

# Childhood Bugs May Protect Women Against RA

BY KATE JOHNSON  
Montreal Bureau

Healthy female babies might not make such healthy adults, at least when it comes to rheumatoid arthritis, according to a group of British researchers.

Exposure to infection in early childhood may help protect women from developing rheumatoid arthritis (RA), reported Dr. C.J. Edwards and colleagues from the Uni-

versity of Southampton and the Southampton General Hospital, United Kingdom.

"It appears that a developing immune system exposed to fewer infectious microorganisms through improved standards of hygiene may be more likely to produce [rheumatoid factor] and perhaps begin the pathological process that leads to [rheumatoid arthritis]," reported Dr. Edwards and colleagues (Ann. Rheum. Dis. 2006;65:401-4).

The researchers' study measured

rheumatoid factor (RF) levels in 675 men and 668 women aged 61-69 years and investigated the association of RF with markers of exposure to childhood infection. These markers included sharing a bedroom during childhood, social class, and birth order.

"Reduced exposure to microorganisms is thought to result from higher social class, fewer siblings, having your own bedroom during childhood, and living in an urban environment," the authors reported.

A positive RF level—defined as 6 IU/ml or higher—was present in 16.6% of the men and 11.8% of the women in the study.

Although no significant relationship was found between markers of childhood infection and the presence of RF in men, women who shared a bedroom during childhood had a significantly lower risk of being RF positive (odds ratio 0.48), they noted.

There also was a trend that associated lower birth order and lower social class with a reduced likelihood of RF positivity in women.

The presence of RF has been shown to confer a risk of developing RA—although

**'It appears that a developing immune system exposed to fewer infectious microorganisms ... may be more likely to produce' rheumatoid factor.**

RF may be present for up to 10 years before clinical disease onset, the authors noted.

Up to 80% of people with RA also have RF; however, 10% of the normal population tests positive for RF, and prevalence increases with age. It is not

clear why the association of RF positivity and increased childhood exposure to infection was found in women and not in men.

The epidemiology of RA, however, is markedly different for the two groups, noted the authors. "Women are three times more likely to have RA than men and have a peak incidence in middle age. In contrast, men have an increasing incidence that becomes equal to that of women later in life."

The authors noted a parallel between the "hygiene hypothesis" linking decreased infectious exposure and allergy.

"Epidemiological evidence has now shown that autoimmune diseases such as type 1 diabetes are more likely in subjects exposed to a 'cleaner' environment during childhood and that atopy has an increased incidence in subjects with autoimmune diseases, including RA," Dr. Edwards and colleagues noted.

## Web Site Offers Handy Mnemonics

The Medical Mnemonics Web site offers a free, online, searchable database of medical mnemonics to help remember important details. The hip's lateral rotators will come to mind with the mnemonic: Piece Goods Often Go on Quilts: Piri-formis, Gemellus superior, Obturator internus, Gemellus inferior, Obturator externus, Quadratus femoris. The database is also available for PalmOS, PDE, Avant-Go, and WAP, and is customizable. For more information, visit [www.medicalmnemonics.com](http://www.medicalmnemonics.com). The Web site is funded in part by an educational grant from HealthFrontier, Inc.

## BONIVA® (ibandronate sodium) INJECTION

BRIEF SUMMARY  
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

### CONTRAINDICATIONS

- Known hypersensitivity to BONIVA Injection or to any of its excipients
- Uncorrected hypocalcemia (see **PRECAUTIONS: General**)

### WARNINGS

BONIVA Injection, like other bisphosphonates administered intravenously, may cause a transient decrease in serum calcium values (see **PRECAUTIONS**). BONIVA Injection must only be administered intravenously. Care must be taken not to administer BONIVA Injection intra-arterially or paravenously as this could lead to tissue damage. Do not administer BONIVA Injection by any other route of administration. The safety and efficacy of BONIVA Injection following non-intravenous routes of administration have not been established.

### PRECAUTIONS: General

**Mineral Metabolism:** Hypocalcemia, hypovitaminosis D, and other disturbances of bone and mineral metabolism must be effectively treated before starting BONIVA Injection therapy. Adequate intake of calcium and vitamin D is important in all patients. Patients must receive supplemental calcium and vitamin D.

