone loss was confirmed.

2.2h. Statistical analysis

Statistical analyses were performed using SAS v 9.4 (SAS Institute, Cary, NC). Descriptive characteristics for the study samples were compared between Cyclic and Daily groups, separately for Rx-Naive and ALN-Rx cohorts, using *t*-tests for continuous and Chi-square or Fisher's Exact test for categorical variables, as appropriate. This was performed once for the study month-0 baseline of the parent trial and again to describe the study month-24 baseline of subjects who enrolled in the extension study. Baseline descriptive variables between the extension cohort and the full cohorts enrolled into the parent study were also compared.

Linear mixed models for repeated measures were used to estimate between treatment group differences in within-subject change over time in subjects who completed the study per-protocol: i.e., fixed effects for treatment group (Daily vs. Cyclic), time and group by time interaction; random effect for subject and a spatial power (linear) covariance structure empirically determined prior to inferential testing to best fit the autocorrelation of the repeated measures. Within-group differences between times and between-group differences at specific times were analyzed with model-estimated means and standard errors. Mixed models were used to assess the change from study month-0, baseline (months 0, 7, 15, 24, 30, 36, 42 and 48). Potential confounders of BMD change were assessed at the values present at the study month-0 baseline values: BMD, age, weight, BMI, years from menopause, and BTM levels.

3. Results

One-hundred-fifteen women completed the 2 year parent study and 89 (75%) enrolled in the extension study, including 48 in Rx-Naïve and

Table 1

Baseline characteristics (month 0) of participants completing 48 months of extension study (n = 74).

Treatment Naïve Group	Cyclic TPTD (n=23)		Daily TPTD (n=16)	
Variable	**Mean**	**Std.**	**Mean**	**Std.**
Age (years)	61.6	7.2	62.2	6.3
Years from Menopause	12.8	8.1	14.8	9.0
BMI	24.4	5.4	25.4	6.0
Spine BMD	0.816	0.076	0.828	0.088
Spine t-score	–3.1	0.62	–3.0	0.77
Total Hip BMD	0.754	0.115	0.754	0.054
Total Hip t-score	–2.0	0.91	–2.0	0.43
% Clinical Fracture >age 50				
No n (%)	15 (65)	-	13 (81)	-
Yes n (%)	8 (35)	-	3 (19)	-
Serum Osteocalcin (ng/ml)	23.9	8.2	23.9	4.8
Serum Propeptide of Type I Procollagen (ng/ml)	50.8	19.1	54.8	23.9
Serum C-telopeptide (pg/ml)	465	186	429	209
Prior Alendronate Treated Group	Cyclic TPTD (n=17)		Daily TPTD (n=18)	
Variable	**Mean**	**Std.**	**Mean**	**Std.**
Age (years)	68.7	8.2	65.4	10.0
Years from Menopause	17.6	8.2	20.2	14.7
BMI	24.0	4.6	23.6	3.0
Spine BMD	0.832	0.107	0.841	0.081
Spine t-score	–2.9	0.93	–2.9	0.64
Total Hip BMD	0.734	0.080	0.741	0.077
Total Hip t-score	–2.2	0.63	–2.10	0.63
% Clinical Fracture >age 50				
No n (%)	10(59)	-	11 (61)	-
Yes n (%)	7(41)	-	7 (39)	-
Serum Osteocalcin (ng/ml)	14.9	4.3	15.3	5.2
Serum Propeptide of Type I Procollagen (ng/ml)	23.2	7.5	23.2	10.2
Serum C-telopeptide (pg/ml)	152	63	182	105

41 in ALN-Rx cohorts (Fig. 1). Seventy-four women (83% of enrolled) completed the 2-year extension: 9 withdrew consent for personal reasons, 4 were lost to follow-up, and 2 withdrew due to an SAE/AE. There were no deaths during the extension study (Fig. 1).

