Biomarkers of Bone Remodeling in Multiple Myeloma Patients to Tailor Bisphosphonate Therapy

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Running title

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*Statement of Translational Relevance*

Aminobisphosphonates (aBPs), such as zoledronate or pamidronate, are highly effective in preventing skeletal-related events in patients with multiple myeloma and solid tumors with bone metastases. aBPs are dosed monthly based on the suppression of NTX, a marker of bone resorption correlated with bone-related morbidity and mortality in cancer patients. NTX levels are suppressed for 4-8 weeks following a single dose of aBP. However, the long-term use of aBPs has highlighted osteonecrosis of the jaw and stress fractures as possible consequences of aBP-related oversuppression of bone-remodeling. Our study found that NTX levels remained stable in the 6 months following cessation of aBPs in 28 of 29 multiple myeloma patients previously treated with aBPs for at least 8-12 doses, suggesting that less frequent dosing of aBPs is feasible.
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Abstract

Background

Multiple myeloma (MM) patients may be susceptible to osteonecrosis of the jaw (ONJ) and stress fractures due to long-term aminobisphosphonate (aBP) therapy. However, it is unknown whether NTX or other bone biomarkers are predictive of skeletal-related events (SRE) or the impact of cessation of aBP therapy on bone remodeling.

Methods

We studied markers of bone turnover over a 6-month period after a single dose of zoledronic acid in 29 MM patients in remission who previously received 8-12 doses of pamidronate or zoledronate (NCT00577642). Our primary objective was to determine the duration of time urinary NTX levels remain suppressed after a single dose of zoledronate. A secondary objective was to identify and correlate other markers of bone remodeling with NTX changes. Thirty cytokines, based on their possible role in bone remodeling, were tested using cytokine arrays. Candidates were confirmed by ELISA.

Results

All patients had continued suppression of NTX levels, except one patient who had an increase in NTX levels associated with an SRE. GDF-15 and decorin were found to decrease, while bone-specific alkaline phosphatase (BSALP) increased. Although not significant in aggregate, osteopontin and osteoprotegerin levels increased in at least half of the patients.
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Conclusion

Our data show that NTX levels continue to be suppressed after aBP therapy and suggest that suppressed NTX levels may be predictive of freedom from SRE in this patient population. Furthermore, osteoblast suppression by aBP may be reversible in myeloma. This data provide the basis for less frequent dosing of aBPs.
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Introduction

Aminobisphosphonates (aBPs) such as zoledronate and pamidronate are a mainstay of treatment of multiple myeloma (MM) and metastatic solid tumors to prevent bone-related morbidity and mortality (1, 2). For MM, most recent consensus guidelines recommend monthly aBP treatment for a period of 2 years (3, 4). However, it is unknown if monthly dosing of aBPs is optimal, as there are consequences of long-term aBP therapy, such as osteonecrosis of the jaw (ONJ) and atypical stress fractures (3-9). Bisphosphonate-related ONJ is characterized by bone that is necrotic and exposed, located in the maxillofacial area, and present for at least 8 weeks in a patient with history of bisphosphonate treatment, but no history of prior radiation to that area (10). While varying incidences of ONJ between 0.94% to 18.6% have been reported, in a longitudinal cohort study, MM patients were more likely to develop ONJ than breast or prostate cancer patients (11). It is thought that ONJ results from oversuppression of bone remodeling by aBPs (12). As overall survival of MM patients has improved, they are exposed to aBPs for longer periods of time, making the issue of optimal aBP dosing even more pertinent.

The pharmacodynamic and pharmacokinetic data of aBPs is limited as these compounds incorporate directly into the bone matrix, targeting osteoclast farnesyl pyrophosphate synthetase and inhibiting protein prenylation (13). The half-life of aBPs in bone is long and on the order of 240 days with zoledronate (14). The activity of aBP can be monitored via surrogates such as urinary N-telopeptide (NTX). The monthly dosing of aBPs is based on the suppression of NTX for 4 to 8 weeks following a single dose of aBP (15, 16). In the context of the bone-related sequelae of long-term aBP therapy, we sought to examine bone remodeling after cessation of long-term aBP therapy for a period of 6 months in MM patients in complete or partial remission with 8-12 prior doses of aBPs. A six-month duration of follow-up was chosen as it is reasonably
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greater than the current monthly aBP dosing interval to be able to document the clinical effects of aBP cessation, yet short enough to minimize the previously uncertain risk of aBP cessation to enrolled patients. We also evaluated if NTX or other potential surrogate markers of aBP activity are predictive of skeletal-related events (SREs) in these patients.

