

Understanding Bisphosphonate Therapy

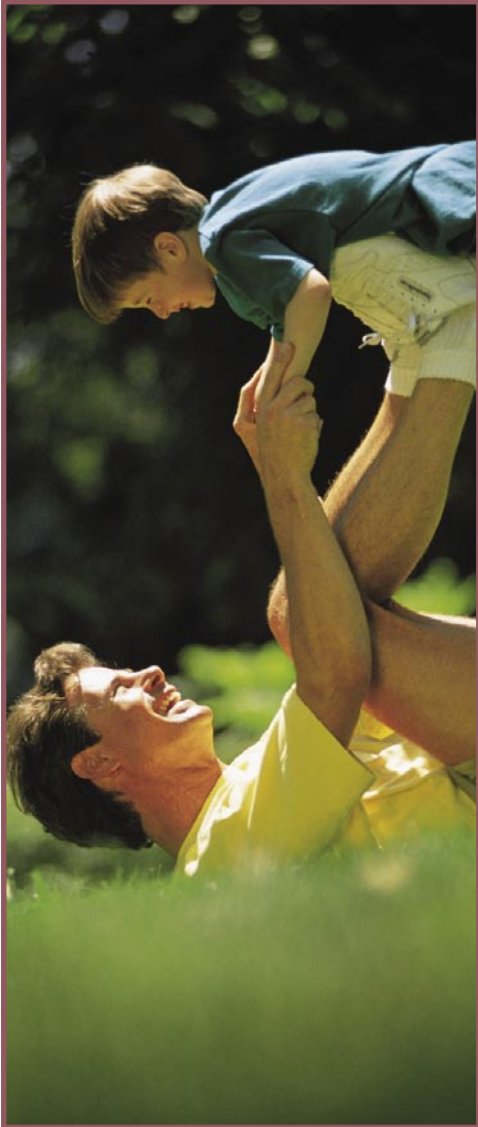


International Myeloma Foundation
12650 Riverside Drive, Suite 206
North Hollywood, CA 91607 USA
Telephone:
800-452-CURE (United States and Canada)
818-487-7455
FAX:
818-487-7454
TheIMF@myeloma.org
www.myeloma.org



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Introduction

Many patients with myeloma develop bone disease. Bone disease can cause the bones to become thinner and weaker (osteoporosis), and it can make holes appear in the bone (lytic lesions). The weakened bone that results is more likely to break under minor pressure or injury (pathologic fracture). The bones most commonly affected are the axial skeleton (spine, pelvis, ribs, and skull) and the upper ends of the long bones of the arms and legs. Myeloma cells cause bone disease by sending signals to certain bone cells called osteoclasts, causing them to break down bone. In addition to giving rise to bone disease, this process also releases calcium; if this release happens too quickly, a condition called hypercalcemia can occur. Both myeloma bone disease and hypercalcemia can be treated with a group of drugs called bisphosphonates.

WHAT ARE BISPHOSPHONATES?

Bisphosphonates are small inorganic molecules that bind to a substance called hydroxyapatite on the surface of damaged bones. At the sites of bone damage, osteoclasts are inhibited and destroyed. Since bone damage is caused by increased numbers and activity of these osteoclast bone cells, bisphosphonates reduce new bone damage and allow an opportunity for bone healing to occur.

Bisphosphonates therefore have several beneficial effects, including:

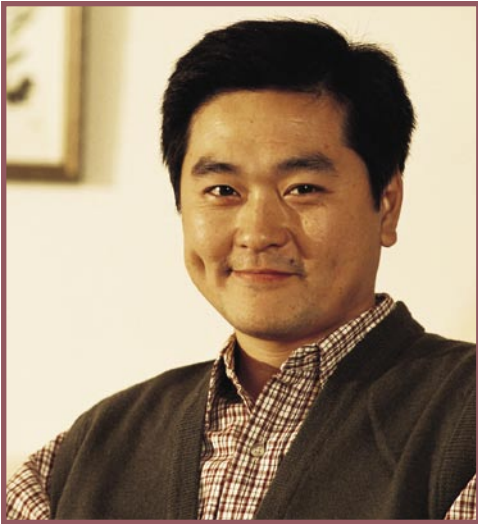
- Preventing further bone damage
- Reducing bone pain and the need for painkillers
- Correcting and preventing hypercalcemia (higher than normal levels of calcium in the blood)
- Reducing the need for radiotherapy
- Reducing pathologic fractures due to myeloma (i.e., fracture at a site where myeloma has weakened the bone)
- Improving quality of life
- Improving the chances of healing and recovery of strength of the bone

ARE BISPHOSPHONATES A TYPE OF CHEMOTHERAPY?

