

Antiretrovirals May Contribute to Bone Loss

BY SHERRY BOSCHERT

FROM A MEETING ON HIV MANAGEMENT

SAN FRANCISCO — People with HIV infection tend to have more risk factors for bone loss than do people without HIV, and antiretroviral medications may be adding to that risk.

The specific role of antiretroviral therapy in bone loss has been controversial: Some studies say there is no association,

but others suggest that the drugs do contribute to bone loss. Results of two small but well-conducted studies recently tipped the emphasis toward concern about the differential effects of antiretrovirals on bone mineral density, Dr. Dolores Shoback said.

“I think it’s very provocative. We certainly need more data, and this needs to be confirmed,” she said at the meeting, which was sponsored by the University

of California, San Francisco.

One randomized, controlled trial of 71 HIV-infected patients suggested that antiretroviral regimens that contain a protease inhibitor booster have a greater negative impact on spinal bone density than do regimens without a boosted protease inhibitor, said Dr. Shoback, professor of medicine at UCSF.

At baseline, 31% of the patients were osteopenic and 3% were osteoporotic.

Bone densities were retested after 48 weeks of combination HIV therapy with a nonnucleoside reverse transcriptase inhibitor (NNRTI) and nucleoside reverse transcriptase inhibitors (NRTIs), or an NNRTI and a boosted protease inhibitor, or two NRTIs and a boosted protease inhibitor. On average, the cohort as a whole lost 4% of lumbar spine bone mineral density and 3% of hip bone density during those 48 weeks (AIDS 2009; 23:817-24). The groups treated with boosted protease inhibitors lost significantly more spinal density—4.4% when combined with an NNRTI and 5.8% when combined with NRTIs—compared with the NNRTI-plus-NRTI arm (1.5%). Changes in hip bone density did not differ significantly by treatment group.



Antiretroviral regimens that contain a protease inhibitor booster have a greater impact on spinal bone density.

DR. SHOBACK

The second study randomized 50 HIV-infected patients to treatment with lopinavir/ritonavir plus zidovudine/lamivudine (ZDV/3TC) or lopinavir/ritonavir plus nevirapine, with bone densities compared at baseline and 2 years. At the start, up to 31% were osteopenic and up to 4% were osteoporotic. The ZDV/3TC group lost 6.3% of bone mineral density in the hip and 5.1% in the spine, compared with smaller losses of 2.3% in the hip and 2.6% in the spine in the nevirapine group. Spinal density decreased mainly in the first year and then stabilized, but hip density continued to fall in the second year (AIDS 2009; 23: 1367-76).

The investigators speculated that ZDV/3TC increased osteoclastic activity.

There are not enough data yet to support changing antiretroviral regimens if bone mineral density is low, she added, but physicians should pay attention to nutrition (especially calcium and vitamin D), lifestyle factors, and weight-bearing exercise in patients with HIV.

Ongoing immune activation in HIV infection leads to high levels of cytokines. “There pretty much isn’t a cytokine that doesn’t have a negative effect on bone,” she said.

Many other risk factors for bone loss and fractures are more common in the setting of HIV. Five of six cross-sectional studies found low levels of hydroxyvitamin D in patients with HIV. Compared with the HIV-negative population, people with HIV have higher rates of smoking and alcohol use, are more likely to be treated with steroids, and are more likely to have periods of immobilization and illness, bouts of weight loss, hypogonadism (in men), and amenorrhea (in women). ■

Disclosures: Dr. Shoback has been a speaker for Novartis.

Zmax® (azithromycin extended release) for oral suspension

Brief Summary of Prescribing Information

INDICATIONS AND USAGE

Zmax is indicated for the treatment with mild to moderate infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below.

Acute bacterial sinusitis in adults due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*.

Community-acquired pneumonia in adults and pediatric patients six months of age or older due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*, in patients appropriate for oral therapy. Pediatric use in this indication is based on extrapolation of adult efficacy.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Zmax and other antibacterial drugs, Zmax should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to Zmax. Therapy with Zmax may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

CONTRAINDICATIONS

Zmax is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin or any macrolide or ketolide antibiotic.

WARNINGS AND PRECAUTIONS

Allergic and skin reactions

Serious allergic reactions, including angioedema, anaphylaxis, Stevens Johnson syndrome, and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy using other formulations. Although rare, fatalities have been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent exposure to antigen has not been determined.

