NEW FEATURE

PURLs®

Priority Updates from the Research Literature from the Family Physicians Inquiries Network

Editorial **PURLS: Translating research into reality** PAGE 981

Annual zoledronic acid infusion lowers risk of fracture, death

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Practice changer

For patients with a recent hip fracture, intravenous zoledronic acid annually is an option for reducing the risk of new fractures and death.[1]

Strength of recommendation (SOR)

B: based on one well-designed randomized controlled trial

Lyles KW, Colon-Emeric CS, Magaziner JF, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007; 357:1799–1809. Epub Sep 17.

ILLUSTRATIVE CASE

A 75-year-old woman comes to see you 1 month after she had surgery to repair a hip fracture. She was diagnosed with osteoporosis 3 years prior to the hip fracture and is currently taking calcium and vitamin D. She tried taking an oral bisphosphonate but couldn't tolerate the gastrointestinal side effects. What treatment can you recommend to reduce her risk of sustaining another fracture?

BACKGROUND

First fracture heightens risk

Patients with a prior hip fracture have 2.5 times the risk of a new fracture compared to age-matched persons without a previous hip fracture.[2] Women who have hip fractures are 3 times more likely to die in the first 6 months after the fracture than women of the same age and health status without fractures.[3] Ten million people in the US have osteoporosis and 300,000 per year suffer hip fracture.[4]

Guidelines from the National Osteoporosis Foundation (NOF) and the Institute for Clinical Systems Improvement (ICSI) include these recommendations for hip fracture patients: discuss adequacy of total calcium and vitamin D intake; address home safety and falls prevention; and encourage specific exercises for muscle strength. They also recommend treating all patients with a prior hip or vertebral fracture with an antiresorptive agent. Options include oral bisphosphonates (alendronate, ibandronate, or risedronate), calcitonin intranasal spray or subcutaneous calcitonin, hormone therapy, parathyroid hormone, and raloxifene.[5,6]

CLINICAL CONTEXT

Are we doing our best?

Most patients with hip fracture are not properly evaluated or treated for osteoporosis. A 2002 study of 500 hip fracture patients treated at 4 Midwestern health systems found that only 12% to 24% of patients had a DXA (dual-energy x-ray absorptiometry) scan either before or after hip fracture, 5% to 27% of the patients received documented advice to take adequate calcium and vitamin D, and 5% to 37% received a

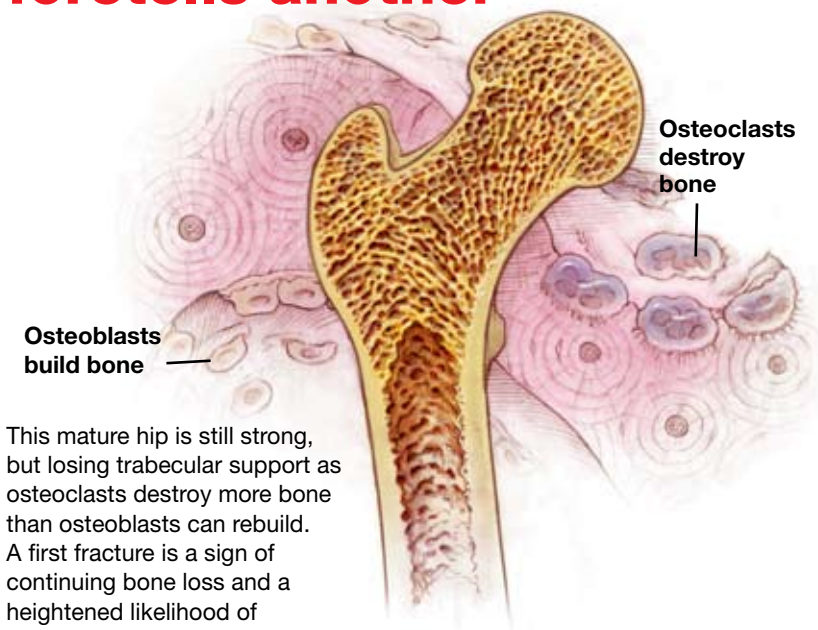
FAST TRACK

The number needed to treat strikes us as a good bargain

PURLS methodology

The criteria and findings leading to the selection of this study as a Priority Update from the Research Literature can be accessed at www.jfponline.com/purls.