Materials and methods

Patients and study design

Patients were enrolled at Massachusetts General Hospital and Dana-Farber Cancer Institute after study approval by the Institutional Review Board and informed consent. This trial is registered at www.clinicaltrials.gov as NCT00577642. The inclusion criteria were age at least 18 years, confirmed diagnosis of MM by International Myeloma Working Group (IMWG) criteria, intravenous bisphosphonate therapy with either pamidronate or zoledronate for 8-12 months, complete response or partial response by European Blood and Marrow Transplantation (EBMT) criteria, and Eastern Cooperative Oncology Group (ECOG) performance status \( \leq 2 \). Patients were excluded if they were on active anti-MM therapy, renal dysfunction with serum creatinine > 2 mg/dL and/or creatinine clearance of < 30 mL/min; or had relapsed, refractory or progressive disease. Maintenance therapy for MM was allowed on study.

At entry into study, patients underwent measurement of urinary NTX (Quest Diagnostics), banking of serum, bone marrow aspiration and core biopsy, and skeletal survey. Patients were then given a single dose of zoledronate 4 mg or adjusted according to institutional guidelines of creatinine clearance, and then followed over a period of 6 months. No further aBP therapy was allowed during the study. Each month, urinary NTX was followed and serum was banked. In
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In our study, if NTX surpassed a threshold of 50 nmol/mmol Cr, or there was disease progression or an SRE, patients were removed from the study. At the end of the study, the testing done at entry was repeated.

**Assay methods**

Antibody-based cytokine arrays were used to evaluate serum samples as per manufacturer protocol (RayBiotech, Inc., Norcross, GA). Thirty cytokines were curated from the literature as being most relevant to the bone microenvironment for inclusion on the array. For bone biomarkers not available on the array, ELISA was used: C-terminal telopeptide of type I collagen (CTX-1), amino-terminal propeptide of type I collagen (P1NP), sclerostin, soluble receptor activator of NF-κB ligand (sRANKL), and bone-specific alkaline phosphatase (BSALP). ELISAs were performed according to the manufacturer protocols supplied with the kits: CTX-1 and P1NP (TSZ ELISA, Waltham, MA), sclerostin (ALPCO, Salem, NH), sRANKL (Antigenix America, Huntington Station, NY), decorin (RayBiotech, Inc., Norcross, GA), BSALP (Quidel, Santa Clara, CA), and activin A and GDF-15 (R & D Systems, Minneapolis, MN).

**Statistical analysis methods**

Paired t-tests were used to compare differences of cytokine levels at study entry v. end-of-study. For antibody-based cytokine array, fluorescence intensities were computed by normalization of fluorescence values using software from the array manufacturer and then log-transformed. Fluorescence intensities without log transformation are reported. GDF-15, decorin, and activin A were selected for validation by ELISA.
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Results

Baseline characteristics are shown in Table 1. Twenty-nine patients were enrolled in the study. Median age at entry into the study was 60 years (range of 46 to 85 years). Most patients had received a combination of drugs including bortezomib and lenalidomide (14 patients) or bortezomib in combination with other drugs (10 patients). Five patients received regimens that did not include bortezomib. Ten of 29 patients in the trial were on maintenance therapy (lenalidomide, 5; thalidomide, 4; bortezomib, 1). The mean time between diagnosis and enrollment on the trial was 13 months. The majority of patients had more than three lytic lesions. No patients had appreciable increase in bone lesions over the course of the study.

The mean urine NTX level was 22.2 nmol/mmol Cr at baseline (Figure 1). All patients had an NTX level at baseline less than 50 nmol/mmol Cr except for one patient, whose baseline was 82 nmol/mmol Cr. A paired t-test comparing NTX levels at earliest and latest available time points in the study for each patient showed a mean increase of only 1.5 nmol/mmol Cr that was not significant (p = 0.38). There was no difference in change in NTX levels in patients on maintenance treatment v. patients on observation alone. The one patient with baseline NTX level of 82 nmol/mmol Cr remained on the study until month 3, as NTX first decreased to 32 nmol/mmol Cr before climbing to 90 nmol/mmol Cr. This patient developed hypercalcemia, which was categorized as an SRE. Another patient showed evidence of disease progression by rising monoclonal protein, without elevated NTX level nor SRE. This patient was removed from study at month 5.