If an allergic reaction occurs, appropriate therapy should be instituted. Physicians should be aware that re-occurrence of the allergic symptoms may occur when symptomatic therapy is discontinued.

Clostridium difficile-associated diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Zmax, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Exacerbation of myasthenia gravis

Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy.

Gastrointestinal Disturbances

A higher incidence of gastrointestinal adverse events (8 of 19 subjects) was observed when Zmax was administered to a limited number of subjects with GFR <10 mL/min.

Prolongation of the QT interval

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization.

Development of drug resistant bacteria

Prescribing Zmax in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

ADVERSE REACTIONS

Clinical studies experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults:

The data described below reflect exposure to Zmax in 728 adult patients. All patients received a single 2-g oral dose of Zmax. The population studied had community-acquired pneumonia and acute bacterial sinusitis.

In controlled clinical trials with Zmax, the majority of the reported treatment-related adverse reactions were gastrointestinal in nature and mild to moderate in severity.

Overall, the most common treatment-related adverse reactions in adult patients receiving a single 2-g dose of Zmax were diarrhea/loose stools (12%), nausea (4%), abdominal pain (3%), headache (1%), and vomiting (1%). The incidence of treatment-related gastrointestinal adverse reactions was 17% for Zmax and 10% for pooled comparators. Treatment-related adverse reactions following Zmax treatment that occurred with a frequency of <1% included the following:

Cardiovascular: palpitations, chest pain

Gastrointestinal: constipation, dyspepsia, flatulence, gastritis, oral moniliasis

Genitourinary: vaginitis

Nervous System: dizziness, vertigo

General: asthenia

Allergic: rash, pruritus, urticaria

Special Senses: taste perversion

Laboratory Abnormalities

In subjects with normal baseline values, the following clinically significant laboratory abnormalities (irrespective of drug relationship) were reported in Zmax clinical trials:

- with an incidence of greater than or equal to 1%: reduced lymphocytes and increased eosinophils; reduced bicarbonate;
- with an incidence of less than 1%: leukopenia, neutropenia, elevated bilirubin, AST, ALT, BUN, creatinine, alterations in potassium.

Where follow-up was provided, changes in laboratory tests appeared to be reversible.

Pediatric Patients:

The data described below reflect exposure to Zmax in 907 pediatric patients. The population was 3 months to 12 years of age. All patients received a single 60 mg/kg oral dose of Zmax. As in adults, the most common treatment-related adverse reactions in pediatric subjects were gastrointestinal in nature. The pediatric subjects all received a single 60 mg/kg dose (equivalent to 27 mg/lb) of Zmax.

In a study with 450 pediatric subjects (ages 3 months to 48 months), vomiting (11%), diarrhea (10%) loose stools (9%), and abdominal pain (2%) were the most frequently reported treatment-related gastrointestinal adverse reactions. Many treatment related gastrointestinal adverse reactions with an incidence greater than 1% began on the day of dosing in these subjects [43%(68/160)] and most [53%(84/160)] resolved within 48 hours of onset. Treatment-related adverse events that were not gastrointestinal, occurring with a frequency \geq 1% were: rash (5%), anorexia (2%), fever (2%), and dermatitis (2%).

In a second study of 337 pediatric subjects, ages 2 years to 12 years, the most frequently reported treatment-related adverse reactions also included vomiting (14%), diarrhea (7%), loose stools (2%), nausea (4%) and abdominal pain (4%).

A third study investigated the tolerability of two different concentrations of azithromycin oral suspension in 120 pediatric subjects (ages 3 months to 48 months), all of whom were treated with azithromycin. The study evaluated the hypothesis that a more dilute, less viscous formulation (the recommended 27 mg/mL concentration of Zmax) is less likely to induce vomiting in young children than a more concentrated suspension used in other pediatric studies. The vomiting rate for subjects taking the dilute concentration azithromycin was 3% (2/61). The rate was numerically lower but not statistically different from the vomiting for the more concentrated suspension. Across both treatment arms, the only treatment-related adverse events with a frequency of \geq 1% were vomiting (6%, 7/120) and diarrhea (2%, 2/120).

