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COMMENTARY

Denosumab in a child with fibrous dysplasia of bone: too much of a good thing?

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Fibrous dysplasia (FD) of bone is a rare genetic non-inheritable bone disease leading to bone pain, fracture or deformity, and sometimes to neurological compression. It may be associated with endocrine manifestations, including peripheral precocious puberty, acromegaly or hyperthyroidism, along with cutaneous café-au-lait spots, also known as McCune–Albright syndrome (MAS). It is due to two types of postzygotic missense mutations in the gene coding for the α subunit of the stimulatory G-protein, Gs,[1,2] responsible for a somatic mosaic. The resulting proteins display reduced GTPase activity, leading to increased adenylyl cyclase activation,[3,4] and thus high levels of cyclic adenosine monophosphate (cAMP).[5,6] Activation of the Gsα/PKA/CREB pathway induces *c-fos* overexpression in FD lesions.[7] It has been suggested that increased cAMP might downregulate the osteoblastic transcription factor Runx2, thus contributing to abnormal osteoblastic differentiation.[8] In those osteoblastic cells, interleukin (IL)-6 secretion is increased as a result of Gs activation, with consequent activation of surrounding osteoclasts, allowing the FD lesion to expand and create osteolytic lesions.[5] The resulting presence of abundant osteoclastic bone resorption within and around the fibrous tissue has been the rationale to treat FD with antiresorptive agents. Therefore, bisphosphonates have been widely used in the treatment of FD over the last 15 years.[9]

Receptor activator of nuclear factor kappa-B ligand (RANKL) expression is potently upregulated among human skeletal progenitors expressing R201C-mutated, constitutively active Gsα, using lentiviral vectors, in association with the osteoclastogenesis observed in FD lesions *in vivo*.[10] RANKL is expressed by osteoblastic cells, is indispensable for osteoclastogenesis and has a role in bone tumorigenesis.[11] Growth of skeletal tumors depends on activation of both RANKL and the cAMP/protein kinase A. RANKL inhibition with denosumab is effective to treat giant cell tumor of bone—which, like FD, derive from stem cells—osteoporosis and skeletal-related events due to solid tumors bone metastases.[11–13] Therefore, Boyce A *et al.*,[14] reasoned that RANKL inhibition with denosumab might be useful in the treatment of FD.

They present the case of a 9-year-old boy with MAS, including extensive polyostotic FD, hyperthyroidism, abnormalities on testicular ultrasound and café-au-lait macules. Despite pamidronate treatment for 1 year, the right femur bone expansion continued and bone pain did not decrease. At the age 8 years, he underwent a disarticulation amputation at the level of the femur–iliac joint. Several months later, the FD in his left femur began a comparable expansion, with significant bone pain requiring narcotic use. To try to avoid a second amputation, a 12-month course of denosumab was undertaken, to be given once monthly, with an initial starting dose of 1 mg kg^{-1} and dose escalations planned at 3-month intervals to 1.25, 1.5 and 1.75 mg kg^{-1}. The eighth dose of denosumab was held after the occurrence of a femoral fracture, in the absence of data on fracture healing in this FD context.

A bone biopsy obtained before treatment revealed sections of typical fibrous tissue and woven bone, abundance of cartilage but few osteoclasts. Immunohistochemical staining was markedly positive for RANKL. The volume of FD in the left femur—as assessed using computed tomography scan—substantially slowed after initiation of denosumab. Markers of bone turnover—which were significantly elevated at onset of therapy—declined dramatically after the first dose of denosumab and remained suppressed throughout follow-up. After one dose, the patient discontinued narcotics in favor of ibuprofen, and after three doses, was able to completely stop analgesics.

Hypophosphatemia with secondary hyperparathyroidism developed shortly after receiving the first injection of denosumab, justifying supplementation with phosphorus, calcitriol and calcium. Two months after the femur fracture and discontinuation of denosumab, the patient presented with severe hypercalcemia. Phosphorus and creatinine were normal, and parathyroid hormone (PTH), PTHrP and 1,25-vitamin D were suppressed. Beta-CTX had returned to approximately baseline levels, but aminoterminal propeptide of type 1 procollagen (P1NP) had rebounded to a level approximately 2.5-fold above the pretreatment level. The patient was treated with intravenous

hydration, calcitonin and pamidronate, but repeated courses of pamidronate or zoledronic acid were necessary to return to normal calcium level, 5 months after denosumab cessation. This was paralleled by progressive return of P1NP to normal.

Obviously, this patient benefited remarkably from the denosumab therapy because he was able to stop analgesics over a few months, whereas severe bone pain can be difficult—or even impossible—to control in this type of patient with MAS, and the bone expansion seemed to slow significantly. Bone resorption has been associated with bone pain, although it is not the sole mechanism of bone pain, so that inhibition of bone resorption is often considered as the one explanation of the pain-relieving effect observed with antiresorptive agents.[15] RANKL inhibition, through its antitumoral effect, might also inhibit ectopic nerve fiber sprouting by analogy with what is observed in cancer bone pain.[15] This case report, however, raises a number of concerns. Studies of denosumab in the field of osteoporosis have shown that bone resorption is almost completely suppressed within a few days after denosumab injection. In this case, the investigators have used doses that were six to seven times greater than the osteoporosis dosage, but about half the dose used in oncology. As expected, bone turnover was markedly suppressed by denosumab, whereas the patient had a very high level of bone turnover to start with, due to young age and bone growth, but mainly to the bone disease. Denosumab, when used in the treatment of postmenopausal osteoporosis, has already been shown to increase PTH, which in turn might increase bone formation, as assessed with P1NP.[16] In case of this young boy, denosumab therapy was responsible for rapid development of secondary hyperparathyroidism, compounded by the usually observed increased FGF-23 of FD resulting in 1,25(OH)2-vitamin D inhibition, both leading to hypophosphatemia. In all conditions, denosumab cessation is associated with a rebound in bone turnover. In this case, the rebound was so important it led to persistent hypercalcemia, which has never been observed in other diseases treated with denosumab. Bisphosphonates that were administered before denosumab treatment—and assumed to have a persistent effect on bone remodeling—did not protect this patient from the development of hypercalcemia. This complication may stem from the combination of very active FD and the higher bone turnover of the growing child.

In severe cases of FD, when bone pain is resistant to bisphosphonate use, denosumab certainly deserves to be tested in the setting of clinical trials. The adverse events observed in this case, however, can teach us to be very cautious using this drug in children, because they have higher bone turnover than adults, with the possibility of exaggerated rebound after treatment discontinuation. Children also have a developing immune system denosumab might interact with.[17] In addition, inhibition of linear growth cannot be ruled out in children. Lower dosage, comparable to the dose used in the treatment of osteoporosis may be adequate, but less likely to lead to excessive bone turnover rebound. It would probably be safer to conduct the next clinical studies in adults, with a lower dosage.

Conflict of Interest

The author declares no conflict of interest

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