Update on Bisphosphonates as a Treatment for Osteogenesis Imperfecta

Since the early 1990’s a class of drugs called bisphosphonates has been investigated as potential treatment for infants, children and adults with OI. Several of these drugs are approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults with Paget’s disease of bone, osteoporosis, or other conditions, but not for the treatment of people with OI. Bisphosphonate therapy for OI is increasingly used worldwide, but continued close scrutiny and knowledgeable use and evaluation of these potent drugs is essential for everyone with OI.

Use of bisphosphonates in people with OI in North America includes pamidronate (Aredia®) and zoledronic acid (Zometa®) given by intravenous infusion, and alendronate (Fosamax®) and risedronate (Actonel®) given in tablet form. Because most of the clinical trials in OI have been uncontrolled (a controlled trial is the most rigorous and regulated form of medical research) and have involved small numbers of OI patients, current research reports contain important information, but they cannot be considered conclusive.

In most of the studies of people with OI, bisphosphonates led to a beneficial increase in apparent bone density (this is measured by DXA) but there is concern that there could be a detrimental increase in bone stiffness and bone “brittleness” after prolonged treatment. The increase in bone density is greater in children with relatively severe forms of OI (Types III and IV), than in the milder forms (Type I), but the increase does vary from child to child. Even in people who appear to have healthy bones, high levels of bisphosphonates and prolonged treatment could increase bone fragility. If bone stiffness increases after treatment with bisphosphonates, then it may take more force to break the bone so the number of fractures may decrease, but the fractures that do occur may be more severe and perhaps slow to heal. If bone brittleness increases after excessive bisphosphonate treatment, then less force than before treatment may cause repeated fractures. These concerns are still being tested.

Patients in uncontrolled studies of bisphosphonate therapy have reported increased endurance and improved confidence for walking and other forms of exercise. This increased activity may by itself contribute to improved bone density, but could also increase the risk of fracture due to falls, etc. Thus the effect of bisphosphonates on fracture rate is not always easy to evaluate.

Length of Treatment:

The point at which medical therapy using a bisphosphonate should be stopped or temporarily suspended is being investigated worldwide. It appears that the optimum length for treatment will vary from one person to another, depending on the person’s age, type of OI, the age when treatment started and the individual response to treatment (including clinical, biochemical and bone density changes). Currently, many researchers and clinicians believe that after 2-3 years and no more than 5 years, the full effects of bisphosphonates are achieved. Some people with OI have maintained their bone density for two years after ending treat-

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ment, but there is not enough experience in this regard to make firm recommendations. Researchers advise that treatment throughout all of childhood is probably not necessary or beneficial. There has been some discussion of taking “time off” from bisphosphonate treatment (a “drug holiday”) and resuming if there is a decline in bone density that may increase fracture risk. It is clear that physicians should continue to monitor all patients after stopping treatment.

Bisphosphonates stay in the bone for many years, and there is a potential risk that accumulation over time could cause detrimental side effects such as abnormal bone shaping, excessive density, and increased stiffness or bone brittleness. These possible detrimental effects of prolonged or high dose administration of bisphosphonates have been seen in mouse models of OI.

Dosage:
Dose is typically calculated based on the patient’s age and weight. There is no universal agreement regarding an approved dosage for children. The “Montreal Protocol” provides a commonly used dosage of pamidronate (Aredia®) for children, although some researchers are testing either higher or lower dosages, or different dosing intervals. The cumulative annual dosage of any bisphosphonate should be carefully monitored to prevent a build up in the bone to a level which may result in unwanted side effects.

Effects of Bisphosphonates on Bone:
Different studies are looking at how bisphosphonates affect specific bones in OI, such as the femur or the spine. Bisphosphonates and other medications used to treat osteoporosis have been shown to have different effects on long bones in the limbs as well as vertebrae. Effects on bone shaping (modeling) and remodeling (turnover) are being investigated. One study suggests that after therapy stops, the bone remodeling activity that had been decreased under treatment starts up again.