Given that NTX levels did not significantly change during the 6-month duration, we studied cytokine levels at baseline and end-of-study using ELISA and antibody-based cytokine arrays.
CTX-1, P1NP, sclerostin, and sRANKL had no significant differences between baseline and end-of-study when tested by ELISA. BSALP had a mean increase of 2.26 U/L (p = 0.003) from baseline to end of study.

The results of the antibody-based cytokine array are shown in Table 2. Although osteopontin and osteoprotegerin were not significant in aggregate, at least half of patients had an increase in these cytokines. Based on the cytokine array results and potential biological relevance, we selected GDF-15, decorin, and activin A for validation by ELISA. Activin A showed no significant difference (p = 0.980), whereas mean GDF-15 level decreased by 231 pg/ml (p = 0.00053) and mean decorin level decreased by 701 pg/ml (p = 0.00025). Waterfall plots for the three significant cytokines measured by ELISA, GDF-15, decorin, and BSALP, are shown in Figure 2.

Discussion

The impact of aBP cessation among MM patients who have achieved a clinical response on urine NTX, the key marker that was employed to originally dose aBPs, heretofore has not been studied. In a study of over 1800 patients with metastatic cancer treated with aBPs, patients with urinary NTX greater than 99 nmol/mmol Cr or 50-99 nmol/mmol Cr have 4-6 and 2-4 times increased risk of SRE, respectively, as compared to patients with NTX less than 50 nmol/mmol Cr (17). However, it is unclear what happens to the association between NTX and SREs with cessation of aBP therapy.

Our study reveals that urine NTX remains suppressed in patients who had a complete or partial response to MM therapy and who had suppressed NTX at baseline (<50 nmol/mmol Cr). This
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observation extends on previous studies showing that patients who respond to anti-myeloma therapy have significant reduction in bone resorption markers (18-20). In a recent study of patients who were consolidated with bortezomib thalidomide, and dexamethasone and who did not receive subsequent bisphosphonate therapy, SREs were uncommon (21). In our study, almost a third of patients in our study were on maintenance therapy, and this may have played a part in suppression of NTX. The one patient who had elevated NTX at baseline later went on to have an SRE. Suppressed NTX may therefore be predictive of freedom from SRE in patients who are in remission, but not necessarily freedom from MM disease progression, as one patient with suppressed NTX was removed from study for disease progression based on monoclonal protein elevation. Although our findings are based on a small sample size, they suggest that the effects of long-term aBP therapy last well beyond 1 month, the current aBP dosing interval.

Of note, the Z-MARK study in MM patients previously treated with 1-2 years of aBPs found that changing the dosing interval of zoledronate from 1 to 3 months based on suppressed NTX levels appears to be safe for patients and only 3.3% of patients experienced an SRE, indicating that SRE risk was not any greater than reported previously in the literature (22). Patients who remained in the 3 month interval dosing group throughout the study were less likely to discontinue aBP treatment and less likely to experience a serious adverse event.

Given that numerous cytokines have been postulated to be involved in the bone marrow microenvironment, we wished to see if a select number of these changed from baseline to end-of-study and if any of these may be suitable surrogates for aBP activity, in addition to urine NTX. BSALP has been shown to increase in patients treated with bortezomib-containing regimens (23, 24), although the effect may be temporary (25). It has been thought that such rise of BSALP may signal possible osteoblast activity with concomitant bone healing (25). In this study, 64%
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of patients (18 of 28) had an increase in BSALP, indicating that osteoblast recovery may be possible with cessation of long-term aBP therapy. There is some evidence that there is increase in osteopontin and osteoprotegerin, which increased in about half of patients, although the results were not significant. Osteoblasts secrete osteoprotegerin, a member of the tumor necrosis receptor super-family, which acts as a negative regulator of osteoclast differentiation by serving as a decoy receptor for RANKL (26). On the other hand, osteopontin, a ligand for endothelial cell αVβ3 integrin, is secreted by osteoclasts and may enhance endothelial cell mediated osteoclastic bone resorption and angiogenesis (27).

GDF-15, a member of the TGF-β superfamily, has been shown to increase during progression of a number of solid malignancies, but there is also evidence that GDF-15 is upregulated by a number of tumor suppressor pathways (28). In MM, GDF-15 appears to be secreted from bone marrow mesenchymal stem cells (29). MM patients with higher levels of GDF-15 have worse event-free survival compared to patients with lower levels of GDF-15 (30). The exact physiologic role of GDF-15 in myeloma is yet to be defined. The cessation of long-term aBP therapy led to a decrease in GDF-15 in this study, potentially conferring a better prognosis, but further research is needed to elucidate the role of GDF-15 in this context.

