Zoledronic Acid Now Indicated for Prevention

BY MICHELE G. SULLIVAN

The Food and Drug Administration has approved dosing the osteoporosis drug zoledronic acid (Reclast) once every 2 years for the prevention of bone loss in postmenopausal women, making it the first bisphosphonate in its class to get the nod for a 2-year indication.

The approval is based on results of the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly (HORIZON) prevention trial in which a single infusion of the zoledronic acid agent significantly increased bone mass relative to placebo at 2 years in postmenopausal women with osteopenia, according to a statement by the drug manufacturer, Novartis Pharmaceuticals Corp.

The 2-year double-blind, placebo-controlled study was presented in April at an international symposium sponsored by the National Osteoporosis Foundation in Washington by Dr. Chris Recknor.

HORIZON comprised 581 women aged 45 years and older with low bone mineral density (T scores of –1 to –2.5) who were randomized to receive one of three regimens: 5 mg zoledronic acid at study onset and at 1 year; 5 mg zoledronic acid at study onset and placebo at 1 year; or placebo at study onset and at 1 year. The subjects' mean age was 60 years. Most (93%) were white.

The study's main outcomes were 24-month changes in bone mineral density (BMD) at the lumbar spine, trochanter, femoral neck, distal radius, and total hip. The secondary end points were changes in markers of bone turnover.

Both of the Reclast treatment groups showed significantly increased BMD, compared with placebo. At 24 months (1 year after the second infusion), both active groups showed similar BMD increases at all sites that were significantly different from BMD changes with placebo (see chart), reported Dr. Recknor, who is an internist specializing in osteoporosis in Gainesville, Ga.

Specifically, treatment with a single zoledronic acid infusion increased spine BMD by 6.3% among women in the early menopause group (within 5 years of menopause) and by 5.4% among those in the late menopause group, according Novartis's June 1 announcement of the new indication.

Both zoledronic acid regimens showed significant reductions in bone turnover markers compared with placebo. Markers in the double-infusion group were significantly lower than those in the single-infusion group.

Adverse events were most commonly observed in the first 3 days after the first infusion, when they were significantly more common in both active groups (60% vs. 25%). The most frequently reported were pain, fever, chills, myalgia, nausea, and headache. Adverse events were significantly lower after the second infusion, occurring in 18% of the double-infusion group, 11% of the single-infusion group, and 12% of the placebo group, Dr. Recknor reported.

Already approved as a once-yearly infusion for the treatment of women with postmenopausal osteoporosis and men with osteoporosis, as well as for the treatment of Paget disease of bone and the prevention and treatment of glucocorticoid-induced osteoporosis, Reclast is now the first and only approved single-dose, biyearly infusion for the prevention postmenopausal osteoporosis, according to the Novartis statement.

At the osteoporosis symposium in April, Dr. Recknor said in an interview using the drug prophylactically "allows clinicians a little more lead time in treating these patients, many of whom are at increased risk of a low-stress fracture." Furthermore, the HORIZON results raise a tantalizing possibility. "You may be able to give this drug a couple of times to perimenopausal women and prevent the entire problem of bone loss."

The less-frequent dosing is being touted as an advance by Dr. Mone Zaidi, director of the Mount Sinai Bone Program at Mount Sinai School of Medicine, New York, because of the convenience of biyearly treatment compared with daily, weekly, and monthly regimens.

"There were not many differences that were either statistically significant or clinically meaningful between the two treated groups in the [HORIZON] study. Once every 2 years is an excellent way to go forward, which would improve compliance in the early postmenopausal woman who rapidly loses bone," he said in an interview after the Novartis's announcement of the new indication.

Another study presented at the osteoporosis symposium shed light on zoledronic acid's role in preventing bone loss in women who've already had a hip fracture.

A subanalysis of a second HORIZON study showed that zoledronic acid indeed benefits patients with a recent fracture—and particularly the very elderly and those with the poorest bone quality.

The HORIZON Recurrent Fracture Trial included 2,127 patients with a recent hip fracture who were randomized to an annual infusion of 5 mg zoledronic acid or placebo and followed for up to 5 years. HORIZON-RFT concluded that the drug reduced the rate of recurrent fracture by 35% (N. Engl. J. Med. 2007;357:1799-809).