Treatment-related adverse reactions with a frequency of <1% following Zmax treatment in all 907 pediatric subjects in the Phase 3 studies were:

Body as a whole: chills, fever, flu syndrome, headache;

Digestive: abnormal stools, constipation, dyspepsia, flatulence, gastritis, gastrointestinal disorder, hepatitis;

Hemic and Lymphatic: leukopenia;

Nervous System: agitation, emotional lability, hostility, hyperkinesia, insomnia, irritability, parasthesia, somnolence;

Respiratory: asthma, bronchitis, cough increased, dyspnea, pharyngitis, rhinitis;

Skin and Appendages: dermatitis, fungal dermatitis, maculopapular rash, pruritus, urticaria;

Special Senses: otitis media, taste perversion;

Urogenital: dysuria.

Laboratory Abnormalities

In subjects with normal baseline values, the following clinically significant laboratory abnormalities (irrespective of drug relationship) were reported in Zmax pediatric clinical trials:

- with an incidence of greater than or equal to 1%: elevated eosinophils, BUN, and potassium; decreased lymphocytes; and alterations in neutrophils;
- with an incidence of less than 1%: elevated SGOT, SGPT and creatinine; decreased potassium; and alterations in sodium and glucose.

Postmarketing experience with other azithromycin products

Because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency or establishing a causal relationship to drug exposure is not always possible.

Adverse events reported with azithromycin immediate release formulations during the post-marketing period for which a causal relationship may not be established include:

Allergic: arthralgia, edema, urticaria and angioedema

Cardiovascular: palpitations and arrhythmias including ventricular tachycardia and hypotension

There have been rare reports of QT prolongation and *torsades de pointes*.

Gastrointestinal: anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis, pancreatitis, oral candidiasis and rare reports of tongue discoloration

General: asthenia, paresthesia, fatigue, malaise and anaphylaxis (rarely fatal)

Genitourinary: interstitial nephritis, acute renal failure, moniliasis and vaginitis

Hematopoietic: thrombocytopenia, mild neutropenia

Liver/Biliary: abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, some of which have resulted in death

Nervous System: convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation and syncope

Psychiatric: aggressive reaction and anxiety

Skin/Appendages: pruritus, rash, photosensitivity, rarely serious skin reactions including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

Special Senses: hearing disturbances including hearing loss, deafness and/or tinnitus and rare reports of taste/smell perversion and/or loss

DRUG INTERACTIONS

Warfarin

Although, in a study of 22 healthy men, a 5-day course of azithromycin did not affect the prothrombin time from a subsequently administered dose of warfarin, spontaneous post-marketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants.

Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects. Pregnancy Category B: Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose concentrations (i.e., 200 mg/kg/day). These daily doses in rats and mice, based on mg/m², are estimated to be approximately equivalent to one or one-half of, respectively, the single adult oral dose of 2 g. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in the treatment of pediatric patients under 6 months of age have not been established.

Community-Acquired Pneumonia: The safety and effectiveness of Zmax have been established in pediatric patients 6 months of age or older with community-acquired pneumonia due to *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenzae* or *Streptococcus pneumoniae*. Use of Zmax for these patients is supported by evidence from adequate and well-controlled studies of Zmax in adults with additional safety and pharmacokinetic data in pediatric patients.

Acute bacterial sinusitis: Safety and effectiveness in the treatment of pediatric patients with acute bacterial sinusitis have not been established.

Geriatric Use

Data collected from the azithromycin capsule and tablet formulations indicate that a dosage adjustment does not appear to be necessary for older patients with normal renal function (for their age) and hepatic function receiving treatment with Zmax.

In clinical trials of Zmax, 17% of subjects were at least 65 years of age (214/1292) and 5% of subjects (59/1292) were at least 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Renal Impairment

No dosage adjustment is recommended for patients with GFR >10 mL/min. Caution should be exercised when Zmax is administered to patients with GFR <10 mL/min, due to a higher incidence of gastrointestinal adverse events (8 of 19 subjects) observed in a limited number of subjects with GFR <10 mL/min.

Gender

The impact of gender on the pharmacokinetics of azithromycin has not been evaluated for Zmax. However, previous studies have demonstrated no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment of Zmax is recommended based on gender.

OVERDOSAGE

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

Please see full Prescribing Information for additional information about Zmax.

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