Written by: Dr C DeVile, Dr J Allgrove, Dr B Crowe, CNS M Heathfield
Approved by: Drugs & Therapeutics Committee
Date Created: May 2017
Reviewed by: Dr C DeVile, Dr J Allgrove, Dr B Crowe, CNS M Heathfield, S Mahal
Date Reviewed: July 2021
Date for next review: Jun 2023
Version: 2
Replaces Version: 1
DTC Ref No. IN00062

Osteogenesis Imperfecta: Use of Intravenous Zoledronic Acid (Zoledronate)

Osteogenesis Imperfecta (OI) encompasses a group of disorders characterised by increased fragility of bone. In the most severe form, fractures are present at birth and continue to occur, often several times a year in response to minimal trauma. In milder forms, fractures may only occur occasionally and the symptoms e.g. back pain, may be more subtle. Generalised osteoporosis is usually also present and may be accompanied by vertebral collapse and severe long bone deformity.

Management of OI should be undertaken as a multidisciplinary team and consists of appropriate physiotherapy and occupational therapy, orthopaedic surgery and family support. Medical treatment to try to strengthen bone and reduce the number of fractures and bone deformity has been tried with some success. The most promising of these approaches has been the use of bisphosphonates to increase bone density and redress the imbalance between bone reabsorption and bone formation, which occurs in OI.

Bisphosphonates have been used for a variety of conditions in childhood where there is bone pain and immobility in association with osteoporosis and/or abnormal bone formation. The most commonly used bisphosphonate in the UK is pamidronate, which has been used with considerable success in several conditions in which generalised osteoporosis occurs, although the longer-acting and more potent zoledronic acid is being increasingly used in children over the age of five years. Apart from OI, conditions treated include Idiopathic Juvenile Osteoporosis, Osteoporosis Pseudoglioma Syndrome, Polyostotic Fibrous Dysplasia and Steroid Induced Osteoporosis. In all cases an increase in bone density was seen with vertebral body remodelling, an early reduction in pain and improved mobility.

As patients with these conditions are rare, they are likely to be under the care of specialist paediatricians in the UK and it is proposed to use a common protocol for the administration of intravenous zoledronic acid, so as to gather uniform data for subsequent audit and research.

Zoledronic acid is a third generation newer and longer acting aminobisphosphonate. The advantage over pamidronate is the shorter infusion time and fewer hospital admissions. It has a similar affinity for mineral and greater potency than pamidronate and thus can be given less frequently, typically every 6 months. It is used for children with Osteogenesis Imperfecta, in whom the practicalities of a 3-day hospital admission every 3 months for pamidronate disodium may pose significant problems e.g. difficult venous access, needle phobia, interruption in schooling and multiple hospital attendances, which can be challenging for the child and family, especially those with increased mobility needs.

This protocol has been developed from published evidence and shared clinical experience from across the 4-centres (Birmingham Women's and Children's Hospital, Bristol Royal Hospital for Children, Great Ormond Street Hospital for Children and Sheffield Children's) comprising the Highly Specialised OI Service in England.

Mechanism of Action

Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates and acts primarily on bone. It has a strong affinity for bone and is an inhibitor of osteoclastic bone resorption.

Presentation[1]

Zerlinda® or Zometa® or generic 4 mg in 100ml solution for infusion.

Indications

- Severe phenotype
- Bone pain requiring regular analgesia

- Recurrent fractures and/or vertebral insufficiency fractures
- Severe bone deformity
- Reduced mobility and function

Baseline Investigations

Radiology:

- Lateral X-ray of whole spine to quantify any evidence of vertebral insufficiency fractures (this will have been done as part of the diagnostic / monitoring process).
- Anterior Posterior (AP) spine only if scoliosis present/suspected.
- DEXA scan (bone densitometry) if not already performed.
  This is a lumbar spine DEXA. There are no normative data below 5 years of age but can be done in younger children (≥ 10 kg), to act as own control.
  GOSH data-set also includes a BMAD Z-score, a 3-dimensional measurement, which adjusts for body size. In cases where spinal fusion or growth rod surgery has been performed, a DEXA scan of hips will take place prior to surgery and be completed thereafter in place of lumbar spine DEXA, as metalwork may affect the bone density readings.
- Urinary tract ultrasound scan (monitoring for nephrocalcinosis).

Biochemistry:

- Plasma calcium, phosphate, urea and electrolytes, alkaline phosphatase and albumin, serum intact PTH and 25-OH vitamin D.

Dosage and Administration Details

Vitamin D:

All children with OI should be taking 400 units (10 µg), 800 units (20 µg) or 1,000 units (25 µg) of oral, over-the-counter purchased vitamin D as a daily dose for maintenance depending on age and as directed by the specialist team.

If baseline 25-OH vitamin D is low (<50 nmol/L), give supplemental vitamin D daily (3000 units/day) for 3 months and check levels again in 2 months.
Defer treatment until 25-OH vitamin D levels are ≥ 50 nmol/L.