First fracture foretells another



This mature hip is still strong, but losing trabecular support as osteoclasts destroy more bone than osteoblasts can rebuild. A first fracture is a sign of continuing bone loss and a heightened likelihood of additional fractures

FAST TRACK

Risk of fracture was reduced by 35% and risk of death by 28%

prescription for any antiresorptive medication (bisphosphonate [2% to 10%], estrogen, calcitonin, or raloxifene).[7]

Bisphosphonates are effective but compliance is poor

Bisphosphonates are effective in preventing recurrence of hip fracture. One cohort study that included over 35,000 women over age 45 who had received a bisphosphonate prescription showed that patients who are adherent to treatment have a 44.5% relative risk reduction over 2 years and an absolute risk reduction of 0.8%, for an NNT of 125.

However, compliance with oral bisphosphonate therapy is poor; only 20% of the women in this study persisted with the therapy for 24 months.[8] Patients must take these medications first thing in the morning with 8 ounces of water and then remain upright for 30 to 60 minutes before eating or drinking. Gastrointestinal side effects, including dyspepsia, nausea, and reflux disease, occur in about 25% of patients, and there is a small risk of developing gastric or duodenal ulcers.

STUDY SUMMARY

The HORIZON Recurrent Fracture Trial was an international, randomized, double blind, placebo-controlled trial of 2127 patients with a recent hip fracture.

- The primary endpoint was a new clinical fracture.
- Secondary endpoints included the change in bone mineral density in the non-fractured hip, new vertebral and hip fractures, and pre-specified safety endpoints, including death.

Patients. Women and men age 50 or older who had undergone a surgical repair of a minimal trauma hip fracture in the previous 90 days were eligible for the study. Ninety-one percent of the patients were white, 76% were female, and the mean age was 74.5 years. Forty-one percent of patients had a T score at the femoral neck of –2.5 or less at baseline (meeting diagnostic criteria for osteoporosis).

Method. Patients were randomized to receive either intravenous zoledronic acid 5 mg or placebo within 90 days of surgical repair of a hip fracture and yearly thereafter for the duration of the study. Patients with serum 25-hydroxyvitamin D levels <15 ng/mL received a loading dose of vitamin D (50,000–125,000 IU) 14 days before the first dose of the study drug. All patients were given daily calcium (1000–1500 mg) and vitamin D (800–1200 IU) supplements. Simultaneous treatment with nasal calcitonin, selective estrogen-receptor modulators, hormone replacement, tobolone, and external hip protectors was permitted "at the discretion of the investigators," and 10.5% of the study patients did receive one of these other osteoporosis therapies.

Patients were followed for up to 5 years. Bone mineral density was tested by DXA at the hip and femoral neck at baseline and then annually. The median follow-up time was 1.9 years; 71.3% of patients completing the trial, and 3% of patients were lost to follow-up.

Results. The patients assigned to zoledronic acid had a 5.3% absolute risk reduction for new clinical fractures,

TABLE 1

The HORIZON study: Rates of fracture and death were lower in the zoledronic group compared to placebo[1]

OUTCOME	PLACEBO (N=1062)	ZOLEDRONIC ACID (N=1065)	HAZARD RATIO (95% CI)	*P* VALUE
Any fracture	139 (13.9%)	92 (8.6%)	0.65 (0.50-0.84)	.001
Hip fracture	33 (3.5%)	23 (2.0%)	0.70 (0.41-1.19)	.18
Vertebral fracture	39 (3.8%)	21 (1.7%)	0.54 (0.32–0.92)	.02
Death	141 (13.3%)	101 (9.6%)	0.72 (0.56-0.93)	.01

Rates of fracture were calculated by Kaplan-Meier methods at 24 months and are not simple percentages

TABLE 2

Bisphosphonates for osteoporosis: Routes, dosage, and cost

GENERIC NAME	BRAND NAME	ROUTE OF ADMINISTRATION	DOSE AND FREQUENCY	APPROXIMATE ANNUAL COST
Alendronate	Fosamax	Oral	10 mg/d or 70 mg/week	$960–$1120
Ibandronate	Boniva	Oral or IV	2.5 mg/d, 150 mg monthly (PO) or 3 mg IV every 3 months	$1140–$1200 PO, $1980 IV
Risedronate	Actonel	Oral	5 mg/d or 35 mg/week	$1000–$1100
Zoledronic acid	Reclast	IV	5 mg once a year	$1200

yielding an NNT of 19 over 2 years to prevent one new clinical fracture (**TABLE 1**). Bone mineral density of the contralateral hip increased in the zoledronic acid group by 2.6% after 1 year, 4.7% after 2 years, and 5.5% after 3 years and declined in the placebo group by 1.0%, 0.7%, and 0.9% respectively.