Bisphosphonates are not a type of chemotherapy. They were first introduced over 20 years ago as an additive for toothpaste to reduce dental decay.

Bisphosphonates are generally very safe and do not have the types of risks or side effects associated with chemotherapy, which is used to directly attack the myeloma. Bisphosphonates are used to treat several types of bone disease, including osteoporosis in women, as well as the bone-thinning effects of steroid treatment.





WHO BENEFITS FROM BISPSPHONATES?

Bisphosphonates are recommended for all patients with myeloma-related bone disease. The American Society of Clinical Oncology has established guidelines, which recommend ongoing use of bisphosphonates for all myeloma patients with documented bone disease who start on systemic treatment for the myeloma.

A randomized study published in the *New England Journal of Medicine* in 1996 documented a reduction in what are called “skeletal-related events” or “SREs” (i.e., new bone damage or fractures), as well as pain reduction and improved quality of life. The bisphosphonate used in this study was Aredia® (pamidronate).

Bisphosphonates are particularly helpful for patients being treated with steroids, such as prednisone or dexamethasone. Steroids reduce bone mass or density. Bisphosphonate use improves this negative effect on bones.

WHAT ARE THE DIFFERENT TYPES OF BISPSPHONATES?

Several bisphosphonates are commercially available, and more potent products have been developed over the years in an effort to achieve better bone healing. Thus far, the various products available have produced “equivalent” major benefits. However, these products are associated with several important differences in:

- Administration: intravenous versus oral delivery and the length of intravenous infusion time
- Potential side effects: e.g., fever, possible kidney toxicity, or bone disease in the jaw
- Potential longer-term benefits: newer, more potent bisphosphonates such as Zometa® may have added longer-term benefits

The bisphosphonates currently approved by the Food and Drug Administration (FDA) for use in multiple myeloma in the United States are pamidronate (Aredia®) and zoledronic acid (Zometa®).

Aredia® was approved based upon the results of the 1996 study in the *New England Journal of Medicine*. Use of Aredia® by monthly

intravenous infusion became the standard of care for myeloma patients. It has become established as a safe, helpful drug for the treatment of myeloma bone disease.

Zometa® was approved in 2001 based upon study results comparing it with Aredia®. Zometa® produces more rapid and prolonged reduction in elevated blood calcium, when elevated levels are present. However, results evaluating effect on SREs showed that Zometa® and Aredia® affect SREs equivalently. The major difference with Zometa®, therefore, proved to be

its much shorter infusion time of 15 minutes versus 2 to 4 hours for Aredia® (see p.16, *How Are Bisphosphonates Given*).

WHAT ARE THE POSSIBLE SIDE EFFECTS OF BISPHOSPHONATES?

Bisphosphonates are generally very well tolerated. The most common side effects are fever, vein irritation, general aches and pains, kidney dysfunction, and osteonecrosis of the jaws (ONJ).

Fever

Fever associated with bisphosphonates is typically mild (i.e., 100° to 101° F), occurring a few hours after the intravenous infusion and lasting for a few hours at most. Fever is usually easily treated or prevented with 1 or 2 Tylenol® (325 mg).

Vein Irritation

Vein irritation (mild phlebitis) can occur at the site of the infusion. It is usually mild and patients typically recover within 1 to 2 days. Careful infusion is recommended to avoid any leakage of medication around the vein. Also, a short infusion of saline at the end of the bisphosphonate infusion can clear the Aredia® or Zometa® from the area and reduce the chance of phlebitis.

General Aches and Pains

These effects sometimes occur briefly, along with fever.



Kidney Dysfunction

The main additional concern relates to kidney side effects. All bisphosphonates are potential toxins for the kidneys. Since myeloma can impact kidney function (e.g., due to myeloma protein damage or elevated blood calcium), the possibility of kidney-related side effects is of particular concern.

