Severe Osteopenia in a Young Boy With Kostmann’s Congenital Neutropenia Treated With Granulocyte Colony-Stimulating Factor: Suggested Therapeutic Approach

Rajagopal V. Sekhar, MD*; Steven Culbert, MD‡; W. Keith Hoots, MD‡; Mary J. Klein, RN*; Hallie Zietz, RN‡; and Rena Vassilopoulou-Sellin, MD*

ABSTRACT. Kostmann’s syndrome is a congenital disorder that causes an impairment of myeloid differentiation in the bone marrow characterized by severe neutropenia, which can be treated with recombinant human granulocyte colony-stimulating factor (G-CSF). We present the case of a 13-year-old boy with Kostmann’s syndrome who was treated with recombinant human G-CSF from age 3.5 years. His growth and development was normal, although complicated by intermittent infections. Bone mineral density (BMD) measurement revealed severe osteopenia at the spine and hips (lumbar spine BMD 0.486 g/cm²; Z score −3.6), and he was referred to the Endocrine Service. Relevant laboratory evaluation showed a pretreatment ionized calcium level at the upper limit of normal (1.28 mmol/L; range: 1.13–1.32 mmol/L), suppressed intact parathyroid hormone (iPTH) level (12 pg/mL; range: 10–65 pg/mL), and a low 1,25-dihydroxy vitamin D level (21 pg/mL; range: 24–65 pg/mL). He had evidence of increased bone turnover evidenced by elevated urinary deoxypyridinoline (DPD) cross-links (46.9 nmol/mmol creatinine; range: 2–34 nmol/mmol creatinine) and a simultaneous increase in markers of bone formation with elevated osteocalcin level (200 ng/mL; normal: 20–80 ng/mL) and alkaline phosphatase level (236 IU/mL; normal: 36–126 IU/mL). Because of clinical concern for his skeletal health, bisphosphonate therapy with intravenous pamidronate was initiated. One month after treatment, the iPTH and DPD cross-links were in the normal range (54 pg/mL and 17.7 nmol/mmol creatinine, respectively) and the 1,25-dihydroxy vitamin D level was elevated (111 pg/mL). Four months after treatment, there was a striking increase in BMD at the lumbar spine (+30.86%), femoral necks (left, +20.02%; right, +17.98%), and total hips (left, +18.40%; right, +15.94%). Seven months after bisphosphonate therapy, his biochemical parameters showed a return toward pretreatment levels with increasing urinary DPD cross-links (28.7 nmol/mmol creatinine) and decreasing iPTH (26 pg/mL). However, the BMD continued to increase (8 months posttreatment), but the magnitude of the increment was attenuated (lumbar-spine, +4.8%; left total hip, +1.2% and right total hip +2.4%), relative to BMD at 4 months. Eight months after the initial treatment, his iPTH was suppressed at 14 pg/mL and he again received pamidronate (at a lower dose); 3 months later, he had an additional increase in BMD (lumbar spine +7.4%, left total hip +3.9%, right total hip +2.7%), relative to the previous study. We hypothesize that prolonged administration of G-CSF as treatment for Kostmann’s syndrome is associated with increased bone resorption, mediated by osteoclast activation and leading to bone loss. In children, the resulting osteopenia can be successfully managed with antiresorptive bisphosphonate therapy with significant improvement in bone density. Measurements of biochemical parameters of bone turnover can be used to monitor the magnitude and duration of the therapeutic response and the need for BMD reassessment and, perhaps, retreatment. Pediatrics 2001;108(3).

ABBREVIATIONS. G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; BMD, bone mineral density; iPTH, intact parathyroid hormone; DPD, deoxypyridinoline; ANC, absolute neutrophil count; M-CSF, macrophage colony-stimulating factor; OPG-L/ODF, osteoprotegerin ligand osteoclast differentiation factor.

Kostmann’s syndrome is a congenital, autosomal recessive disorder characterized by an arrest in the maturation of myeloid progenitor cells, leading to severe neutropenia and frequent severe bacterial infections.1 Long-term treatment with the hematopoietic growth factor recombinant human granulocyte colony-stimulating factor (G-CSF) is the current treatment used to elevate neutrophil counts to the normal range and reduce the incidence of infections.1 However, the use of recombinant human G-CSF has been associated with bone loss in recent animal studies2–5 and clinical reports.6–9 Although increased bone resorption has been considered, the cause of bone loss remains unclear, and the efficacy of antiresorptive therapies in children has not been well-documented. In addition, appropriate strategies for the long-term surveillance of skeletal health are not defined. We had the opportunity to evaluate and treat a young boy with Kostmann’s syndrome and on G-CSF therapy, who presented to our clinic with severe osteoporosis. Here we discuss the potential mechanisms of bone loss, effective therapeutic approaches, and strategies used to monitor response to therapy.
CASE HISTORY
A 13-year-old white boy with severe osteopenia was referred to the Pediatric Endocrinology Clinic at M. D. Anderson Cancer Center. He had a history of Kostmann’s syndrome complicated by frequent bacterial infections. At the age of 2.8 years, he was briefly treated with granulocyte-macrophage colony stimulating factor (GM-CSF); however, GM-CSF was stopped after only 2 cycles because of adverse reactions. Nine months later, at the age of 3.5 years, he started treatment with G-CSF at a dose of 3 U/kg body weight twice daily (approximately 25 U BID) with excellent clinical response. G-CSF was continued over the next 9 years, with a significant improvement in neutrophil counts and reduction in the frequency and severity of bacterial infections. Over the years, the G-CSF dose was adjusted to keep the neutrophil counts within the normal range. As a young child, he exhibited physiologic growth and development, growing at the 5th percentile for age- and gender-adjusted height. At the time of initial endocrine evaluation, he had no unusual physical findings; his Tanner pubertal development was stage 1–2. His bone age was congruent with his chronologic age.