Calcium:

Calcium levels should be checked before each infusion.
Calcium supplements **must** be given one week before and one week after infusion at a dose of a minimum of 1 mmol/kg/day in one, or 2 divided doses.
The following preparations are suitable:

- Cacit 500 mg (12.5 mmol) effervescent tablets
- Adcal 600 mg (15 mmol) chewable tablets
- Calcichew 500 mg (12.5 mmol) chewable tablets
- Cacit D3 effervescent granules sachets (calcium carbonate 12.5 mmol), colecalciferol 440 units)
- Calcichew D3 Forte (calcium carbonate 12.5 mmol, colecalciferol 400 units)
- Sandocal effervescent tablets (25 mmol)

Liquid preparations may be available for younger children. In addition, children should be encouraged to drink milk and to consume calcium-

rich foods (e.g. dairy produce, such as cheese and yoghurt) for at least a week following the infusion.

Zoledronic Acid: Zoledronic acid is generally used at Great Ormond Street Hospital from 5 years of age, up to and beyond adolescence. Doses are listed as standard regimens, although the child's medical records should be **always** checked before prescribing, as doses may be modified following clinical review. A full cycle consists of one infusion every 6 months.

On first infusion of first treatment cycle, half the usual dose should be given to minimise an acute phase reaction (see below). Doses should not exceed a total of 2 mg.

A maximum dose regimen of 0.05 mg/kg/dose, and maximum dose of 4 mg as a single infusion should not be exceeded.

Age / yrs	Dosage	Reconstitution	Duration of Infusion	Frequency	Max Single Dose
<5 1st dose*	0.0125 mg/kg	50-100mls of normal saline	45 minutes	3 months	1 mg
<5 2nd dose*	0.025 mg/kg	50-100mls of normal saline	45 minutes	3 months	2 mg
≥5 1st dose	0.025 mg/kg	100mls of normal saline	45 minutes	6 months	2 mg
≥5 2nd dose	0.05 mg/kg	100mls of normal saline	45 minutes	6 months	4 mg

*Children under 5 yrs. of age may be occasionally treated with zoledronic acid; the dose regimen will be directed by the OI specialist team.

As a minimum, the first two infusion cycles are given at the tertiary unit when bisphosphonate naive in order to monitor for side-effects (see below). Once these settle satisfactorily and in liaison with the local referring hospital, subsequent infusions may be given as an outpatient. For children switching from pamidronate to zoledronic acid there is no need to give a half dose of zoledronic acid initially, as they are not bisphosphonate naïve – these children should receive the full dose regimen from their first infusion. They typically only require one infusion at the tertiary unit if tolerated, before transitioning back to the care of their local hospital for ongoing infusions as an outpatient.

Monitoring During Treatment

- Prior to each treatment cycle: Plasma calcium, phosphate, urea and electrolytes, alkaline phosphatase, albumin, serum intact PTH & 25-OH vitamin D.

- Patients must be assessed prior to administration of zoledronic acid to ensure that they are adequately hydrated.

- Only monitor blood pressure if there are clinical concerns. "Routine" 4-hourly blood pressures should **not** be performed due to risk of fracture. In rare cases where blood pressure measurements are required, they should be taken manually, with a sphygmomanometer and doppler/stethoscope and not with an automated device such as

a Dinomap. All other observations should be completed in line with Trust policy. This may vary across centres.

- Day after infusion: at the tertiary centre, plasma calcium, phosphate and albumin should be taken at 6 am in order to be checked before discharge.

- Corrected calcium should be above 2.1 mmol/L. To calculate corrected calcium the following formula may be used:
  (40 – serum albumin level g/L) x 0.02 + plasma calcium mmol/L.

  Therefore corrected calcium for an uncorrected calcium of 2.25 mmol/L and albumin of 35 g/L would be calculated as 40 – 35 = 5 x 0.02 = 0.1 + 2.25 = 2.35 mmol/L.

- It is **not** necessary to repeat 25-OH vitamin D once known that baseline level is replete; a 6 monthly check is sufficient. Isoenzyme monitoring is not required. 1,25-OH vitamin D is not required for monitoring purposes.

- At the end of one year of treatment and at subsequent annual monitoring:
  Repeat baseline investigations. The DEXA scan should be performed on the same machine as previously. This will be usually undertaken at the tertiary centre. In some cases based on clinical need a DEXA scan may be performed after 6 months in order to monitor response and adjust treatment dose.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Renal failure (GFR<30ml/min/1.73m2)
- Pregnancy
- Vitamin D deficiency

Precautions for Use

- Vitamin D deficiency – do not give zoledronic acid until the level is replete.
- It is strongly recommended that such treatment be undertaken in conjunction with a paediatric metabolic bone disease specialist, although it will be up to individual clinicians to decide where treatment should take place.
- Zoledronic acid is a viscous drug that if given in too small a volume or too rapidly can lead to venous irritation and tracking marks along the vein.