The subanalysis examined response rates within specific patient groups, said Denise Orwig, Ph.D., who presented the trial data during a poster session at the meeting. The analysis showed that patients at the highest risk for a recurrent fracture—those who were at least 85 years old or who had a T score of less than –2.5 at the total hip—benefited the most from the treatment.

Although Dr. Orwig said it's unclear why the oldest, least-dense bones benefited the most, the finding does carry a strongly positive clinical implication.

"These patients who are at the highest risk are also the ones who are the least likely to be treated," said Dr. Orwig of the department of epidemiology and preventive medicine at the University of Maryland Medical Center, Baltimore.

"The thought may be that they have already had multiple fractures and there is probably not a lot more that can be done. But this study showed us that these individuals can benefit and that we can have a big short-term impact on their bone density and possibly even reduce the risk of more fractures due to continued bone loss," said Dr. Orwig.

Novartis Pharmaceuticals Corp. sponsored the HORIZON studies. Dr. Orwig has received research funding from the company. Dr. Recknor and Dr. Zaidi are on the Novartis speakers bureau. ■

Diana Mahoney contributed to this report.

HORIZON Prevention Study: 24-Month Changes in Bone Mineral Density

	2 ZOL Infusions	ZOL + Placebo	2 Placebo Infusions
Lumbar spine	5%	4.4%	–1.3%
Total hip	3%	2.3%	–1.5%
Femoral neck	2%	1.6%	–1.4%
Trochanter	4.8%	4%	–1%
Distal radius	–0.07%	–0.18%	–2.4%

Source: Novartis Pharmaceuticals Corp.

ELSEVIER GLOBAL MEDICAL NEWS

Bisphosphonates Don't Raise Atrial Fib Risk, Study Shows

BY BRUCE JANCIN

ORLANDO — Further evidence that bisphosphonates do not really increase the risk of atrial fibrillation has come from an observational study involving more than 47,000 patients.

"We were unable to find an association between bisphosphonate therapy and atrial fibrillation. However, patients who received bisphosphonates were older and had more cardiovascular disease that we suspect accounts for the increased arrhythmia risk reported in other trials," Dr. John D. Day reported at the annual meeting of the American College of Cardiology.

The study population comprised 37,485 enrollees in a Rocky Mountain health plan followed for an average of 4.6 years and 9,623 consecutive patients in a coronary angiography database with an average follow-up of 4 years.

The 7,489 health plan enrollees on bisphosphonate therapy for osteoporosis and fracture prevention had a 37% baseline prevalence of hyperlipidemia, significantly greater than the 30% rate among plan members not on a bisphosphonate. The bisphosphonate users were older, too. Yet their rates of new-onset atrial fibrillation, MI, and all-cause mortality during follow-up were no different than nonusers', according to Dr. Day of Intermountain Medical Center, Murray, Utah.

In the coronary angiography cohort, the patients on bisphosphonates were significantly older than were bisphosphonate nonusers, were more likely to be hypertensive by a margin of 56% to 45%, and had a 4.1% prevalence of heart failure compared with 0.7% in patients not on a bisphosphonate. A prior MI was present at baseline in 12.2% of bisphosphonate users and 4.8% of nonusers.

The all-cause mortality rate was 32.7% in bisphosphonate users in the angiography cohort and 18.8% in nonusers. Yet the rates of new-onset atrial fibrillation in the two groups were essentially the same: 10.2% among bisphosphonate users, 10.1% in nonusers.

In November 2008, the Food and Drug Administration reported that based on its review of the data from clinical trials involving nearly 40,000 patients treated with alendronate (Fosamax), ibandronate (Boniva), risedronate (Actonel), zoledronic acid (Zometa), or placebo, there is "no clear association" between the use of drugs in this class and the rate of serious or nonserious atrial fibrillation. The FDA report concluded that physicians "should not alter their prescribing patterns for bisphosphonates."

However, because of discordance among some of the studies, agency officials left the door open to possible future epidemiologic studies addressing the issue, prompting Dr. Day and coinvestigators to look at their patients' experience.

The FDA review was prompted by published reports of an apparent increase in serious atrial fibrillation events with zoledronic acid in the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly Pivotal Fracture Trial (HORIZON) and with alendronate in the Fracture Intervention Trial (FIT) (N. Engl. J. Med. 2007;356:1809-22, 1895-6).

Dr. Day reported having no financial conflicts of interest relating to the study. ■

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