Effect of Bisphosphonates on Healing:
Questions about healing of fracture and osteotomy (a surgical cut) in OI bone are also being investigated. Current experience suggests that OI bone is often slow to heal after bisphosphonate therapy. Incomplete healing (non-union) of fractures and slow healing of osteotomies does occur in individuals with OI who have never received bisphosphonate treatment, but it seems to occur more often in individuals who have received bisphosphonates. There is some evidence that bisphosphonates can slow repair of fractured long bones, and some clinicians may temporarily halt bisphosphonate treatment during the repair phase. However, the lack of sufficient data about the natural frequency of these problems (outside of bisphosphonate therapy) makes it difficult to determine if bisphosphonates make the problem worse. Research suggests that the use of an oscillating (vibrating) saw rather than a hand held saw during bone surgery may actually slow healing in bisphosphonate-treated bone.

Effect of Bisphosphonates on Infants & Toddlers:
Recent studies have used pamidronate to treat very young patients with severe OI. A few reports indicate that bone density, vertebral area, and self directed movement increased. Fracture rate and pain may decrease. No negative effects on growth have been reported, but it is not possible to predict how much each child might ultimately achieve in height. Long-term effects on long bone remodeling and on teeth have not yet been determined.

Effect of Bisphosphonates on Mild (Type I) Children with OI:
There is not enough reliable data concerning bisphosphonate treatment for the mildest (Type I) children with OI. Carefully designed clinical trials should address this question. Current trials are testing the use of pamidronate in children with Type I OI who have had three or more fractures per year for two consecutive years and vertebral crush fractures.

Effect of Bisphosphonates on Adults with OI:
Adults with OI appear to have minimal response to oral or IV bisphosphonate therapy. Bisphosphonates may help to maintain adult bone density or decrease the risk of age-related osteoporosis and possibly reduce symptoms of bone pain, but further studies are needed.

Pain:
Bisphosphonates have been reported to reduce “bone pain” in uncontrolled studies. Parents of some young children with OI, in particular, have described an increase in their children’s physical comfort. The effect on “bone pain” in OI appears to be related to age. Young, growing children seem to perceive less pain while using bisphosphonates. Older children and adults may perceive smaller amounts of pain relief. Exercise may also decrease pain. Bone pain is difficult to mea-

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sure and “placebo effects” have often been reported in previous studies of medical therapies in other bone disorders. (“Placebo effects” occur when a patient feels improvement while taking a pretend or “placebo” version of a drug.) Current research is evaluating this topic. Pain is not easy to assess and should not be used as an indicator for altering the dosage or the interval between cycles.

Pregnancy:
In the few known instances where a young woman with OI who was taking bisphosphonates became pregnant, the drug was stopped as soon as the pregnancy was noted. The babies born to these women did not appear to have been harmed by the presence of any bisphosphonate in their mothers’ systems. It is hypothesized that peril to the developing fetus would be greatest at the time of an intravenous infusion, before all of the bisphosphonate is trapped in the mother’s bone. There is little data on pregnancy outcome in women with prolonged prior bisphosphonate exposure. Animal studies have shown that high doses of bisphosphonate already in the maternal bone may be detrimental to fetal bone.

Many questions remain to be answered about the effects of bisphosphonates on children and adults with OI. Some are listed here:

- What is the most appropriate annual dose for each bisphosphonate?
- What is the most beneficial and safest length of treatment?
- Do individuals with different types of OI respond to bisphosphonates differently, or are differences in response related to the specific collagen mutation?
- Is one bisphosphonate safer or more effective than another?
- Will guided exercise or physical rehabilitation improve the effect of the drug and prolong the benefit after drug treatment stops?
- Because the drug remains in the bone for a long time, could a toxic dose accumulate over time?
- Does prolonged treatment with bisphosphonates slow down fracture and osteotomy healing, and if so, for how long?
- Does treatment reduce skeletal pain in all types of OI and/or age groups?
- Does prior or current treatment with bisphosphonates endanger a pregnancy?