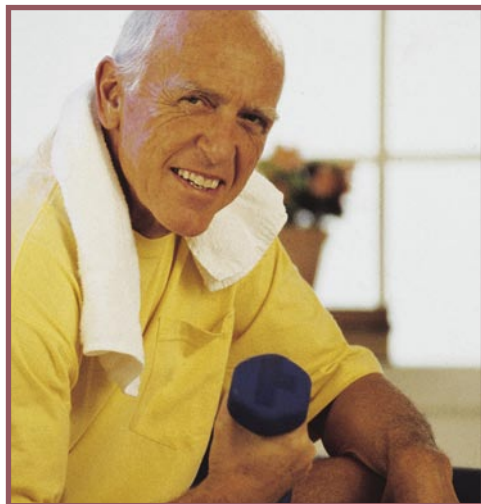
Aredia® has been used widely for over ten years, including the initial trials period. The type of kidney toxicity that has emerged is an excess of a serum protein, called albumin, in the urine (known as albuminuria or nephrotic syndrome). This toxicity has occurred predominantly with uses of higher than recommended doses (e.g., 180 mg versus 90 mg) and/or more frequent than recommended dosing schedules (e.g., every 2 weeks versus once/month). This side effect is usually reversible with dose and/or schedule adjustments or, in occasional severe cases, discontinuing Aredia®. Very rare irreversible damage has occurred. Periodic monitoring (e.g., every 3 to 6 months) of urine protein levels with 24-hour urine collection is recommended to prevent any significant kidney damage.

Zometa® has also been used for about 10 years, including the clinical trial period. The major kidney toxicity-related concern that has emerged with Zometa® is an increase in serum creatinine, which is an indication of kidney dysfunction. Reports of

both increased creatinine and occasionally more severe kidney damage have raised concern that this much more potent bisphosphonate must be used more cautiously with respect to kidney function.

To minimize the potential for kidney-related problems, your doctor should follow several recommendations:

- Your doctor should be especially cautious with the use of Zometa® if there is concern from the outset for kidney dysfunction (i.e., with Bence Jones myeloma, diabetes, long-standing high blood pressure, or in elderly or frail patients). Zometa® should not be used in patients with known kidney deterioration as determined by creatinine level over 3 mg/dl.



- Your doctor should check your serum creatinine level before each dose of Zometa®.
- If the serum creatinine value has increased by 0.5 mg/dl in a patient with normal renal function at the outset, the doctor should hold the next dose until the value returns to within 10% of baseline.
- If the serum creatinine value has increased by 1.0 mg/dl in a patient with abnormal renal function at the outset, the doctor should hold the next dose until the value returns to within 10% of baseline.
- In a patient who has experienced a mild elevation in serum creatinine value that has returned to 10% of baseline, the doctor may consider adjustments to the treatment schedule. Adjustments may include increasing the time of infusion from 15 to 30 minutes or more, using a larger volume of diluting fluids, or delaying the administration of the next dose. The doctor should use his or her judgment to determine which option is the most appropriate for an individual patient.
- Your doctor should be aware that certain medications with the potential to affect kidney function may be more likely to do so if they are given at the same time as bisphosphonates. Some examples of these medications are nonsteroidal anti-inflammatory drugs (NSAIDs), thalidomide, and certain antibiotics.

Osteonecrosis of the Jaws

Osteonecrosis of the Jaws (ONJ) is a previously rare jaw problem now being observed in a small percentage of myeloma patients taking Aredia® and Zometa®. This condition produces pain, swelling, and bone damage around the tooth sockets in the jaws. There is bone necrosis or loss of bone which can lead to loose teeth, sharp edges of exposed bone, bone spurs, and the breaking loose of small bone spicules or dead bone. Symptoms may not be obvious at first, or may include pain, swelling, numbness or a “heavy jaw” feeling, or loosening of a tooth.

- Consultation with an oral surgeon or dental oncologist familiar with osteonecrosis is strongly recommended for patients who suspect that they may have ONJ.



Management without surgery is recommended as a first step. Minor dental work to reduce sharp edges or remove injured tissue may be required. A protective mouth guard may also be helpful.

- Antibiotic treatment is recommended if there is infection. The type of therapy selected depends upon the type of infection that is documented. Oral rinses can also be used.
- If problems persist and/or if healing is slow, consideration can be given to stopping bisphosphonate therapy for 2-4 months to facilitate recovery. Although study results are lacking, there are anecdotal reports of benefit with brief interruption of Aredia® or Zometa® treatment.



- If surgery is absolutely required, interruption of bisphosphonate therapy is strongly recommended. Current data indicate very poor healing with continued bisphosphonates in this setting.
- Dentures can be worn, but many need adjustment. Placement of dental implants appears to be contraindicated. Use of hyperbaric oxygen does not appear to be helpful.
- Careful monitoring and follow-up are required.
- Prevention can help patients avoid or reduce the scope of the problem. Be aware and inform your dentist about this potential risk for patients who take bisphosphonates; maintain excellent oral hygiene, and make sure that you have regular visits to the dentist. Avoid tooth extraction and/or any elective jaw surgery if at all possible. If there is an opportunity, proceed with careful dental evaluation and any required preventative dental care before starting bisphosphonate therapy.
- There is every reason to hope that with appropriate awareness and early management, serious problems from osteonecrosis can be avoided.

