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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: How soon after hip fracture surgery should a patient start bisphosphonates?

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A: Patients with an osteoporotic hip fracture suffer from profound morbidity and are at a heightened risk of death. It is therefore essential that they receive treatment with a bisphosphonate known to modify the subsequent risk of fracture at any site—eg, alendronate (Fosamax), risedronate (Actonel), or zoledronic acid (Reclast).

However, there is concern that starting a bisphosphonate too soon after surgery could disrupt bone remodeling and delay fracture repair.

Only one clinical study addressed the timing of bisphosphonate therapy after hip fracture repair. In this study, Eriksen et al[1] performed a post hoc analysis of data from the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly Recurrent Fracture Trial (HORIZON-RFT)[2] and concluded that the optimal time to give intravenous zoledronic acid is 2 to 12 weeks after surgical repair of the fracture.

In a frail, elderly patient with comorbidities, a single intravenous 5-mg dose of zoledronic acid guarantees adequate treatment, obviating issues of poor compliance and oral absorption and loss to follow-up. Sufficient levels of vitamin D and calcium should be ensured.

THE EVIDENCE

The original HORIZON-RFT study,[2] published in 2007, compared intravenous zoledronic acid against placebo in elderly patients with osteoporotic hip fracture. Most of the patients were white women; their mean age was 74; 1,065 received intravenous zoledronic acid, and 1,062 received placebo. All received vitamin D and calcium.

The trial showed a clear reduction in the rate of recurrent fractures at other sites (a primary end point) and a reduction in the rate of all-cause mortality in patients treated within 90 days of fracture. A total of 424 fractures occurred in 231 patients. The risk of any new clinical fracture was 35% lower with treatment than with placebo (occurring in 8.6% vs 13.9% of patients, $P = .001$), and the number of deaths due to any cause was 28% lower with treatment than with placebo (occurring in 101 vs 141, $P = .01$).[2]

The mean time to fracture was 39.8 months in the treated group vs 36.4 in the placebo group. The fracture risk reduction began to be apparent by 12 months, and the reduction in mortality rate by 16 months.[2]

In a post hoc analysis of the trial, Eriksen et al[1] attempted to ascertain the optimal time for therapy in terms of fracture risk and mortality reduction. Analyzing the data by 2-week intervals beginning after the surgical repair of the fracture, the authors found that only 56 patients (5.3%) had received zoledronic acid within 2 weeks of surgery and only 47 had received placebo, and they saw no advantage to intravenous zoledronic acid compared with placebo in these first 2 weeks with respect to bone mineral density, fracture risk, or risk of death. However, excluding this small subset, antifracture efficacy and reduction in mortality rate were present when patients were treated with zoledronic acid in the 2 to 12 weeks after hip fracture repair, and improvement in bone mineral

Any patient with an osteoporotic fracture deserves effective therapy to lower the risk of future fractures

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density at the hip was noted at 12 months in all cohorts.

Colón-Emeric et al[3] performed another post hoc analysis, attempting to explain the lower mortality rate seen in patients treated with zoledronic acid. It had been an unexpected finding, and determinants of mortality rate reduction were hampered by a limited knowledge of the true cause of death or the circumstances of care after fracture. The authors concluded that only 8% of the reduction in mortality rate evident early in the second year of treatment with zoledronic acid could be attributed to a reduction in fractures.[3] Other mechanisms by which the mortality rate reduction occurred remained unclear.

Curiously, in another large randomized controlled trial of zoledronic acid, in women with postmenopausal osteoporosis, Black et al[4] reported that more patients died in the treated group (130 of 3,862) than in the placebo group (112 of 3,852). This difference was not statistically significant, but neither was it explained.

A meta-analysis by Bolland et al[5] examined the effect of other osteoporosis treatments on mortality rate, using randomized controlled trials that lasted more than 12 months and that reported more than 10 deaths. The authors concluded the following:

- In the trials in which bisphosphonates reduced the mortality rate, the mortality rate in the placebo group was higher than 10 per 1,000 patient-years
- The effect of osteoporosis treatment on the mortality rate in a frail, elderly population is evident using agents with proven efficacy in reducing vertebral and nonvertebral fractures, eg, alendronate, risedronate, and zoledronic acid.[5]

Based on limited data, bisphosphonate therapy is best started 2–12 weeks after fracture repair

THE SCIENCE

Osteoporotic fractures occur with minimal trauma, with the failure of bone attributed to impaired integrity of bone microarchitecture. The ultimate goal of fracture repair is to restore bone size, shape, and tissue properties. The issue of when to treat with a bisphosphonate after hip fracture arises because bisphosphonates are known to disrupt bone remodeling and so delay fracture repair.

After fracture, both anabolic and catabolic phases occur.[6] The final outcome depends on the following:

- The type of intervention to stabilize the fracture site (eg, surgical repair)
- The inflammatory cytokines and growth factors released by the cellular elements in bloody and disrupted tissue.

Oxygen tension, angiogenesis, and osteoblasts are critical to primary bone formation, and osteoclasts are essential in remodeling this initial bone deposition. These late phases of fracture repair are most vulnerable to the bisphosphonates, through suppression of osteoclast resorption and possibly through decreased angiogenesis.[6] Callus formation is sustained, but bone remodeling is delayed.

Amanat et al[7] examined the timing of a single dose of zoledronic acid after fracture repair in a rat model of diaphyseal fracture and found that the callus was larger and stronger if the bisphosphonate dose had been delayed 1 or 2 weeks. The animals treated with zoledronic acid showed a remarkable trabecular network of bone between the original femoral cortex and the new cortical bone that was not present in the control group, perhaps contributing to the enhanced mechanical properties of the callus. Other studies suggest single dosing rather than continuous dosing may be advantageous in fracture healing.[8]

THE REALITY

Healthy dogs or growing rats with linear diaphyseal fractures are imperfect models for elderly osteoporotic patients with hip fracture, as Dr. Herbert Fleisch noted in his editorial, "Can bisphosphonates be given to patients with fractures?"[9] Still, if retained primary bone can be used in the process of fracture repair to gain an early mechanical advantage, then perhaps delayed remodeling will permit early mobilization and further fracture prevention in humans.

How soon after hip fracture surgery should a patient start a bisphosphonate? The only data we have are from a single randomized controlled trial designed to measure fracture risk reduction in osteoporotic patients with hip fracture using intravenous zoledronic acid 5 mg compared with placebo.[2] A post hoc analysis of

this study[1] generated the limited clinical data we have on the optimal timing of the treatment. Linking these study data with the laboratory data, one would intuit that delaying the infusion of zoledronic acid for at least 2 weeks after hip fracture repair would offer a clinical reduction in fracture risk and improvement (or stabilization) in bone mineral density by 12 months, and a reduction in the rate of all-cause mortality beginning at 16 months. ■

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