Skeletal evaluation with bone mineral density (BMD) was performed based on clinical concerns related to his treatment regimen. It revealed severe osteopenia at the lumbar spine (L-spine BMD 0.486 g/cm²; Z score −3.6). The average BMD of the femoral necks and total hips was 0.670 g/cm² and 0.745 g/cm², respectively; because of unavailability of validated standards, the BMD at the hips could not be compared with age- and gender-adjusted normals. Other causes of osteopenia in children such as malabsorption, steroid use, parathyroid disorders, vitamin D deficiency state, or immobilization were excluded by clinical history or laboratory tests. Pertinent laboratory tests are summarized in Table 1, and were interpreted as suggesting increased osteoclastic activity of the bone.

Because of the severity of osteopenia, and recent reports of successful therapeutic improvements of BMD in other children with increased bone resorption, the endocrine and pediatric medical teams in conjunction with the family agreed that intervention with antiresorptive therapy was appropriate. He received intravenous pamidronate at a dose of 3 mg/kg × 3 doses, as reported by Glorieux et al.10 Two weeks later, there was a striking response, with a decrease in ionized calcium (1.2 mmol/l), elevation of intact parathyroid hormone (iPTH) into the normal range (34 pg/mL), and six-fold rise in 1,25 vitamin D (120 pg/mL). Osteocalcin (153.9 ng/mL) and alkaline phosphatase (173 IU/L) levels fell, and there was a sharp decline in deoxypyridinoline (DPD) cross-links (17.7 nmol/mmol). These responses were maintained at similar levels up to 3 months (Table 1).

The BMD measurements were repeated 4 and 8 months after the first pamidronate infusion and showed significant increments at both the L-spine and the hips (Fig 1). Four months after treatment, BMD had increased by +30.86%, +23.8%, +20.02%, and +17.98% at the left and right femoral necks, respectively; and by +18.40% and +15.94% the left and right total hips respectfully. Between 4 and 7 months, the BMD was still increasing, but the improvement was attenuated at the L-spine (+4.8%), the femoral necks (left +0.49%, right −1.2%), and total hips (left +2.4%, right +1.2%). During this interval, there was a transient decrease in the absolute neutrophil count (ANC) without clinical consequences. A significant gain in height was also noted, coincident with a rise in serum testosterone levels (52 ng/mL at the time of treatment and 238 ng/mL 8 months later).

Biochemical measurements after 7 months revealed a trend toward the pretreatment levels with decreasing iPTH and increasing DPD cross-link levels. iPTH was again suppressed after 8 months (Table 1), and he again received pamidronate therapy but at a lower dose (60 mg).

Bone density measured at 11 months revealed an additional increase when compared with the previous study, at the lumbar spine (+7.4%) and both hips (right +2.7%, left +3.9%).

DISCUSSION
The prognosis of patients with severe congenital neutropenia has improved significantly with the availability of G-CSF therapy.1 Enthusiasm for this approach, however, has been recently tempered by the realization that significant bone loss may follow therapy.6,9,11 Bonilla et al11 reported osteoporosis in almost one third of children so treated. Bishop et al6 reported 1 child with biopsy evidence of enhanced bone resorption and good skeletal and auxologic response to anabolic steroid and bisphosphonate administration. This interpretation is corroborated by animal studies,2–5 and early-age exposure to G-CSF appears to be relevant.5 Information regarding the mechanism, response to therapy, and methods for monitoring patients long-term remains sparse.

Our patient presented with severe osteopenia associated with G-CSF treatment. We assessed markers of bone turnover over 11 months through 2 cycles of bisphosphonate intervention. Evaluation bone markers showed increased evidence of bone formation and resorption, with the latter outweighing the former, as evidenced by the magnitude of bone loss. Because of increased osteoclast-mediated bone resorption, there was a relative hypercalcemia resulting in appropriate suppression of iPTH, and 1,25-dihydroxy vitamin D, which further compromised calcium absorption. Although we were unable to collect 24-hour urine for calcium measurement from this boy, another boy with similar disease and G-CSF treatment background (who also had osteopenia and suppressed iPTH levels) had a urine calcium level of 300 mg/24 hours, consistent with this interpretation.