3.1. Baseline characteristics

Table 1 illustrates the baseline characteristics for all Rx-Naive and ALN-Rx subjects who completed the extension study (n = 74 in total). There were no significant differences in baseline descriptive variables between the extension cohorts and the full cohorts enrolled into the

Baseline Cohort	Enrolled in parent study		Protocol 0-24* month parent study	Completers of parent study	Enrolled in extension study		Protocol 24-48 months extension study	Completers of extension study
Treatment Naïve Women	n = 43	→	Daily TPTD for 24 months	n = 30	n = 23	→	Alendronate for 24 months	n = 16
	n = 43	→	Cyclic TPTD for 24 months** (3 months on, 3 months off)	n = 32	n = 25	→	Continue cyclic TPTD for 24 months**	n = 23
Alendronate Treated Women	n = 30	→	Daily TPTD and continued Alendronate for 24 months	n = 25	n = 21	→	Continue Alendronate for 24 months	n = 18
	n = 34	→	Cyclic TPTD for 24 months** (3 months on, 3 months off) with continued alendronate	n = 28	n = 20	→	Cyclic TPTD for 24 months** and Continue Alendronate	n = 17

Baseline for extension study includes closeout for original protocol.
**TPTD given: 0-3, 6-9, 12-15, 18-21 months for parent study and 24-27, 30-33, 36-39, 42-45 months in the extension study.

Fig. 1. Protocol design and study flow.
Overall study flow is shown for the parent study with the 2 year completers for the Rx-Naïve cohort and the ALN-Rx Cohort and enrollees and completers for the two-year extension study.

parent study. The Rx-Naïve and ALN-Rx cohorts, Daily and Cyclic groups had similar age, height, weight, body mass index (BMI), spine and hip BMD, prior clinical fracture history, prevalent vertebral fracture rate and serum BTM levels, with no significant differences.

3.2. Biochemical Bone Turnover Markers

3.2.1. Rx-Naïve cohort (Fig. 2 left)

Biochemical turnover marker data (serum P1NP, Osteocalcin and C-telopeptide) are shown for the full 4 year study for the participants who completed the 2 year extension. In the Rx-Naïve cohort, after 2 years

daily TPTD, BTM levels were still above baseline, although below the peak levels seen at approximately 1 year. In the Cyclic group, BTM levels continued to increase during each 3 month cycle of TPTD and decrease during each off TPTD period throughout the 4 years, most notably with P1NP and osteocalcin.

In the Daily group, after transition to ALN, serum BTM levels declined promptly and stayed low during ALN treatment (24–48 months).

3.2.2. ALN-Rx cohort (Fig. 2, right)

In the ALN-Rx cohort, with daily TPTD, serum BTM levels increased to a lesser extent than seen in Rx-Naïve, but levels stayed elevated
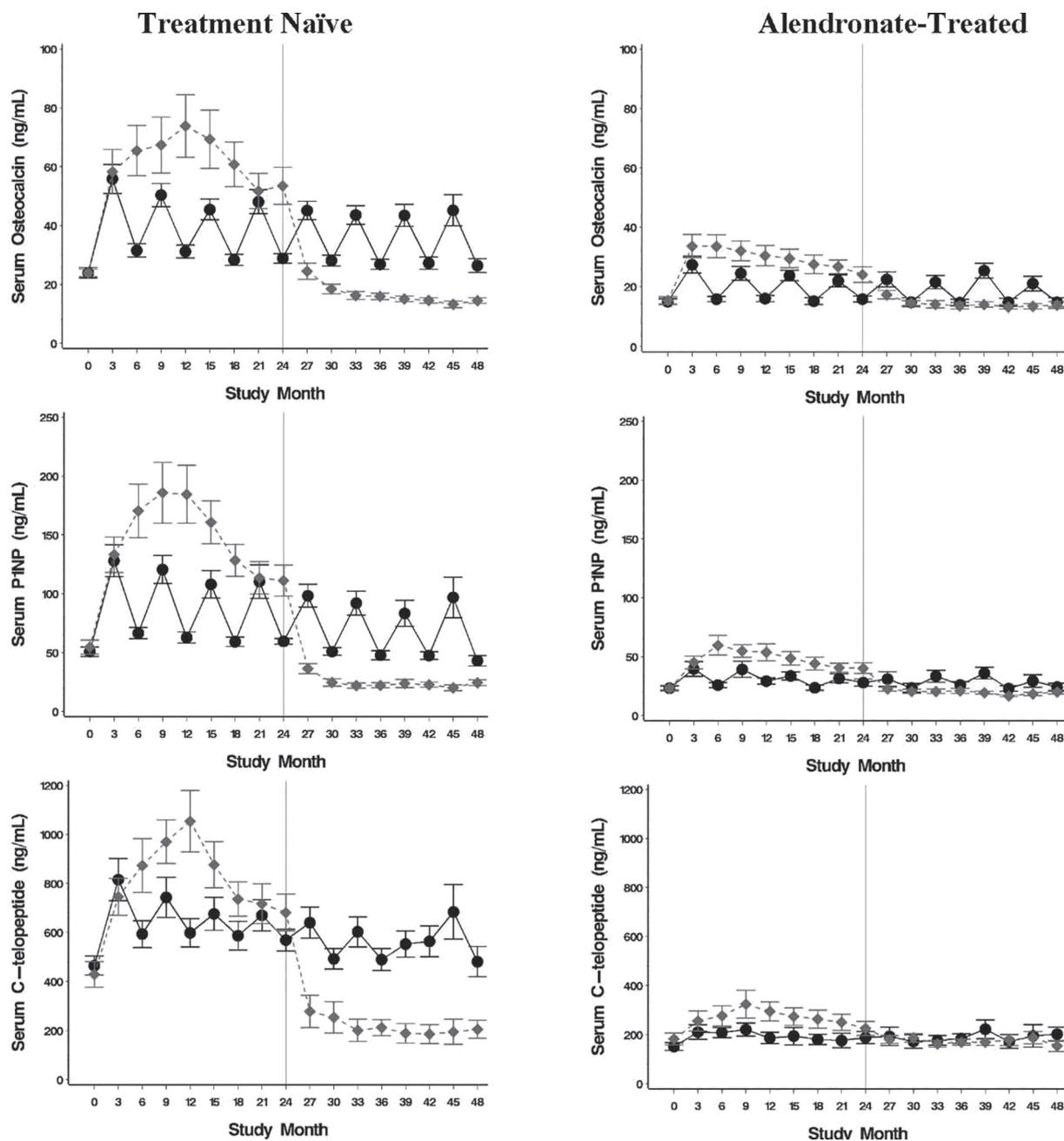
Fig. 2. Serum Biochemical Bone Turnover Marker levels (mean + SEM; OC, PINP, CTX) during TPTD treatment given daily or cyclically over 2 years in Rx-Naïve women (left column) and ALX-Rx women (right column) followed by ALN in the daily groups for months 24 to 48.