**Renal Impairment:** Treatment with intravenous bisphosphonates has been associated with renal toxicity manifested as deterioration in renal function (ie, increased serum creatinine) and in rare cases, acute renal failure. No cases of acute renal failure were observed in controlled clinical trials in which intravenous BONIVA was administered as a 15- to 30-second bolus. The risk of serious renal toxicity with other intravenous bisphosphonates appears to be inversely related to the rate of drug administration. Patients who receive BONIVA Injection should have serum creatinine measured prior to each dosage administration. Patients with concomitant diseases that have the potential for adverse effects on the kidney or patients who are taking concomitant medications that have the potential for adverse effects on the kidney should be assessed, as clinically appropriate. Treatment should be withheld for renal deterioration. BONIVA Injection should not be administered to patients with severe renal impairment (ie, patients with serum creatinine >200 µmol/L [2.3 mg/dL] or creatinine clearance [measured or estimated] <30 mL/min).

**Jaw Osteonecrosis:** Osteonecrosis, primarily in the jaw, has been reported in patients treated with bisphosphonates. Most cases have been in cancer patients undergoing dental procedures, but some have occurred in patients with postmenopausal osteoporosis or other diagnoses. Known risk factors for osteonecrosis include a diagnosis of cancer, concomitant therapies (eg, chemotherapy, radiotherapy, corticosteroids), and co-morbid disorders (eg, anemia, coagulopathy, infection, pre-existing dental disease). Most reported cases have been in patients treated with bisphosphonates intravenously but some have been in patients treated orally. For patients who develop osteonecrosis of the jaw (ONJ) while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

**Musculoskeletal Pain:** In postmarketing experience, severe and occasionally incapacitating bone, joint and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis (see **ADVERSE REACTIONS**). However, such reports have been infrequent. This category of drugs includes BONIVA (ibandronate sodium) Injection. Most of the patients were postmenopausal women. The time to onset of symptoms varied from one day to several months after starting the drug. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

**Information for Patients:** BONIVA Injection must be administered intravenously only by a health care professional. Patients should be instructed to read the Patient Information Leaflet carefully before BONIVA Injection is administered and to re-read it each time the prescription is renewed. BONIVA Injection should be administered once every 3 months. If the dose is missed, the injection should be administered as soon as it can be rescheduled. Thereafter, injections should be scheduled every 3 months from the date of the last injection. Do not administer BONIVA Injection more frequently than once every 3 months. Patients must receive supplemental calcium and vitamin D.

### Drug Interactions

See **FULL PRESCRIBING INFORMATION, CLINICAL PHARMACOLOGY: Drug Interactions**

**Drug/Laboratory Test Interactions:** Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with ibandronate have not been performed.

**Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** In a 104-week carcinogenicity study, doses of 3, 7, or 15 mg/kg/day were administered by oral gavage to Wistar rats (systemic exposures in males and females up to 3 and 1 times, respectively, human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). There were no significant drug-related tumor findings in male or female rats. In a 78-week carcinogenicity study, doses of 5, 20, or 40 mg/kg/day were administered by oral gavage to NMRI mice (exposures in males and females up to 96 and 14 times, respectively, human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). There were no significant drug-related tumor findings in male or female mice. In a 90-week carcinogenicity study, doses of 5, 20, or 80 mg/kg/day were administered in the drinking water to NMRI mice. A dose-related increased incidence of adrenal subcapsular adenoma/carcinoma was observed in female mice, which was statistically significant at 80 mg/kg/day (32 to 51 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). The relevance of these findings to humans is unknown.

**Mutagenesis:** There was no evidence for a mutagenic or clastogenic potential of ibandronate in the following assays: *in vitro* bacterial mutagenesis assay in *Salmonella typhimurium* and *Escherichia coli* (Ames test), mammalian cell mutagenesis assay in Chinese hamster V79 cells, and chromosomal aberration test in human peripheral lymphocytes, each with and without metabolic activation. Ibandronate was not genotoxic in the *in vivo* mouse micronucleus tests for chromosomal damage.

**Impairment of Fertility:** In female rats treated from 14 days prior to mating through gestation, decreases in fertility, corpora lutea and implantation sites, and increased preimplantation loss were observed at an intravenous dose of 1.2 mg/kg/day (117 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). In male rats treated for 28 days prior to mating, a decrease in sperm production and altered sperm morphology were observed at intravenous doses ≥0.3 mg/kg/day (≥40 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison).

**Pregnancy: Pregnancy Category C:** In pregnant rats given intravenous doses of 0.05, 0.15, or 0.5 mg/kg/day from Day 17 post-coitum until Day 20 postpartum, ibandronate treatment resulted in dystocia, maternal mortality, and early postnatal pup loss in all dose groups (≥2 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison).

