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Opinion

Zoledronic Acid in Children with Osteogenesis Imperfecta: An Update

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Osteogenesis imperfecta (OI) comprises a group of inherited disorders that arise from mutations in the genes for type I collagen (COL1A and COLA2). These defects result in impaired bone formation, increased bone fragility and low bone mass, causing the so called "brittle bone disease. The clinical classification system published by Sillence in 1979 is widely used and divides the condition into Types I-IV. More recently, additional OI types (V-VII) have been identified from within the Type IV phenotype, and have distinct clinical and molecular characteristics. The severity of the clinical characteristics increases as follows: type I < types IV, V, VI, VII < type III < type II.

The consequence is recurrent fractures resulting in severe deformity and short stature. The treatment for OI includes physical therapy, rehabilitation, pain management and orthopedic surgery to correct deformities.

The most promising long-term results have come from studies using intravenous pamidronate, a second-generation bisphosphonate.

Zoledronic acid (ZA) is a third-generation bisphosphonate that inhibits osteoclastic bone resorption with very high potency. It binds tightly to calcified bone matrix and inhibits osteoclast-mediated bone resorption more effectively than earlier generation bisphosphonates, like pamidronate, at doses that do not impair bone mineralization. As a bone resorption inhibitor, ZA has demonstrated therapeutic use in several diseases involving enhanced bone turnover, like OI and primary/secondary juvenile osteoporosis.

The recommended dose for 1 to < 3 years old child is 0,025 mg/kg, diluted in 50 ml of normal saline in 60 minutes infusion at the first time and 30 to 45 m infusion in follow-up treatment, that can be 6/6 months interval, according to the clinical, radiological and bone marker results. From 3 to 17 years of age, the dose is 0.05 mg/kg, diluted in 100 ml of normal saline, with 30 minutes infusion. The maximum single dose is 4 mg. The patient will be admitted for approximately one to two days for the first infusion. Subsequent, ZA infusions can be given during a day care admission.

Calcium (elemental) in a dose of 50 mg/kg/day, up to 1500 mg, TID and calcitriol, 0.05 g/kg/day up to 1g, BID, need to be given the night before the patient is admitted.

Before infusion, we need to check for hemogram and platelets, ionogram, urea, creatinine, magnesium, phosphorus, alkaline phosphatase, vitamine D, parathormone, DEXA and renal ultrasound. After 48-72 hours post infusion, we check for urea, creatinine, ionogram, calcium, phosphorus, alkaline phosphatase and parathormone. The DEXA examination and renal ultrasound control will be done at 6 months and one year later.

Adverse side effects include: 'Flu like illness", fever, musculoskeletal aches and pains, and vomiting. In this case, we can give regular paracetamol or ibuprofen 4 - 6 hourly.

Hypocalcaemia and hypophosphataemia occurred in 10% of cases. Vitamin D and calcium supplementation before infusion of ZA will reduce the risk. Adequate calcium intake should be maintained throughout time on treatment.

Hypo/hypertension is rare, around 0.001% of cases. We must monitor the blood pressure of the patient during the infusion.

In less than < 0.001%, we can find abnormal liver function tests, increase in serum creatinine and urea.

Infusions of ZA showed similar effects compared to pamidronate in terms of the primary endpoint of increase in LS-BMD after 12 months of treatment. Similarity between ZA and pamidronate was also shown regarding sustained reductions in serum markers of bone resorption and bone formation. The proportion of patients who had clinical fractures during the 12 months of treatment was similar between the ZA and pamidronate treatment groups.

No significant differences were observed regarding LS-BMD Z-score at 6 and 12 months and femoral neck and total body BMC.

In comparison with pamidronate, ZA seems to be associated with more pronounced risks for acute phase reactions and hypocalcemia, mostly asymptomatic and transient.

Zoledronic acid is a good alternative treatment for patients with osteogenesis imperfecta.

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