above baseline for the full 2 year treatment period. Upon cessation of TPTD and continuation of ALN alone, BTM levels decreased to baseline. In the cyclic group, BTM levels increased during each TPTD cycle and declined during each off period. These changes were most obvious for the formation markers while the cyclic pattern for serum C-telopeptide levels was much less apparent.

Although BTM patterns were very similar between the 2 cohorts, considering both the Daily and Cyclic arms, changes appear to be substantially dampened in the ALN-Rx cohort.

3.3. Bone density by DXA (Fig. 3)

All BMD changes and group differences were assessed after controlling for baseline BMD. Each of the models for the BMD results were also repeated with the inclusion of additional baseline covariates (age, weight, BMI, years from menopause, and BTM levels) to assess their influence on the main findings. None of these adjusted models changed the reported significance between or within groups.

3.4. Rx-Naïve cohort (left)

3.4.1. Primary analysis (equal TPTD doses)
In Rx-Naïve, BMD changes after 24 months of Daily TPTD vs. 48 months of Cyclic TPTD were: LS 8.6% vs. 6.9%; TH 2.5% vs. 2.6%, FN 1.6% vs. 2.2%; TR 2.7% vs. 4.1% and RAD −5.0% vs. −5.6%. None of the BMD changes differed significantly in daily vs. cyclic groups (comparing equal TPTD dosing). All BMD changes were significant within groups at 24 months in Daily and at 48 months in Cyclic (all p < 0.01 except for FN where Daily p = 0.17 and Cyclic p = 0.09).

3.4.2. Secondary analysis (equal treatment times)
BMD increases at LS, FN and TR did not differ significantly at the final 48 month time point (LS: 9.4% Daily vs. 6.9% Cyclic; FN: 3.4% Daily vs. Cyclic 2.2%; TR: 6.1% Daily vs. 4.2% Cyclic). In the TH, at the 48 month time point, the BMD increment was higher in Daily vs. Cyclic (4.7% vs. 2.6% p = 0.036). RAD BMD declined similarly in both groups (−5.9% Daily vs. −5.6% Cyclic; no 48 month group difference. BMD changes within each group were significant over 48 months (all p < 0.01 except for FN where Daily p = 0.03 and Cyclic p = 0.09).