Reduced body weight at birth was observed at 0.15 and 0.5 mg/kg/day (≥4 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). Pups exhibited abnormal odontology that decreased food consumption and body weight gain at 0.15 and 0.5 mg/kg/day (≥18 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). Periparturient mortality has also been observed with other bisphosphonates and appears to be a class effect related to inhibition of skeletal calcium mobilization resulting in hypocalcemia and dystocia. Exposure of pregnant rats during the period of organogenesis resulted in an increased fetal incidence of RPU (renal pelvis ureter) syndrome at an intravenous dose of 1 mg/kg/day (≥47 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). In this spontaneous delivery study, dystocia was counteracted by perinatal calcium supplementation. In rat studies with intravenous dosing during gestation, fetal weight and pup growth were reduced at doses ≥0.1 mg/kg/day (≥5 times human exposure at the recommended intravenous dose of 3 mg every 3 months, based on cumulative AUC comparison). In pregnant rabbits given intravenous doses of 0.03, 0.07 or 0.2 mg/kg/day during the period of organogenesis, maternal mortality, reduced maternal body weight gain, decreased litter size due to increased resorption rate, and decreased fetal weight were observed at 0.2 mg/kg/day (19 times the recommended human intravenous dose of 3 mg every 3 months, based on cumulative body surface area comparison, mg/m<sup>2</sup>). Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (eg, skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established. There are no adequate and well-controlled studies in pregnant women. BONIVA Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

**Nursing Mothers:** In lactating rats treated with intravenous doses of 0.08 mg/kg, ibandronate was present in breast milk at concentrations of 8.1 to 0.4 ng/mL from 2 to 24 hours after dose administration. Concentrations in milk averaged 1.5 times plasma concentrations. It is not known whether BONIVA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BONIVA Injection is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use:** Of the patients receiving BONIVA Injection 3 mg every 3 months for 1 year (DIVA study), 51% were over 65 years of age. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity in some older individuals cannot be ruled out.

### ADVERSE REACTIONS

**Daily Oral Tablet:** Treatment with BONIVA 2.5 mg daily oral tablet was studied, in over 3900 patients in postmenopausal osteoporosis trials of up to 3 years duration. The overall adverse event profile of BONIVA 2.5 mg once daily tablet in these studies was similar to that of placebo.

Most adverse events were mild or moderate and did not lead to discontinuation. The incidence of serious adverse events was 20% in the placebo group and 23% in the BONIVA 2.5 mg daily oral tablet group. The percentage of patients who withdrew from treatment due to adverse events was approximately 17% in both the BONIVA 2.5 mg daily oral tablet group and the placebo group. Overall, and according to body system, there was no difference between BONIVA daily oral tablet and placebo, with adverse events of the digestive system being the most common reason for withdrawal.

**Table 1** lists adverse events from the Treatment and Prevention Studies reported in ≥2% of patients and in more patients treated with BONIVA 2.5 mg daily oral tablet than patients treated with placebo. Adverse events are shown without attribution of causality.

**Table 1: Adverse Events Occurring at a Frequency ≥2% and in More Patients Treated with BONIVA 2.5 mg Daily Oral Tablet than in Patients Treated with Placebo in the Osteoporosis Treatment and Prevention Studies**

Body System	BONIVA 2.5 mg daily	
	Placebo (n=1134)	% (n=1140)
<b>Body as a Whole</b>		
Back Pain	12.2	13.5
Pain in Extremity	6.4	7.8
Infection	3.4	4.3
Asthenia	2.3	3.5
Allergic Reaction	1.9	2.5
<b>Digestive System</b>		
Dyspepsia	9.8	11.9
Diarrhea	5.0	6.8
Tooth Disorder	2.3	3.5
Vomiting	2.1	2.7
Gastritis	1.9	2.2
<b>Metabolic and Nutritional Disorders</b>		
Hypercholesterolemia	4.2	4.8
<b>Musculoskeletal System</b>		
Myalgia	5.1	5.7
Joint Disorder	3.3	3.6
Arthritis	2.7	3.2
<b>Nervous System</b>		
Headache	5.8	6.5
Dizziness	2.6	3.7
Vertigo	2.5	3.0
Nerve Root Lesion	1.9	2.2
<b>Respiratory System</b>		
Upper Respiratory Infection	33.2	33.7
Bronchitis	6.8	10.0
Pneumonia	4.3	5.9
Pharyngitis	1.5	2.5
<b>Urogenital System</b>		
Urinary Tract Infection	4.2	5.5

**Quarterly IV Injection:** In a 1-year, double-blind, multicenter study comparing BONIVA Injection administered intravenously as 3 mg every 3 months to BONIVA 2.5 mg daily oral tablet in women with postmenopausal osteoporosis, the overall safety and tolerability profiles of the two dosing regimens were similar. The incidence of serious adverse events was 8.0% in the BONIVA 2.5 mg daily group and 7.5% in the BONIVA Injection 3 mg once every 3 months group. The percentage of patients who withdrew from treatment due to adverse events was approximately 6.7% in the BONIVA 2.5 mg daily group and 8.5% in the BONIVA Injection 3 mg every 3 months group.