Other Side Effects

Other side effects are generally rare. As with most drugs, however, other reactions occasionally occur and may include rash, stomach upset, blurred vision, headache,

and shortness of breath. Severe allergic reactions are very rare, although possible.

WHO SHOULD NOT TAKE BISPHOSPHONATES?

- Patients without documented myeloma-related bone disease should not take bisphosphonates. This means that, in general, patients with monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma *without* bone disease do not need or benefit from bisphosphonates. However, this remains an area of ongoing research and clinical trials.
- As noted, bisphosphonates must be used with caution in patients with pre-existing kidney disease or known elevation in serum creatinine, especially >3.0 mg/dl but also any value above the normal range.
- Patients who have allergic reactions or are intolerant to bisphosphonate treatment should not take bisphosphonates.

HOW ARE BISPHOSPHONATES GIVEN?

Both Aredia® and Zometa® are given intravenously on a monthly basis. Aredia® is given over 2 to 4 hours by intravenous infusion, and premedication with 1 or 2 Tylenol® (325 mg) can be helpful. Zometa® is given over 15 to 45 minutes by intravenous infusion, and premedication may also be beneficial.

Toxicities associated with both medications, especially potential renal toxicities, are related to dose, time of infusion, and frequency of infusion. If kidney toxicity is a concern, the infusion time of Aredia® can be

increased to 4 hours and the infusion time of Zometa® can be increased from 15 minutes to 30 to 45 minutes.

If, for any reason, difficulty with intravenous bisphosphonates exists, oral bisphosphonates can be considered. Administering the oral bisphosphonates Fosamax® (e.g., once per week by mouth) and/or Actonel® (daily dosing by mouth) is not approved specifically for myeloma by the FDA. Nonetheless, occasional patients can benefit from oral bisphosphonates, especially patients who are intolerant of intravenous infusion, have nephrotoxicity, and/or are concomitantly using steroids. Oral bisphosphonates can cause esophagitis and/or other gastrointestinal complaints, which preclude use.

CAN BISPHOSPHONATES BE COMBINED WITH OTHER THERAPIES?

In general, bisphosphonates can be safely combined with most other therapies. Your physician may decide *not* to give Aredia® or Zometa® on or close to the same day as administration of intravenous chemotherapy. Caution about potential nephrotoxicity has been noted above.

WILL INSURANCE COVER THE COSTS OF BISPHOSPHONATES?

Since Aredia® and Zometa® are FDA, commercially approved medications, Medicare and most insurance programs reimburse for bisphosphonate use. Any problems with reimbursement should be brought to the attention of your physician and/or Novartis.

WHAT OTHER APPROACHES TO BONE CARE ARE AVAILABLE?

Kyphoplasty provides a new tool that may impact bone care for myeloma patients. This procedure involves the injection of liquid cement using the balloon technique in an attempt to provide acute pain relief and improvement in the structural integrity of collapsed vertebrae or other damaged bones. Although results from large studies are not available, the procedure has been found safe and effective in selected patients.

General measures to improve bone health are recommended, including:

- Adequate pain control to allow moving about and exercise.
- Radiation therapy and/or orthopedic surgery to restore structural integrity of bones and recovery of full mobilization. Radiation therapy should be used sparingly for acute problems such as spinal cord compression, severe refractory pain, and treatment or prevention of pathologic fracture. Since radiation therapy can impair local bone healing, many physicians prefer to use systemic steroids and/or other antimyeloma therapy. Orthopedic surgery should be used as necessary.
- Exercise, especially walking and/or swimming, to enhance bone strength, flexibility, and endurance.
- Avoidance of risky activities (e.g., climbing ladders), which can increase the likelihood of falls and/or fractures.

- Regular re-evaluation and follow-up testing of bones by x-ray/scan/bone density testing to rule out new bone disease and assess the impact of treatment.

WHAT DOES THE FUTURE HOLD?

Considerable new research is ongoing to investigate myeloma bone disease. Of particular interest is treatment that can improve bone cell function with activation of osteoblasts to promote bone healing. The future looks promising for useful new drug treatments.

QUESTIONS TO ASK YOUR DOCTOR

Some questions you may want to ask your doctor about your medication are:

- For how long will I be taking bisphosphonates?
- How do I get repeat prescriptions?
- Of which side effects should I be aware?
- Is there anything I need to avoid while taking bisphosphonates?
- May I see a patient information leaflet about my medicine?