3.5. ALN-Rx cohort (right)

3.5.1. Primary analysis (equal TPTD dosing)
In the ALN-Rx cohort, BMD changes at 24 months after Daily TPTD vs. 48 months after Cyclic TPTD were: LS 7.5% vs. 7.2%; TH 3.8% vs. 4.1%, FN 3.2% vs. 2.5%; TR 4.9% vs. 5.7% and RAD −0.5% vs. −4.3%. The Daily vs. Cyclic group BMD changes did not differ significantly with equal TPTD dosing, except in the RAD (p = 0.03). All BMD changes were significant within each group (p < 0.01) except for RAD Daily 24 month (NS).

3.5.2. Secondary analysis (equal treatment times)
At 48 months, in the LS, BMD increased 5.2% in Daily and 7.2% in Cyclic. BMD gains at 48 months in the TH, TR and FN were 3.8%, 5.6%, and 3.7% in the Daily group and 4.1%, 5.7%, and 2.6% in the Cyclic group respectively (no significant group difference at any site). RAD BMD declined in both groups (−2% Daily, −4.1% Cyclic), with no group difference. Over 48 months, BMD changes were sigificant within groups at all skeletal sites.

3.6. Fractures

Clinical fractures over the entire 4 year trial (recorded as AEs or SAEs) occurred in a total of 10 of 89 subjects enrolled: 1 woman in the

Rx-Naïve Daily, 3 in Rx Naïve Cyclic, 3 in ALN-Rx Daily and 3 in the ALN-Rx Cyclic. These fractures included: 2 pelvic, 4 wrist, 2 rib, 1 elbow and 1 shoulder. Incident radiographic vertebral fractures occurred in 4 subjects over the 4 year trial (3 in the ALN-Rx Daily and 1 in Rx-Naïve Daily).

3.7. Safety

A total of 7 SAEs occurred in 6 subjects during the extension study. None of these events was thought related to the treatment protocol. One subject had a fall resulting in tibia, fibula and metatarsal fractures and another had a radius fracture. That latter subject also had an elective total hip replacement. Another patient had an elective total knee replacement. One subject had an abdominal surgery for lysis of adhesions, another had chest pain requiring coronary artery stent placement and another had a cerebral transient ischemic attack. No hypercalcemia was seen and there were no subjects who had excessive bone loss confirmed on a second BMD measurement.

4. Discussion

The hypothesis underlying this study was that cyclic administration might be a more effective way to build skeletal mass rather than daily therapy for 2 years, based on the concepts of maximizing formation over resorption and avoiding skeletal tachyphylaxis to TPTD with short therapy cycles. In our prior manuscript, based on the 2 year parent study [22], we showed that TPTD administered either daily or cyclically over 24 months in both Rx-Naïve and ALN-Rx women increased BMD in the spine and hip, and decreased BMD in the radius. In Rx-Naïve women, BMD gains in the spine were consistent with the 50% lower cumulative dose of TPTD medication administered at that time. In contrast, in the setting of ongoing ALN treatment, cyclic TPTD over 24 months produced a similar BMD gain to daily treatment despite the 50% lower total dose of TPTD given. The data presented here from the 2 year extension indicate that continued biochemical responses were seen during all of the 3 month TPTD cycles over 48 months. These were associated with continued gains in spine and hip BMD in the Cyclic groups (both Rx-Naïve and ALN-Rx) during the latter 2 years. However, overall in both the Rx-Naïve and ALN-Rx cohorts, considering either the primary (*equal TPTD dose*) or secondary analyses (*equal treatment time-48 months*), cyclic administration did not benefit BMD more than daily administration. Therefore, our original hypothesis was not supported; there is no apparent BMD advantage to administering TPTD cyclically.

It is notable that in the Rx-Naïve cohort, in total over the 4 year study, the Daily group had 2 years of ALN treatment in addition to 2 years of TPTD treatment, whereas the Cyclic group had only the equivalent of 2 years of TPTD. (Five subjects actually received zoledronic acid instead of ALN), Therefore, one might expect greater BMD accrual in the Daily group after 4 years, just due to the addition of ALN (or Zoledronic Acid). It is tempting to speculate that BMD might increase more in the Cyclic group over a subsequent 2 years of newly administered ALN therapy, compared with the BMD plateau expected with continued ALN in the Daily group, if continued, from years 4–6. However, our hypothesis predicted greater effects in Cyclic treated patients over 4 years and these were not seen. Furthermore, our protocol did not include further treatment or observation beyond 4 years.