**Table 2** lists the adverse events reported in >2% of patients without attribution of causality.

**Table 2: Adverse Events With an Incidence of at Least 2% in Patients Treated with BONIVA Injection (3 mg once every 3 months) or BONIVA Daily Oral Tablet (2.5 mg)**

Body System/Adverse Event	BONIVA	
	2.5 mg Daily (Oral) (n=465)	3 mg q 3 mo (IV) (n=469)
<b>Infections and Infestations</b>		
Influenza	8.0	4.7
Nasopharyngitis	6.0	3.4
Cystitis	3.4	1.9
Gastroenteritis	3.4	1.5
Urinary Tract Infection	3.2	2.6
Bronchitis	2.8	2.1
Upper Respiratory Tract Infection	2.8	1.1
<b>Gastrointestinal Disorders</b>		
Abdominal Pain*	5.6	5.1
Dyspepsia	4.3	3.6
Nausea	4.3	2.1
Constipation	4.1	3.4
Diarrhea	2.4	2.8
Gastritis	2.2	1.9
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Arthralgia	8.6	9.6
Back Pain	7.5	7.0
Localized Osteoarthritis	2.4	1.5
Pain in Extremity	2.2	2.8
Myalgia	0.9	2.8
<b>Nervous System Disorders</b>		
Dizziness	2.8	1.9
Headache	2.6	3.6
<b>Vascular Disorders</b>		
Hypertension	7.1	5.3
<b>Psychiatric Disorders</b>		
Insomnia	2.6	1.1
Depression	2.2	1.3
<b>General Disorders and Administration Site Conditions</b>		
Influenza-like illness†	1.1	4.9
Fatigue	1.1	2.8
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash‡	2.8	2.3
<b>Metabolism and Nutrition</b>		
Hypercholesterolemia	4.3	1.5

\*Is a combination of abdominal pain and abdominal pain upper.

†Combination of influenza-like illness and acute phase reaction.

‡Combination of rash, rash pruritic, rash macular, dermatitis, dermatitis allergic, exanthem, erythema, rash papular, rash generalized, dermatitis medicamentosa, rash erythematous.

**Acute Phase Reaction-like Events:** Symptoms consistent with acute phase reaction (APR) have been reported with intravenous bisphosphonate use. The overall incidence of patients with APR-like events was higher in the intravenous treatment group (4% in the BONIVA 2.5 mg daily oral tablet group vs. 10% in the BONIVA Injection 3 mg once every 3 months group). These incidence rates are based on reporting of any of 33 potential APR-like symptoms within 3 days of an IV dose and for a duration of 7 days or less. In most cases, no specific treatment was required and the symptoms subsided within 24 to 48 hours.

**Injection Site Reactions:** Local reactions at the injection site, such as redness or swelling, were observed infrequently, but at a higher incidence in patients treated with BONIVA Injection 3 mg every 3 months (<2%; 8/469) than in patients treated with placebo injections (<1%; 1/465). In most cases, the reaction was of mild to moderate severity.

**Ocular Adverse Events:** Bisphosphonates may be associated with ocular inflammation such as uveitis and scleritis. In some cases, these events did not resolve until the bisphosphonate was discontinued.

**Laboratory Test Findings:** There were no clinically significant changes from baseline values or shifts in any laboratory variable with oral ibandronate. As expected with bisphosphonate treatment, a decrease in total alkaline phosphatase levels was seen with 2.5 mg daily oral ibandronate compared to placebo. There was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, hypocalcemia, or hypophosphatemia. There also was no evidence that BONIVA Injection 3 mg every 3 months induced clinically significant laboratory abnormalities indicative of hepatic or renal dysfunction compared to BONIVA 2.5 mg daily oral tablet.

**OVERDOSAGE:** No cases of overdose were reported in premarketing studies with BONIVA Injection. Intravenous overdose may result in hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively. Dialysis would not be beneficial unless it is administered within 2 hours following the overdose.

Distributed by: Co-promoted by Roche Laboratories Inc. and

Roche Pharmaceuticals GlaxoSmithKline  
Roche Laboratories Inc., 340 Kingsland Street, Nutley, New Jersey 07110-1199, www.rocheusa.com  
GlaxoSmithKline, Research Triangle Park, NC 27709, www.gsk.com

Issued: February 2006  
Copyright © 2006 by Roche Laboratories Inc. All rights reserved.