Owner: Pediatric Department	Protocol Code: PR-PED-005
Title of The Protocol: Zoledronic Acid (ZA) Infusions in Children with Metabolic Bone Diseases	

Background:

- Zoledronic acid (or zoledronate) is a third-generation bisphosphonate therapy.
- It binds strongly to the bone mineral and interferes with bone remodeling by slowing the process of osteoclastic bone resorption.
- Since its successful use in 1998 in a large series of children with osteogenesis imperfecta (OI), bisphosphonates have been increasingly used in children suffering from primary and secondary osteoporosis, as well as various skeletal disorders.
- Zoledronic acid (ZA), a highly potent intravenous bisphosphonate (BP), has been increasingly used in children with primary (Osteogenesis imperfecta) and secondary osteoporosis.
- Many studies have also demonstrated beneficial effects of ZA in cases in other conditions such as hypercalcemia of malignancy, fibrous dysplasia (FD), chemotherapy-related osteonecrosis (ON) and metastatic bone disease.
- ZA treatment offers greater ease and convenience of use, as compared to pamidronate, as it is administered as a single intravenous infusion over a shorter duration of 30 minutes, with a longer interval between infusions. This dosing schedule greatly reduces the need for repeated venous cannulation and is more cost effective in terms of health care utilization. This makes ZA an attractive and efficient treatment option.

Important Notices:

- Consent should be taken prior to commence Zoledronic acid (ZA) therapy.
- So far, no data, for the optimum dose, frequency of infusion, how long will be the therapy and long-term side effects!
- BMD scan should be done annually unless younger age group (Below 5 years of age), KAUH radiology department doesn't have software data.
- Zoledronic acid is very potent, and has long half-life, 3 -6 monthly infusion regimen initially, clinical, and bone markers results should be reviewed every 6 months.
- *In KAUH, ZA first 5 infusions will be given every 3 months, then shifted to 6 monthly provided good response (clinical, biochemical markers and BMD Z score improvements).*

- *As soon as BMD Z score value of 0 (50th, Percentile), ZA infusion will be given yearly.*

- ZA has been used in children with primary and secondary osteoporosis at "King Abdul-Aziz university hospital since 2004. So far, these trials showed complete safety and no long-term side effects with major change in the patient's clinical improvement as well bone markers, data was published. (Osteoporosis treatment with Zoledronic acid in pediatric population at a university hospital in Western Saudi Arabia. A 13-year experience. November 2015, Saudi medical journal 36(11):1312-1318.

PROTOCOL:

Arrangements prior to the first dose of therapy:

- Serum calcium, phosphate, urea, creatinine, alkaline phosphatase, 25OH vitamin D and parathyroid hormone (PTH) need to be all measured (these tests should be done with every admissions).

- Serum 25OHD should have been demonstrated to be ≥ 75 nmol/l, otherwise a therapeutic dose of vitamin D therapy rather than prophylactic dose should be given.

- Bone markers including osteocalcin, CTX should be done as baseline, then every 6 months.

- Dental review should have been requested.

- If a child has known significant dental or gingival disease, then this review should take place prior to treatment.

- *On admission: Clerk and examine the patient. Pay attention to the following:*

  - Fractures since their last admission, and what treatment was instigated.
  - Pain (where, how long etc.) and what analgesia taken.
  - Mobility (and if any change).
  - Dentition and / or caries.
  - How they have been generally.

Medical Imaging

- Total body DXA (or equivalent) will be performed initially and every 12 monthly intervals.

- Renal ultrasound initially and every 12 monthly intervals.

- Other medical imaging as per orthopedic surgery request.
- Lumbar spine x rays initially if indicated (discuss with consultant).

Zoledronic Acid Infusion

- *The dose of Zoledronic acid intravenous infusion over 30 minutes varies according to the age:*
  - Neonates and children less than two years, dose is 0.025 mg/ kg.
  - Children above 2 years of age, dose is 0.05 mg/kg.
- Five infusions initially will be given three monthly intervals, afterward spaced to six monthly intervals depending on clinical, biochemical markers and radiological improvements.
- *Maximum dose is 4 mg intravenously every 6-12 months.*

Important notice:

- Due to the risk of clinically significant deterioration in renal function that may progress to renal failure.
- *In children with a baseline creatinine clearance of 50 to 60 ml/minute, the dose should be reduced by 15% from the actual dose. Furthermore, 20% reductions are required in children with baseline creatinine clearances ranging from 40 to 50 ml / minute and 25% reduction in children with creatinine clearance of 30 mL /min or less.*

Hospitalization

The patient will be admitted for two days for the first infusion. Subsequent infusions to be given during a day care admission.

Adverse effects

Manifesting as flu-like symptoms including low-grade fever, nausea, myalgia and bone pain, or fatigue, are the most common adverse effect of ZA and, when it occurs, typically develops with-in 48 hours of the first infusion. Subsequent infusions usually have no acute adverse effects.

Osteonecrosis of the Jaw (ONJ) represents a severe dento-alveolar bone defect related to poor bone healing. Although the association of increased ONJ rates in adults treated with high dose

bisphosphonates has been fully established, to date, there has been no reported case of ONJ in children treated with bisphosphonates.

Precautions during first dose Admission:

- Intravenous fluid maintenance during admission as poor appetite / intake is expected.
- To avoid hypocalcemia occurring during first infusion, ensure that the patient is receiving an adequate oral calcium intake, 1200 mg/day, in addition to intravenous calcium of 200 mg/ kg/ day during 48 hours of first admission.
- Vitamin D may be required if low level of 25 OH vitamin D is present or if significant hypocalcaemia occurs following the first infusion. If the milkintake is not optimum, daily intake of calcium supplement is needed to compensate for poor dietary content of calcium. Commence on vitamin D 500 units daily as prophylaxis, if vitamin D level is normal.
- Ibuprofen, 10 mg/kg, three to four times per day is suggested during the first infusion to minimize the fever and myalgia that is frequently seen.

References

1. Chen JS, Sambrook PN. Antiresorptive therapies for osteoporosis: a clinical overview. Nat Rev Endocrinol 2011; 8:81-91. 10.1038/nrendo.2011.146.

2. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc 2008; 83:1032-45. 10.4065/83.9.1032.

3. Green JR. Zoledronic acid: pharmacologic profile of a potent bisphosphonate. J Organomet Chem 2005; 690:2439-48. 10.1016/j.jorganchem.2004.09.069.

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Flowchart

Stage	Infusion	24, 48 hours	12 weeks	6 months	12 months
Zoledronic acid infusion Axiology	X		X	X	X
DXA	X			X	X
Renal Ultrasound (lumbar spine x rays)	X				X
Urea, creatinine, electrolytes	X	X	X	X	
Serum calcium	X	X	X	X	
Serum phosphate, alkaline phosphatase	X	X	X	X	
PTH	X	X	X	X	
Vitamin D metabolites.	X		X	X	
Serum osteocalcin	X		X	X	
CBC	X		X	X	

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