The 3 month cycle length chosen for this study was based on the original observation that the greatest gain in bone mass would likely be achieved during the time that formation is maximally stimulated with less stimulation of resorption. It is certainly possible that other cyclic regimens involving a longer cycle length (for example, six months) would still be valid regimens to try to maximize BMD gains. It is also possible that the lack of continued stimulation of osteoblast activity during the 3 month off period allows bone resorption to dominate
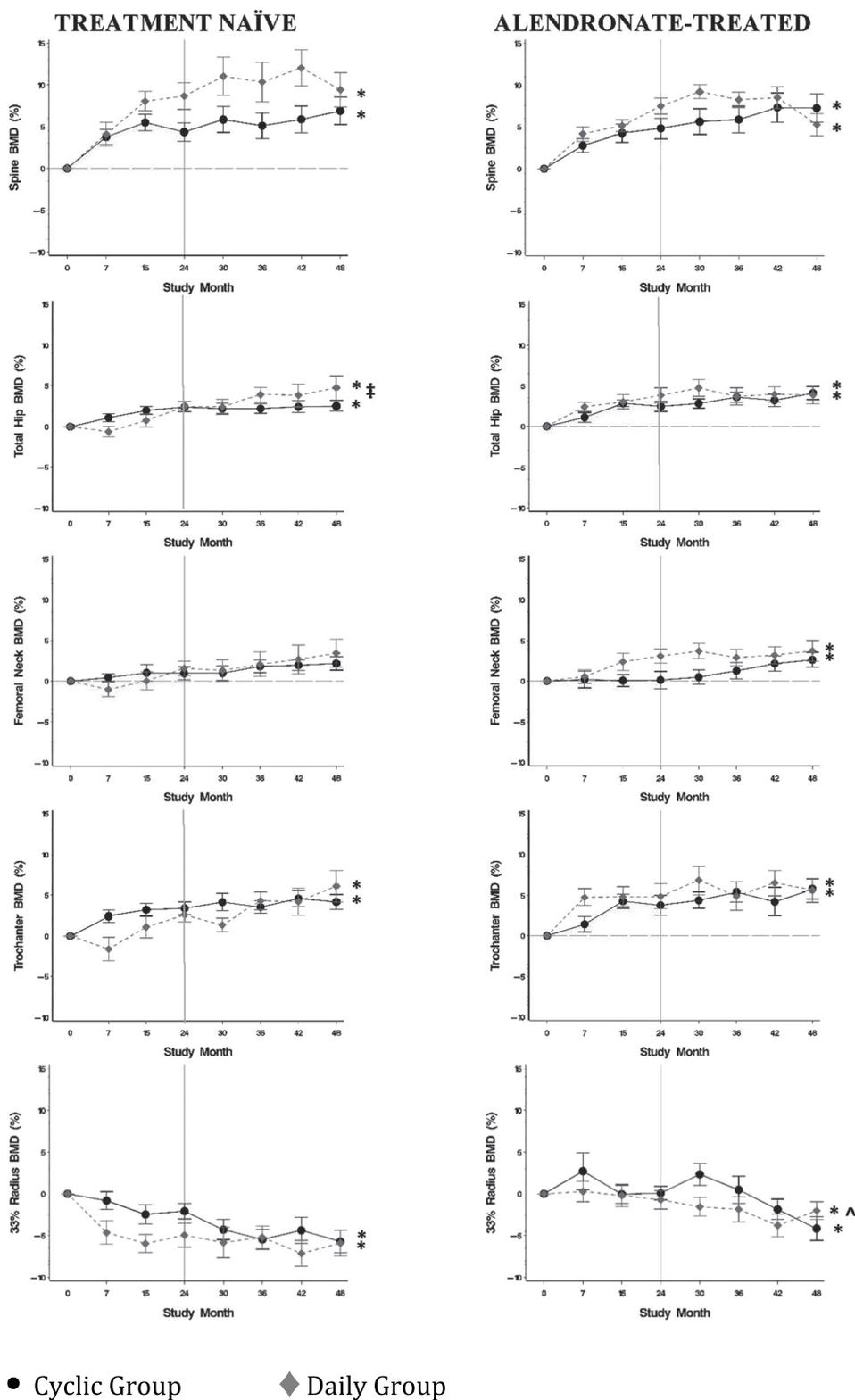
Fig. 3. Bone density (by DXA) percent changes during TPTD treatment given daily or cyclically over 2 years in Rx-naïve women (left column) and ALN-RX women (right column) for different skeletal sites (from top to bottom: LS, TH, FN, TR, RAD).