Adverse Effects

There is a risk of an acute phase reaction, especially to the first dose. This usually occurs within 3 days of administration of zoledronic acid and includes:

- bone pain
- fever
- flu-like syndrome (including fatigue, rigors, malaise and flushing)

Symptoms usually resolve within a few days. These often settle with paracetamol and/or ibuprofen and do not usually recur on subsequent infusions. This is far less likely to occur in children who have previously received other intravenous bisphosphonates, such as pamidronate.

In neonates, the acute phase reaction may include respiratory distress, especially if there is pre-existing respiratory difficulty. Management is with appropriate supportive care.

Other common adverse effects include headache, anaemia, hypophosphataemia, hypocalcaemia and renal impairment.

There may be a potential risk of delayed bone healing (non-union) after orthopaedic procedures, such as osteotomy, or after prolonged treatment. If a patient requires surgery, then we would usually advise not giving zoledronic acid within 2-4 weeks of surgery, although there is limited evidence to support this timing and variance in practice across OI centres. Post-operatively we would advise to withhold zoledronic acid until there is evidence of bone healing confirmed on X-ray (usually confirmed by the orthopaedic team who conducted the surgery at around 6 weeks but may be longer).

In the event of an acute long bone fracture (not requiring surgical management), occurring at the time zoledronic acid is due, then in children with severe OI, treatment should proceed unless specified by the OI specialist. In children with milder OI, the decision or not to delay treatment is usually made on an individual basis in consultation with the OI specialist and review of radiographs of the fracture.

It has been suggested that there is a risk of osteonecrosis of the jaw (ONJ) in association with bisphosphonate treatment. Whilst this may occur in adults, usually those who have been treated for some form of cancer, ONJ has **never** been described in children and is not regarded as a risk.

Note:

- Paracetamol & ibuprofen should be prescribed as a PRN medication.
- In female patients of childbearing potential, it is important to ask whether there is any chance of them being pregnant. If there is any doubt or suspicion, then obtain a pregnancy test and, if positive, withhold treatment and inform the consultant.

Points of Contact

Role	Preferred Contact Method
CNS (MH)	Email, Ext 5824 or EPIC
Lead OI Consultant (CDV)	Ext 8191 or Bleep 0120
OI Consultant (BC)	Ext 1501 PA Ext 5293/1198
Endocrine Consultant (JA)	07779 823 573

For fuller details of adverse effects see Summary of Product Characteristics for zoledronic acid. For pamidronate disodium guidelines, please see separate guidelines.

References

- Barros ER, Saraiva GL, de Oliveira TP, Lazeretti-Castro M. Safety and efficacy of a 1-year treatment with zoledronic acid compared with pamidronate in children with osteogenesis imperfecta. J Pediatr Endocrinol Metab. 2012; 25:485-491.
- Brown JJ, Zacharin MR. Safety and efficacy of intravenous zoledronic acid in paediatric osteoporosis. J Pediatr Endocrinol Metab. 2009; 22:55-63.
- EMEA. Assessment report for Zometa (zoledronic acid). Doc. Ref No: EMA/35729/2010. 2010.
- Guideline for the use of intravenous bisphosphonates (pamidronate and zoledronic acid) in children. Version 1. Central Manchester University Hospitals NHS FT 2013.
- http://emc.medicines.org.uk. Zoledronic acid (Zometa®). Summary of Product Characteristics, UK. Last updated 25/11/2020 Accessed 13/07/2021

- Intravenous zoledronic acid (ZOL) compared to IV pamidronate (PAM) in children with severe osteogenesis imperfecta. Glorieux FH et al. Calci Tissue Int. 2008: 82(1 supplement);S85
- Ooi HL, Briody J et al. Intravenous zoledronic acid given every 6 months in childhood osteoporosis. Horm Res Paediatr. 2013; 80(3):179-84
- Panigrahi I, Das RR, Sharda S, Marwaha RK, Khandelwal N. Response to zoledronic acid in children with type III osteogenesis imperfecta. J Bone Miner Metab. 2010; 28:451-455.
- Protocol for the use of intravenous zoledronic acid (zoledronate) in Children, Protocol from Birmingham Children's Hospital, Birmingham, UK.
- Simm PJ, Johannesen J, Briody J, McQuade M, Hsu B et al. Zoledronic acid improves bone mineral density, reduces bone turnover and improves skeletal architecture over 2 years of treatment in children with secondary osteoporosis. Bone. 2011; 49:939-943.
- Vuorimies L et al. Zoledronic acid treatment in children with osteoporosis imperfect. Horm Res Paediatr 2011;75(5)346-53
- Zoledronate (ACLASTA) Treatment, Protocol from Shriners Hospital, Montreal, Canada.
- Zoledronate Protocol 2011. Dr Hogler W & Dr Shaw NJ. Metabolic Bone Team, Birmingham Children's Hospital.
- Zoledronic acid. Medusa Injectable Medicines Guide. Last updated 07/12/2020. Accessed online on 11/07/2021.
-