Suggestions
When a drug is being used “off label,” as is the case in the United States for any of the bisphosphonates as a treatment for children or adults with OI, it is best for the person to be in a clinical trial or be under the care of a physician who specializes in metabolic bone disorders and is knowledgeable about bisphosphonates. Programs that treat many children with OI are likely to offer greater benefit and safety than treating a child with OI in isolation. Individuals who cannot travel to a research center may still be treated according to a research protocol and have all of their medical information forwarded to a supervising researcher, although this is less desirable than direct monitoring of all aspects of OI by a specialist.

Expert medical supervision is necessary to ensure that all possible signs of changes in the bone are being monitored. This includes gathering laboratory as well as clinical and radiologic (X-ray) information.

- Data about function—the individual’s ability to move, take care of self, and participate in other activities, also needs to be collected.
- Expert follow-up after bisphosphonate treatment stops is necessary to determine whether unexpected complications develop, and to determine the length of time the increased bone density persists.
- Bone healing should be monitored after fracture or osteotomy in people receiving bisphosphonates. If callus formation is delayed, consideration can be given to interruption of physical therapy or a longer interval without weight bearing.
- People with OI who take a bisphosphonate should have a bone density test prior to treatment, and then be monitored to see if bone density increases.
- Women who are attempting to or become pregnant should discontinue taking bisphosphonates. Women who are part of a research protocol should have a pregnancy test prior to each bisphosphonate infusion if they are receiving intravenous therapy. If an unexpected pregnancy is detected, bisphosphonate therapy should be stopped.

Parents of children with OI should discuss with the bone specialist the “pros and cons” of treating their child with bisphosphonates based on their child’s clinical and radio-
graphic severity, age, and ability to function. Treatment plans should include the lowest effective dose, and a defined end point for treatment based on time and/or reaching target bone density and overall clinical response.

Adults with OI need to discuss with their bone specialist whether they would benefit from a bisphosphonate as part of their treatment plan for reducing the effects of osteoporosis as they age. OI

Additional fact sheets or information resources available from the OI Foundation that may be of interest include:

- Adult Health Issues
- Bone Densitometry
- Bone Structure in OI
- Clinical Trials
- Novel forms of OI
- Osteoporosis
- Osteoporosis and OI
- Pain Management
- Post Surgical Care
- Surgical Considerations
- Understanding Type 1 OI

These are available at www.oif.org, by calling the Foundation at (800) 981-2663, or by writing to bonelink@oif.org.

This information update was prepared by the OI Foundation’s Medical Advisory Council.

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The OI Foundation’s Medical Advisory Council is made up of physicians and researchers currently treating patients with OI and/or involved in research or clinical trials in search of treatments or a cure for OI. The council works to:

• improve the Foundation’s medical research program and assist the Foundation’s Board of Directors in setting research goals and direction,
• increase awareness of OI among medical professionals by assisting in the development of resource materials and targeting of appropriate audiences,
• provide information to Foundation staff to aid in responding to medical inquiries, and
• review all OI Foundation information resources to verify the validity and medical accuracy of the information provided to the OI community.

The OI Foundation is the only national voluntary health organization dedicated to helping people cope with the problems associated with osteogenesis imperfecta. The Foundation’s mission is to improve the quality of life for individuals affected by OI through research to find better treatments and a cure, education, awareness and mutual support. For more information, contact the OI Foundation offices at (800) 981-2663, by writing to bonelink@oif.org, or by visiting www.oif.org.

Please feel free to share this statement with your physician(s) by copying it or removing it from this issue. The update is also available to be viewed or downloaded from the OI Foundation’s website at www.oif.org. Reprints can be requested by calling (800) 981-2663, emailing bonelink@oif.org, or writing to The OI Foundation, 804 W. Diamond Ave., Suite 210, Gaithersburg, MD 20878.