Bisphosphonate Therapy for Osteoporosis: Benefits, Risks, and Drug Holiday

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ABSTRACT

The amino-bisphosphonates are first-line therapy for the treatment of most patients with osteoporosis, with proven efficacy to reduce fracture risk at the spine, hip, and other nonvertebral skeletal sites. Further, bisphosphonates have been associated with a significant decrease in morbidity and increase in survival. Following the use of bisphosphonates in millions of patients in clinical practice, some unexpected possible adverse effects have been reported, including osteonecrosis of the jaw, atypical femur fractures, atrial fibrillation, and esophageal cancer. Because bisphosphonates are incorporated into the skeleton and continue to exert an antiresorptive effect for a period of time after dosing is discontinued, the concept of a drug holiday has emerged, whereby the risk of adverse effects might be decreased while the patient still benefits from antifracture efficacy. Patients receiving bisphosphonates who are not at high risk for fracture are potential candidates for a drug holiday, while for those with bone mineral density in the osteoporosis range or previous history of fragility fracture, the benefits of continuing therapy probably far outweigh the risk of harm.

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KEYWORDS: Amino-bisphosphonates, Drug holiday, Fracture

Amino-bisphosphonates decrease bone resorption by inhibiting osteoclast function and have proven antifracture efficacy in patients with osteoporosis. At least 4 million American women were prescribed bisphosphonates to treat osteoporosis in 2008. In addition, many men with osteoporosis and patients receiving glucocorticoids are receiving bisphosphonate therapy. With such a large number of patients receiving bisphosphonate therapy for ever-longer durations, there is an increasing chorus of questions about their long-term use.

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Conflict of Interest: See last page of article.

Authorship: See last page of article.

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The majority of data about the fracture reduction efficacy and safety of bisphosphonates come from randomized, placebo-controlled phase III regulatory trials in postmenopausal women, mostly 3 years in duration, with fewer than 50,000 total subjects. Some trials were extended, with alendronate out to 10 years, but clinical trial data for long-term use of bisphosphonates are scarce, with no placebo-controlled data beyond 5 years.

This commentary weighs the known antifracture benefits of bisphosphonate therapy with their potential risks and provides guidance as to when a bisphosphonate drug holiday may be appropriate.

LONG-TERM RETENTION OF BISPHOSPHONATE IN THE SKELETON

The effects of most therapies resolve soon after discontinuation. Bisphosphonates are unique in that they bind to hydroxyapatite in bone and can remain there for years. During remodeling, which is significantly decreased by bis-
Fracture risk: Hip fracture incidence decreased between 1996 and 2007 in the US when bisphosphonate use was widespread, supporting the beneficial effects of bisphosphonate therapy in reducing the risk of hip fracture. Bisphosphonates are approved for the treatment of osteoporosis and bone marrow metastasis.

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CLINICAL SIGNIFICANCE

- Protection from important fractures persists with long-term bisphosphonate therapy. Patients with higher affinity for bisphosphonates have generally smaller benefits provided that the bisphosphonate is taken as directed. 
- The risk of osteonecrosis of the jaw is increased with bisphosphonate use. 
- The risk of atrial fibrillation is increased with bisphosphonate use.

DATA FROM STUDIES

Table 1: Absolute Fracture Risk Reduction by Medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Clinical Trial</th>
<th>Y Frx</th>
<th>Non-V Frx</th>
<th>Hip Frx</th>
<th>Y Frx</th>
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<tbody>
<tr>
<td>Alendronate</td>
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<td>Risedronate</td>
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Table 2: Relative Fracture Risk Reduction by Medication

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ARTIFICIAL FIBRILLATION

In addition to prevention of other factors, atrial fibrillation is also associated with risk factors including age, gender, and diabetes. It is often triggered by paroxysmal atrial fibrillation, which is a common arrhythmia of the atria. The condition is characterized by rapid, uncoordinated atrial contractions, leading to an irregular heart rhythm that affects the heart's ability to pump blood effectively. This condition can be preventable by addressing risk factors and managing the underlying causes.

ATYPICAL FEMUR FRACTURES

According to the report, there were no differences between groups in terms of abuse. The authors note that further research is needed to fully understand the factors associated with atypical femur fractures and to develop effective prevention strategies. The study highlights the importance of continued investigation into this area of research to improve patient outcomes and reduce the burden of this condition.

OSTEONECROSIS OF THE JAW

The report discusses the association of bisphosphonate therapy with osteonecrosis of the jaw (ONJ). It highlights the need for increased awareness among healthcare providers and patients about the potential risks associated with bisphosphonate use, particularly in individuals at increased risk, such as those with conditions that increase the risk of osteoporosis. The report also emphasizes the importance of monitoring patients for signs of ONJ and implementing appropriate management strategies. The authors call for continued research to better understand the underlying causes and mechanisms of ONJ and to develop more effective prevention and treatment strategies.

THERAPY

The report concludes by stressing the importance of preventative measures and early intervention to minimize the risk of ONJ in patients using bisphosphonates. It highlights the need for multidisciplinary approaches involving healthcare providers, patients, and their families to optimize care and improve outcomes. The report encourages ongoing research and collaboration to advance our understanding of the complex factors involved in the development of ONJ and to develop evidence-based guidelines for effective management.
Inflammation of the lung can be acute or chronic. Acute pulmonary inflammation can be caused by infections such as pneumonia or allergic reactions. Chronic pulmonary inflammation can be caused by conditions such as aspirin-exacerbated respiratory disease or sarcoidosis.

The symptoms of pulmonary inflammation can include coughing, chest pain, shortness of breath, and fever. Treatment depends on the cause of the inflammation and may include antibiotics for infections, corticosteroids for allergic reactions, or immunosuppressive drugs for sarcoidosis.


disease, it is important to rule out other causes of chest pain such as heart disease, lung cancer, or other serious conditions. If you have symptoms of pulmonary inflammation, you should see a doctor for a proper diagnosis and treatment plan.

**Diagnosing Pulmonary Inflammation**

A diagnosis of pulmonary inflammation usually involves a combination of physical examination, medical history, and laboratory tests. X-rays or CT scans of the chest may be done to look for signs of inflammation. Bronchoscopy or pulmonary function tests may also be performed to evaluate the lungs.

**Treating Pulmonary Inflammation**

The treatment for pulmonary inflammation depends on the cause of the inflammation and may include medications such as corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or biologic agents. In some cases, surgery may be necessary to remove a lung mass or other obstructing lesion.

**Preventing Pulmonary Inflammation**

To prevent pulmonary inflammation, it is important to avoid exposure to substances that can cause lung irritation, such as tobacco smoke, air pollution, and dust. Vaccinations, such as the vaccine against influenza, can also help prevent lung infections that may lead to inflammation.

**Summary**

Pulmonary inflammation can be caused by a variety of factors and can affect individuals of all ages. Diagnosis and treatment of pulmonary inflammation require a thorough evaluation and a tailored approach based on the cause and severity of the inflammation. By understanding the causes and symptoms of pulmonary inflammation, individuals can take steps to prevent this condition and seek prompt medical attention if symptoms develop.
MONITORING A DRUG HOLIDAY

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