**Table 1.** Biochemical Parameters of Bone Turnover in a Young Boy With Kostmann’s Syndrome and Osteopenia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Range</th>
<th>Less Than 3 Months</th>
<th>Baseline*</th>
<th>More Than 1 Month</th>
<th>More Than 7 Months</th>
<th>More Than 8 Months</th>
<th>More Than 11 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH</td>
<td>10–65 pg/mL</td>
<td>12</td>
<td>&lt;10</td>
<td>34</td>
<td>26</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Vitamin D 1,25</td>
<td>24–65 pg/mL</td>
<td>21</td>
<td>120</td>
<td>79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D 25</td>
<td>17–54 ng/mL</td>
<td>53</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>8.4–10.2 mg/100 mL</td>
<td>9.5</td>
<td>10</td>
<td>9.4</td>
<td>9.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ionized calcium</td>
<td>1.13–1.32 mmol/L</td>
<td>1.28</td>
<td>1.2</td>
<td>1.14</td>
<td>1.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>2.5–4.5 mg/L</td>
<td>5.4</td>
<td>5.7</td>
<td>4.8</td>
<td>5.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>38–126</td>
<td>238</td>
<td>173</td>
<td>237</td>
<td>163</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>Tanner 1 M 20–89 ng/mL</td>
<td>160</td>
<td>186.3</td>
<td>153.9</td>
<td>135.5</td>
<td>153.1</td>
<td></td>
</tr>
<tr>
<td>DPD cross-links</td>
<td>2–34 nmol/mmol</td>
<td>46.9</td>
<td>17.7</td>
<td>28.7</td>
<td>14.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>10–20 mg/dL</td>
<td>1.7–7.3 K/UL</td>
<td>2.07</td>
<td>1.18</td>
<td>0.22</td>
<td>3.31</td>
<td>0.74</td>
</tr>
<tr>
<td>Testosterone</td>
<td>241–827 ng/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>1.7–7.3 K/UL</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

* Pamidronate was administered after baseline measurements.
† Change in laboratory performing test.
‡ Average of 4 available measurements.
After antiresorptive therapy, the biochemical abnormalities improved. Measurement of BMD after the first pamidronate course revealed an initial rapid rise, but this increment began to plateau after 4 months, with bone markers gradually drifting toward pretreatment levels, in association with a suppressed serum iPTH. Based on reversal of the bone markers and the attenuated increase in BMD, pamidronate therapy was repeated at a reduced dose. Over the next 3 months, there was an additional modest rise in BMD, with the lower rate of increment perhaps related to dose reduction.

G-CSF acts by stimulating the myeloid precursor cells thereby increasing neutrophil counts. The early stages of osteoclastogenesis proceed along a similar pathway as hematopoiesis, implying that the cytokines and colony-stimulating factors involved in hematopoiesis also govern osteoclast development. Studies of bone dynamics in murine models with overexpression of G-CSF in transgenic mice, or during parenteral administration in rats, have been shown to result in bone loss attributable to a tremendous increase in osteoclastic activity, with an inhibition of bone formation. The molecular mechanisms governing these changes are under investigation, and with specific relevance to bone loss, they seem to be mediated via the permissive effect of macrophage colony-stimulating factor (M-CSF) on the osteoprotegerin ligand osteoclast differentiation factor (OPG-L/ODF). Activation of OPG-L/ODF leads to osteoclast differentiation, enhancement of mature osteoclast activity, and inhibition of osteoclast apoptosis, all of which act in concert to increase bone resorption, and severe osteopenia has been observed after administration of OPG-L. It is possible that chronic stimulation of marrow stem cells by G-CSF in children over a prolonged period of time initiates a cascade of events that leads to osteopenia. However, G-CSF does not seem to influence the M-CSF pathway, implying that additional, yet undefined mechanisms may be involved in G-CSF mediated development of osteopenia.

Bisphosphonates represent a class of antiresorptive agents widely used for the treatment of osteoporosis, and in oncology, for the management of hypercalcemia and the control of skeletal destruction by neoplastic tissue suggesting that these agents may have additional complex effects in bone homeostasis. The effective use of bisphosphonates in children is mentioned with increasing frequency in recent case reports and small series primarily for treatment of osteogenesis imperfecta.

With the initial pamidronate therapy, we noted a transient decrease in the ANC in our patient, which may well have been related to poor compliance to G-CSF therapy during the school year, as his counts improved considerably when the G-CSF medication was turned over to health care personnel in summer camp. Nevertheless, given the complex interactions of bisphosphonates with marrow and bone metabolism, it is important to clarify whether they may have the potential to adversely affect the therapeutic benefit of growth factor therapy. Finally, we noted a significant improvement in height after pamidronate administration; such auxologic benefit was also described by Bishop et al because the patient’s serum testosterone level also rose during this period, his growth may be more related to coincident onset of puberty.

We suggest that chronic G-CSF administration in children may contribute to a sustained increase in bone resorption leading to impaired skeletal mass acquisition and consequent osteopenia. Pamidronate administration provided our patient with marked improvement of BMD and biochemical markers of bone turnover. This improvement was sustained for several months, and a similar, but attenuated response was observed after a second pamidronate infusion. Serial measurements of iPTH appear to be a simple and reliable way to monitor such patients, and when suppressed, additional evaluation and, perhaps, treatment may be initiated as clinically appropriate.
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