There was a 3.7% absolute risk reduction of death, with an NNT of 27 for 2 years to prevent one death.

Adverse events that were more common in the zoledronic acid group included fever (8.7% vs 3.1%) and musculoskeletal pain (3.1% vs. 1.2%). There were no reported cases of jaw osteonecrosis in either group and no statistically significant delay in the healing of fractures with zoledronic acid. Both groups had similar rates of renal and cardiovascular events, including atrial fibrillation and stroke.

Novartis provided funding for the study. An independent data and safety monitoring board oversaw the conduct and safety of the study and recommended that it be stopped early after having surpassed the pre-specified efficacy boundaries. Independent statisticians confirmed the data analysis that was performed by the sponsor.[1]

FAST TRACK

No jaw osteonecrosis was reported in either group

WHAT'S NEW

The adherence advantage

The obvious advantage of zoledronic acid over other bisphosphonates is the high level of adherence that is possible under the controlled environment of a once yearly infusion administered under medical supervision. Considering the low rates of adherence to oral bisphosphonates, this is a significant medical advance.

This study shows that a yearly infusion of zoledronic acid is highly effective in preventing subsequent clinical fractures in patients who have recently suffered a hip fracture. It is the first randomized-controlled trial of a bisphosphonate for

secondary prevention in patients with recent hip fracture, regardless of their bone mineral density status.

In a previous 3-year randomized controlled trial of 5mg zoledronic acid once yearly vs placebo for postmenopausal women with osteoporosis, the risk of vertebral fractures was reduced by 70% (3.3% vs 10.9% placebo) and the risk of hip fracture was reduced by 41% (1.4% vs 2.5% placebo).[9]

The NNT of 19 for 2 years to prevent one clinical fracture and NNT of 27 for 2 years to prevent one death strikes us as a good bargain compared to many modern medical interventions. Are these results too good to be true? We don't think so.

No serious design flaws

This was a well done trial with no serious flaws in design. The number of deaths, however, was relatively small, so the NNT may be as high as 50 by our rough calculations. As a "worst case" for the benefit, however, this still seems worthwhile.

CAVEATS

Patients with uncorrected hypocalcemia or creatinine clearance <35 mL/min should not take bisphosphonates, including zoledronic acid. Although this study did not show any evidence of an increased risk of atrial fibrillation or report any cases of osteonecrosis of the jaw, providers should monitor patients for these potential adverse events.

FAST TRACK

The biggest barrier for solo physicians and small practices will likely be the up-front cost, $1200 per dose

CHALLENGES TO IMPLEMENTATION

$1200 per dose

The FDA approved Reclast (zoledronic acid 5 mg) as a once-yearly treatment for postmenopausal osteoporosis and Paget's disease in August 2007. (Zometa is the brand name for zoledronic acid 4 mg that is indicated for multiple myeloma, bone metastasis, and hypercalcemia of malignancy.) Medicare and most insurance plans will reimburse Reclast infusion for these FDA-approved indications when billed by a provider using a CPT code. It is administered intravenously over 15-minutes and there are no risks beyond those associated with local infiltration.

The greatest barrier to implementing this practice for solo physicians or small group practices will likely be the up front expense of buying the drug; one dose is approximately $1200. Patients can be referred to larger practices or hospitals with the capital to have zoledronic acid on hand and the capability of providing the infusion.

The cost is comparable to the annual cost of oral bisphosphonates and less than the cost of the other IV bisphosphonate (ibandronate), which is administered every 3 months (**TABLE 2**). ■

PURLS methodology

This study was selected and evaluated using FPIN's Priority Updates from the Research Literature Surveillance System methodology. The criteria and findings leading to the selection of this study as a PURL can be accessed at www.jfponline.com/purls.

References

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