About the IMF

*"One person can make a difference,
Two can make a miracle."*

Brian D. Novis
IMF Founder

Myeloma is a little-known, complex, and often misdiagnosed bone marrow cancer that attacks and destroys bone. Myeloma affects approximately 75,000 to 100,000 people in the United States, with more than 15,000 new cases diagnosed each year. While there is presently no known cure for myeloma, doctors have many approaches to help myeloma patients live better and longer.

The International Myeloma Foundation (IMF) was founded in 1990 by Brian and Susie Novis shortly after Brian's myeloma diagnosis at the age of 33. It was Brian's dream that future patients would have easy access to medical information and emotional support throughout their battle with myeloma. He established the IMF with the 3 goals of treatment, education, and research. He sought to provide a broad spectrum of services for patients, their families, friends, and health care providers. Although Brian died 4 years after his initial diagnosis, his dream didn't. Today the IMF reaches out to an international membership of more than 125,000. The IMF was the first organization dedicated solely to myeloma, and today it remains the largest.

The IMF provides programs and services to aid in the research, diagnosis, treatment, and management of myeloma. The IMF ensures that no one must brave the myeloma battle alone. We care for patients today, while working toward tomorrow's cure.

How Can the IMF Help You?

PATIENT EDUCATION

INFORMATION PACKAGE

Our free IMF InfoPack provides comprehensive information about myeloma, treatment options, disease management, and IMF services. It includes our acclaimed *Patient Handbook*.

INTERNET ACCESS

Log on to www.myeloma.org for 24-hour access to information about myeloma, the IMF, education, and support programs.

ONLINE MYELOMA FORUM

Join the IMF Internet Discussion Group at www.myeloma.org/listserve.html to share your thoughts and experiences.

MYELOMA MINUTE

Subscribe to this free weekly email newsletter for up-to-the-minute information about myeloma.

PATIENT & FAMILY SEMINARS

Meet with leading experts in myeloma treatment to learn more about recent advances in therapy and research.

MYELOMA MATRIX

On our website and in print, this document is a comprehensive guide to drugs in development for myeloma.

MYELOMA TODAY NEWSLETTER

Our quarterly newsletter is available free of charge by subscription.

SUPPORT

MYELOMA HOTLINE: 800-452-CURE (2873)

Toll-free throughout the United States and Canada, the IMF hotline is staffed by trained information specialists and is in frequent interaction with members of our Scientific Advisory Board.

SUPPORT GROUPS

A worldwide network of more than 100 myeloma support groups hold regular meetings for members of the myeloma community. The IMF conducts annual retreats for myeloma support group leaders.

RESEARCH

BANK ON A CURE®

This DNA bank will provide genetic data research in new drug development.

THE INTERNATIONAL STAGING SYSTEM

This updated staging system for myeloma will enhance physicians' ability to select the most appropriate treatment for each patient.

RESEARCH GRANTS

Leading the world in collaborative research and achieving extraordinary results, the IMF Grant Program supports both junior and senior

researchers working on a broad spectrum of projects. The IMF has attracted many young investigators into the field of myeloma, and they have remained in the field and are actively pursuing a cure for this disease.

Glossary

Albuminuria: The presence of an excess of serum protein in the urine.

Axial skeleton: Spine, pelvis, ribs, and skull. Along with the upper ends of the long bones of the arms and legs, the axial skeleton is most commonly affected by pathologic fracture.

Bence Jones myeloma: Myeloma characterized by the presence of Bence Jones protein, an abnormal protein in urine or plasma.

Bisphosphonate: A small inorganic molecule that binds to the surface of damaged bones. Bisphosphonate therapy is used in patients with bone disease to reduce new bone damage and allow an opportunity for bone healing to occur.

Chemotherapy: Drugs that are used to kill cancer cells.

Creatinine: A compound excreted in the blood and urine. A high level of creatinine is an indication of kidney dysfunction.

Esophagitis: Inflammation of the esophagus (the tube that transports food from the mouth to the stomach).

Hydroxyapatite: A compound found on the surface of bones that gives them rigidity.

Hypercalcemia: Higher than normal levels of calcium in the blood.

Kyphoplasty: The injection of liquid cement into damaged bone using a balloon technique. This procedure may provide acute pain relief and improvement in structural integrity of collapsed vertebrae or other damaged bones.

Lytic lesions: Holes in the bone.

