Clinical Consent for BisphosphonateTherapy

Introduction: Your child is going to start treatment with a medicine called pamidronate (PAM) or zoledronate (ZOL). Both of these drugs are in a class of drugs called bisphosphonates which appear to increase bone strength and reduce the risk of fractures in large studies in adults. There is less experience with bisphosphonates in children but the studies suggest that bisphosphonates reduce the number of fractures in osteogenesis imperfecta (a “brittle bone” disorder) and other conditions as well. Both PAM and ZOL work in the same way to reduce bone loss but they have some differences in how they are given. We want you to be aware of these differences and of possible side effects from the medicines.

If you consent for PAM therapy, your child will receive the medicine by intravenous infusion (a small needle in a vein), given over four hours as an outpatient in our Short Stay Unit. For patients younger than 2 years or those with a history of breathing problems, we provide the first dose of PAM in the hospital over a two-day stay. This is to observe for possible breathing problems as described below under the section on risks. The total yearly dose of the medicine is approximately 4 milligrams per kilogram of body weight (to a maximum of 120 milligrams per year). In children younger than age 3, the infusions are given every 8 weeks. For children over age 3, the infusions are given every 3 months.

ZOL is a newer bisphosphonate that is stronger than PAM (so we use a lower dose) and can be given over one hour instead of four hours. The intravenous infusions can also be given less often than with PAM: every 3 months for children under age 2 and every 6 months for older children. For patients who have never received any bisphosphonate therapy, the first dose of ZOL is 0.0125 mg per kilogram of body weight to reduce the chance of causing low calcium or phosphorus level. For children less than age 2, this dose is repeated every 3 months. For children over age 2, we will give a dose of 0.025 mg per kilogram of body weight in three months. This dose will then be repeated every six months. The total yearly dose is 0.05 milligrams per kilogram of body weight per year (to a maximum of 4 mg). As with PAM, children under age 2 are hospitalized when receiving the first dose of ZOL to watch for breathing problems.

We will decide on the length of treatment with PAM or ZOL as we see how bone strength changes during therapy and as we consider the risk factors for bone fractures. A typical course of treatment is 3 years using the schedule described above. After that, we recommend maintaining treatment at half the original dose for children who are still growing and have ongoing risk factors for bone fractures. This means infusions every 6 months for PAM and once a year for ZOL.

You have the option to discontinue treatment at any time.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with PAM and ZOL. These deserve careful thought. You should talk with the doctor if you have any questions. Below you will find a list of the side effects that have been described in adults using PAM or ZOL. Experience in children has shown some, but not all, of the reactions listed below:

General

- Nearly 40%-60% of patients develop **"flu-like"** symptoms beginning a few hours after the first infusion, including muscle aches, fatigue, fever, nausea or weakness. These symptoms usually last up to 48 hours, and typically do not happen again with later doses of PAM or ZOL. We recommend treating the pain and fever with over the counter medicines like acetaminophen (Tylenol). We can prescribe medicines to treat nausea or vomiting if it occurs.
- A smaller number of patients complain of **bone pain** after PAM or ZOL.
- Rarely patients complain of a **rash**.

Blood and blood vessels

- A small percentage of adults using PAM or ZOL have a **lower-than-normal white blood cell count**, (the cells used for fighting infection). The white blood cells return to normal after stopping the medication.
- Rarely patients treated with high dose PAM or ZOL complain of **redness, swelling and pain** during treatment **around the skin site** where the needle is placed in the vein.

Central nervous system

- **Seizures** (convulsions) occurred in 4 people during US trials, 2 of whom had seizures before receiving PAM.

Metabolic

- A **low level of calcium** may develop in patients treated with PAM or ZOL. It usually causes no problems, but on rare occasion needs treatment with calcium supplementation. To prevent this problem, we make sure the body's stores of vitamin D are adequate (blood level of 25 hydroxyvitamin D level of 20 ng/ml or greater) before the first infusion. We recommend taking vitamin D (1000-2000 international units a day) and adequate calcium for general bone health as well.
- **Low potassium, magnesium and phosphate** have been noted less commonly. To monitor for these problems, we will order a blood test 3-5 days after the first infusion.

If there are no abnormalities, we do not need to do this post infusion test after future treatments.

Optic/Eye

- **Redness, irritation, excessive tearing and blurred vision** were reported in 23 out of 50,000 people. These symptoms were seen in the first 2 days in most of the patients and resolved with directed therapy, or with observation alone.

Bone

- Studies from another medical center found that **bone healing after insertion of metal rods into bone** was more common in children with osteogenesis imperfecta treated with PAM than in similar patients who had not received PAM treatment. The dose of PAM associated with delayed healing was more than twice the dose your child would receive. No problem of delayed bone healing has been reported with the lower dose your child would receive. However, if your child is going to have this type of surgery, we can discuss with your surgeon how best to schedule the timing of bisphosphonate treatment.
- Some adult patients treated with PAM or ZOL have developed avascular necrosis of the jaw (damage to the jaw bone because of poor blood supply). This complication has been reported mostly in elderly patients, many of whom have been treated for some type of cancer. The jaw problem is a very rare occurrence and may or may not be due to the bisphosphonates. This condition has never been observed in any child treated with bisphosphonates. In fact, some physicians have used bisphosphonates to treat avascular necrosis in other parts of the body in children.
- Rarely, atypical fractures of the femur (an unusual break in the thigh bone) have occurred in adult patients who received bisphosphonates. These occurred only in patients who had received bisphosphonates for a long time and 25% had received glucocorticoid drugs that can weaken bone. The risk of this complication for adults is very low and increases with long-term bisphosphonate treatment. As estimated 1 fracture will occur per 1000 patients treated for > 5 years with these drugs. However, it is estimated that 15 fractures from osteoporosis are prevented for each 1 fracture that might occur as a complication of the bisphosphonate treatment. Atypical femur fractures have been reported in a very small number of children with osteogenesis imperfecta treated with PAM or ZOL. These fractures have also occurred in children who have never received these medications. Thus, atypical femur fractures appear to be related to the severity of osteogenesis imperfecta rather than to PAM or ZOL treatment.

Respiratory/Lungs – In Children < Age 2

- Four of 59 infants (under age 2) in one series developed difficult breathing

(respiratory distress) within 1-2 days after receiving their first PAM treatment cycle. All of the children who became ill after PAM had a prior history of prior breathing problems. All recovered from the breathing problems in hospital and the problems did not recur with later PAM treatment cycles. Because of this report, we admit patients younger than two years to receive their first PAM or ZOL as described above.

Risks of Blood Draws

- To watch for side effects such as low calcium or blood counts, blood will be drawn at various times when children are receiving PAM or ZOL. There is a risk of bruising, bleeding or infection, along with fainting when blood is drawn.

Although most of the risks stated above are infrequent and/or resolve spontaneously, we will be monitoring your child for the duration of the time that they are receiving the medication. In addition to these risks, PAM or ZOL could involve risks that are currently unforeseeable. Every precaution consistent with the best medical care will be taken with regard to treatment with PAM or ZOL. Although both PAM and ZOL have been used for many children with bone fragility, the FDA has not approved the use of these medications in pediatrics because the large treatment trials needed to obtain FDA approval have not been conducted in children.

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Signature of Parent or Legally Authorized Representative Date

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this treatment, risks and benefits, or alternative courses of treatment, you should ask your doctors in the Division of Pediatric Endocrinology at 650-721-1811.