* p < 0.05 for differences from baseline within each group over 48 months.

‡ p < 0.01 group difference between cyclic and daily at 48 months (*equal time*).

^ p < 0.05 for 24 months daily vs. 48 months cyclic (*equal dose*).

during the off cycle, and bone loss occurs during those intervals, mitigating overall BMD accrual. In ALN-Rx patients, ongoing ALN protects against bone loss during the off-TPTD cycle and helps dampen the more prominent pulsatile gains and losses seen in individuals who are not on underlying antiresorptive therapy. A greater degree of secondary mineralization might also occur during the off cycles in patients on ALN with overall slower bone remodeling rate. Providing a short term antiresorptive agent only during the off-TPTD cycle, might help enhance gains with cyclic treatment. Indeed we have a separate ongoing trial with this study design, evaluating sequential vs. cyclic TPTD and denosumab.

This study included two totally separate cohorts and was not designed primarily to compare effects across cohorts. Nevertheless, there are some interesting observations. In the spine, comparing Rx-Naïve and ALN-Rx individuals who received Daily TPTD therapy at 2-years, there was a only a 15% greater BMD gain in the Rx-Naïve vs. ALN-Rx cohorts (8.6% in Rx-Naive vs. 7.5% in ALN-Rx). In addition, hip BMD increments (total and subregions) with Daily TPTD treatment were actually greater in ALN-Rx compared with Rx-Naïve women. This is consistent with prior studies [3,23] suggesting that ongoing ALN with TPTD added does not blunt the effect on hip BMD, but in contrast, might enhance the effect of TPTD in the hip region [6,24], especially compared to switching from bisphosphonates to TPTD [24,25]. These observations could potentially extend to ongoing treatment with denosumab as well, where BMD declines prominently in the hip region in patients who switch to TPTD [26]. Similarly, RAD BMD decline was mitigated in ALN-Rx individuals compared with Rx-Naïve women when comparing groups that received daily treatment. Interestingly when comparing the Cyclic groups across cohorts, BMD changes uniformly favored the ALN-Rx group at all skeletal sites. This suggests that the antiresorptive is needed to protect the skeleton during the off-TPTD cycles. Again, this could portend positively for alternative study designs with cyclic TPTD and antiresorptive therapy.

The limitations of this study include a small sample size with limited power to ascertain small differences in BMD and no power to evaluate fracture outcomes. The latter would require a very large study since all patients received potent therapy over the 4 year trial. Because the two cohorts (Rx-Naïve and ALN-Rx) were not randomized, we must be cautious about conclusions drawn from cross cohort comparisons. Analyses were done only on completers because of the known interindividual variability in BMD and the relatively small groups in the study. The strengths of our investigation include fairly good study retention with 75% of the group that completed the parent study entering the extension study (with no differences in characteristics between the extension cohort and the full population) and 83% of those who entered the extension, completing it. The study was randomized for the main outcomes assessed and allowed us to reject our hypothesis regarding cyclic therapy.

In conclusion, our final 4 year data from this study evaluating Daily vs. Cyclic therapy in 2 cohorts of women suggest that there is no significant difference in ultimate effect on either spine or hip BMD when TPTD is administered cyclically over 4 years compared to a standard approach where TPTD is given daily for 2 years, followed by ALN for 2 subsequent years. Notably, however, there is no clear disadvantage to cyclic administration of TPTD. For some patients, there could be economic or compliance issues, for which cyclic TPTD administration might be advantageous. Furthermore, since patients who have an atypical femur fracture avoid potent antiresorptive therapy, there may be a benefit to prolonging their anabolic treatment course to 4 years given cyclically, rather than 2 years- given the likely absence of post TPTD follow-up therapy. However, in general, we would not recommend cyclic TPTD administration to achieve greater BMD gain compared with the standard approved therapeutic approach.

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