Decorin, a small-leucine rich proteoglycan secreted by mesenchymal stem cells and osteoblasts, appears to inhibit angiogenesis and osteoclastogenesis (31). Knockdown of decorin has been shown to increase primary myeloma cell survival (31). In monoclonal gammopathy of unknown significance (MGUS) and MM patients, decorin has been shown to be downregulated as compared to healthy volunteers (32). Thus, given that decorin seems to reduce survival of myeloma cells, the decrease in decorin at the end of study warrants further study. Our group is currently investigating the change in decorin expression with differentiation of osteoblasts and...
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the effect of recombinant decorin on both osteoblasts and primary myeloma cells. This data further underscores the continued use of aBPs, although less frequent dosing is potentially feasible.

While involving a small number of patients, our study suggests that suppressed NTX levels may be predictive of freedom from SRE among patients in response to MM therapy, over a period of 6 months. Furthermore, osteoblast suppression by aBPs is reversible in myeloma, as indicated by the significant rise in BSALP. Importantly, the role of other surrogates such as decorin and GDF-15 need further validation and are the subject of ongoing studies. Taken together, these findings may provide a rationale for less frequent aBP dosing in MM patients with at least a partial response to primary myeloma therapy to help lower the incidence of long term toxicities such as ONJ and stress fractures, by allowing limited recovery of bone remodeling without adverse effects on MM progression.

Acknowledgements

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References

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Tables

Table 1. Baseline Characteristics of Enrolled Multiple Myeloma Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number</th>
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<tr>
<td>Age</td>
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<td>≥65</td>
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<tr>
<td>&lt;65</td>
<td>19</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Male</td>
<td>16</td>
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<tr>
<td>Female</td>
<td>13</td>
</tr>
<tr>
<td>ISS Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>11</td>
</tr>
<tr>
<td>II</td>
<td>9</td>
</tr>
<tr>
<td>III</td>
<td>9</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
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<tr>
<td>Bortezomib + lenalidomide</td>
<td>14</td>
</tr>
<tr>
<td>Bortezomib + other</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
</tr>
<tr>
<td>Autologous Transplant</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
</tr>
<tr>
<td>No</td>
<td>16</td>
</tr>
<tr>
<td>Bone lesions</td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td>20</td>
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<tr>
<td>≤3</td>
<td>9</td>
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### Table 2. Cytokine Array. Change at End-of-Study Relative to Baseline

