Denosumab Treatment of Severe Disuse Osteoporosis in a Boy With Spinal Muscular Atrophy

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Abstract- Denosumab is a fully human recombinant monoclonal antibody to the receptor activator of nuclear factor-κB ligand. Denosumab is used in the treatment of postmenopausal osteoporosis and cancer-related bone disorders. There are only very scarce data on denosumab treatment in children. 14-year-old boy with spinal muscular atrophy (SMA) and severe disuse osteoporosis (spinal bone mineral density L1-L4 BMD-6.2SD Z-score) and two prevalent fragility fractures was treated with denosumab. He received 60 mg subcutaneous injection at the baseline and seven months later. Six months after the initial injection there was a 19% increase in L1-L4 BMD. The injections were well tolerated without any adverse reactions. Calcemia remained stable (2.3-2.4 mmol/L). He was scheduled for the third denosumab injection six months later. Prior to this date, he acquired pneumonia and died due to respiratory failure, which is a frequent cause of death in patients with SMA. There was no relation to the denosumab treatment. In conclusion, one dose of denosumab significantly increased BMD in a child with severe osteoporosis.

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Keywords: Denosumab; Spinal muscular atrophy; Fractures; Bone; Osteoporosis; Bone mineral density

Introduction

Denosumab is a fully human recombinant monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL). In postmenopausal osteoporotic women subcutaneous (s.c.) denosumab administration of 60 mg every 6 months increases bone mineral density at the lumbar spine, total hip, and/or femoral neck, and significantly reduces markers of bone turnover, thus reducing the risk of vertebral, nonvertebral, and hip fractures (1,2). Denosumab is also marketed for the treatment of cancer-related bone disorders (1), where the dose of 120 mg is administered every month. There are only scarce data about denosumab treatment in children and adolescents with metabolic bone disease (3-11).

Case Report

A 14-year-old boy presented with severe disuse osteoporosis due to spinal muscular atrophy (SMA), where molecular biology analysis revealed SMA type II; exon 7 deletion in survival motoneuron-SMN1 gene). His mental status was normal. He was wheelchair-bound with severe muscle weakness, severe joint contractures of extremities, quadriparesis, kyphoscoliosis of the thoracic spine, swallowing difficulties and suffered from recurrent respiratory infections, all typical symptoms of SMA. He was short (120 cm, -4.6 SD-standard deviation) and underweight (21 kg, -2.9 SD) for age, his BMI was 14.6 (-1.7 SD). He was taking valproate (300 mg/day orally). In the past six months, he experienced two low-energy trauma fractures of the right femur and left tibia, respectively. His spinal bone mineral density (L1-L4 BMD) was very low (0.406 g/cm^{2,} i.e. -6.2 SD Z-score; DXA Lunar GE), regardless whether related to age- or height-adjusted BMD reference data. Serum calcium level (S-Ca) was 2.43 mmol/L, serum phosphate level (S-P) 1.4 mmol/L, serum alkaline phosphatase (S-ALP) 2.3 μkat/L (all normal), S-parathyroid hormone (S-PTH) 1.1 pmol/L (normal 1.1-5.8). With regard to the history of fractures and very low BMD, osteoporosis treatment was clearly indicated in this patient. However, intravenous bisphosphonates were out of the question due to patient´s personal history of poor tolerance to increased body temperature including convulsions that

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were triggered in the past by fever and even low-grade fever. Considering therapy with intravenous bisphosphonates, such as pamidronate or zoledronate, possible feverish flu-like reaction with imminent convulsions was anticipated. Furthermore, neither oral bisphosphonates could be applied, due to difficult swallowing and risk of consequent esophageal or gastric ulceration. In addition, the patient´s family rejected even short-time hospitalization necessary for intravenous bisphosphonate infusion. Therefore, denosumab treatment was considered and proposed, followed by the patient´s and parents´ consent. The patient was also maintained on oral 500-1000 mg calcium/day and 1000 IU cholecalciferol/day. On baseline, he received 60 mg of denosumab s.c. The injection was well tolerated, and there were no adverse reactions following the application. The following week his S-Ca was 2.3 mmol/L. Six months later his L1-L4 BMD has increased by 19% to 0.485 g/cm^2 (Z-score -5.8 SD). The biochemical data were: S-Ca 2.33 mmol/L, S-P 1.57 mmol/L, S-ALP 1.61 µkat/L, S-PTH 1.55 pmol/L (all normal) and he was scheduled for the second denosumab injection. Unfortunately, the same day he fell from the wheelchair on the concrete floor and broke his right femur. He received his second denosumab injection one month later (i.e. on month 7), without any complications. Following the injection, S-Ca was 2.3 mmol/L. He was scheduled for the third denosumab injection and control BMD measurement 6 months later. Unfortunately, just prior to the planned visit and third injection, he acquired pneumonia and consequently died within two days due to respiratory failure.

Discussion

SMA is characterized by degeneration of nerve cells (motor nuclei) within the lower brainstem, and anterior horn cells, leading to motoneuron loss, progressive and symmetric muscle weakness of the truncal and extremity muscles initially, followed by chewing, swallowing and breathing difficulties. SMA is classified by the age of clinical onset, and maximum motor function achieved. While type I SMA (Werdnig-Hoffmann disease), the most common subtype, is characterized by disease onset within 6 months of age and death within 2 years, the onset of type II SMA occurs between 6 and 18 months of age, and patients gain the ability to sit upright but not walk and they might survive until their teens (12). As a result of muscular atrophy and weakness, disuse osteoporosis is encountered in patients with SMA. Treatment of pediatric osteoporosis/bone fragility usually rests in the application of bisphosphonates either i.v. or p.o. (13). There are very scarce data consisting of few anecdotical reports on pediatric experience with denosumab. In the first report on denosumab application in a child, the drug was indicated to slow down rapid bone destruction in a 9-year-old boy with fibrous dysplasia (3). Furthermore, denosumab was successfully used to decrease metastatic giant-cell tumor of bone in a 10-year-old girl (4), and in the treatment of central giant cell granuloma of the mandible in two patients (5). Denosumab treatment also decreased the level of bone turnover markers in a girl with juvenile Paget's disease (6) and was also effective in the treatment of expansive aneurysmal bone cysts in 3 boys aged 8, 11 and 5 years, respectively (7,8). Denosumab was also used to treat four children with osteogenesis imperfecta type VI, decreasing rapid bone turnover and increasing BMD (9,10). In addition, denosumab was also applied to a child with post-bone-marrow-transplantation hypercalcemia in osteopetrosis (11).

Our patient with SMA could not be treated with bisphosphonates, as mentioned above. Therefore, we opted for s.c. denosumab 60 mg at six-monthly intervals. The dose of 60 mg (i.e., 3 mg/kg/dose) did correspond with the dose given at the same time by other authors to patients with giant cell tumors or fibrous dysplasia (3-6). At the time of the treatment, i.e., in the years 2011-2012, there were no reports on denosumab-triggered hypocalcemia and/or resulting secondary and tertiary hyperparathyroidism. Denosumab was well tolerated by our patient and resulted in a very impressive increase in BMD in just six months without any significant changes in serum calcium, phosphate, and PTH. The fracture he suffered on month 6 could be attributed to the high-energy trauma mechanism and still persisting very low BMD. His death was not related to the denosumab treatment, as respiratory failure is a frequent cause of death in patients with SMA (12).

One dose of s.c. denosumab significantly increased BMD in a child with severe disuse osteoporosis. Denosumab might present a suitable treatment option for children with bone fragility.

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