<table>
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<tr>
<th>Cytokine</th>
<th>Baseline</th>
<th>End-of-study</th>
<th>%change</th>
<th>p value</th>
<th>FDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activin A</td>
<td>96 ± 17</td>
<td>135 ± 36</td>
<td>41.2</td>
<td>0.0384</td>
<td>0.345</td>
</tr>
<tr>
<td>BDNF</td>
<td>605 ± 88</td>
<td>684 ± 81</td>
<td>13</td>
<td>0.184</td>
<td>0.402</td>
</tr>
<tr>
<td>BMP-7</td>
<td>440 ± 33</td>
<td>471 ± 24</td>
<td>6.9</td>
<td>0.0791</td>
<td>0.402</td>
</tr>
<tr>
<td>Decorin</td>
<td>4113 ± 240</td>
<td>3669 ± 239</td>
<td>−10.8</td>
<td>0.276</td>
<td>0.439</td>
</tr>
<tr>
<td>DKK1</td>
<td>451 ± 33</td>
<td>430 ± 32</td>
<td>−4.7</td>
<td>0.382</td>
<td>0.573</td>
</tr>
<tr>
<td>GDF15</td>
<td>3928 ± 427</td>
<td>3127 ± 322</td>
<td>−20.4</td>
<td>0.00183</td>
<td>0.0493</td>
</tr>
<tr>
<td>HGF</td>
<td>313 ± 132</td>
<td>304 ± 84</td>
<td>−3.1</td>
<td>0.109</td>
<td>0.402</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>2522 ± 1359</td>
<td>2224 ± 981</td>
<td>−11.8</td>
<td>0.074</td>
<td>0.402</td>
</tr>
<tr>
<td>IGF-1</td>
<td>152 ± 10</td>
<td>157 ± 7</td>
<td>3.6</td>
<td>0.483</td>
<td>0.653</td>
</tr>
<tr>
<td>IGFBP3</td>
<td>336 ± 34</td>
<td>318 ± 25</td>
<td>−5.4</td>
<td>0.889</td>
<td>0.923</td>
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<tr>
<td>IL-3</td>
<td>435 ± 30</td>
<td>478 ± 27</td>
<td>10</td>
<td>0.136</td>
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<tr>
<td>IL-1α</td>
<td>1049 ± 82</td>
<td>1038 ± 77</td>
<td>−1.1</td>
<td>0.799</td>
<td>0.899</td>
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<tr>
<td>IL-1β</td>
<td>215 ± 15</td>
<td>236 ± 16</td>
<td>9.6</td>
<td>0.12</td>
<td>0.402</td>
</tr>
<tr>
<td>IL-6</td>
<td>1103 ± 85</td>
<td>1098 ± 83</td>
<td>−0.5</td>
<td>0.862</td>
<td>0.923</td>
</tr>
<tr>
<td>IL-7</td>
<td>1076 ± 77</td>
<td>1124 ± 71</td>
<td>4.5</td>
<td>0.238</td>
<td>0.431</td>
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<tr>
<td>IL-8</td>
<td>1190 ± 235</td>
<td>1036 ± 70</td>
<td>−13</td>
<td>0.963</td>
<td>0.963</td>
</tr>
<tr>
<td>MCSF</td>
<td>207 ± 18</td>
<td>191 ± 14</td>
<td>−8</td>
<td>0.547</td>
<td>0.703</td>
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<tr>
<td>MIP-1α</td>
<td>175 ± 17</td>
<td>188 ± 20</td>
<td>7.4</td>
<td>0.643</td>
<td>0.789</td>
</tr>
<tr>
<td>MMP-9</td>
<td>10346 ± 2171</td>
<td>8644 ± 2525</td>
<td>−16.5</td>
<td>0.403</td>
<td>0.573</td>
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<tr>
<td>Osteopontin</td>
<td>1466 ± 238</td>
<td>1507 ± 157</td>
<td>2.8</td>
<td>0.267</td>
<td>0.439</td>
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<tr>
<td>Osteoprotegerin</td>
<td>142 ± 10</td>
<td>157 ± 12</td>
<td>10.9</td>
<td>0.193</td>
<td>0.402</td>
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<tr>
<td>Procalcitonin</td>
<td>443 ± 45</td>
<td>384 ± 35</td>
<td>−13.3</td>
<td>0.0254</td>
<td>0.343</td>
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<tr>
<td>TGF-β1</td>
<td>1079 ± 67</td>
<td>1185 ± 83</td>
<td>9.8</td>
<td>0.173</td>
<td>0.402</td>
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<tr>
<td>VCAM-1</td>
<td>2389 ± 189</td>
<td>2562 ± 179</td>
<td>7.3</td>
<td>0.24</td>
<td>0.431</td>
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<tr>
<td>VEGF</td>
<td>216 ± 22</td>
<td>201 ± 14</td>
<td>−7</td>
<td>0.742</td>
<td>0.871</td>
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<tr>
<td>VEGF-C</td>
<td>352 ± 39</td>
<td>302 ± 23</td>
<td>−14.2</td>
<td>0.185</td>
<td>0.402</td>
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<td>VEGF-D</td>
<td>196 ± 11</td>
<td>179 ± 12</td>
<td>−8.6</td>
<td>0.182</td>
<td>0.402</td>
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</table>

Values reported are mean relative fluorescence units ± SE in 21 out of 28 patients. P values are from paired t-tests of log-transformed measurements. BMP-4, MIP-3α, SDF-1α are not reported; measurements were not above baseline. Of note, comparisons of cytokine measurements may not necessarily be directly possible from this platform.
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Figure legends

Figure 1. Urine NTX levels by month

Urine NTX levels were measured monthly. There was no significant change in NTX throughout the study. Blue bars indicate mean measurements. One patient (gray circle) had elevated urine NTX at baseline and later developed hypercalcemia, which was classified as an SRE.

Figure 2. Change at end-of-study compared to baseline for selected biomarkers.

Selected biomarkers were measured by ELISA at baseline and end-of-study. Data for GDF-15, decorin, and BSALP (bone-specific alkaline phosphatase) are shown as waterfall plots. Horizontal line indicates mean difference from baseline to end-of-study. P values are from paired t tests.
Figure 1
Figure 2

GDF-15

p = 0.000531

decorin

p = 0.000253

BSALP

p = 0.00304
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