

A once-yearly intravenous infusion of zoledronic acid prevented fractures in postmenopausal women with osteoporosis

Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356:1809-22.

Clinical impact ratings: Endocrine ★★★★★☆ Geriatrics ★★★★★☆ Rheumatology ★★★★★★

QUESTION

In postmenopausal women with osteoporosis, does a once-yearly intravenous infusion of zoledronic acid reduce the incidence of fractures?

METHODS

Design: Randomized placebo-controlled trial (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly [HORIZON]).

Allocation: Not concealed.*

Blinding: Blinded (outcome assessors).*

Follow-up period: 36 months.

Setting: Clinics in 25 countries in Europe, North and Latin America, Australia, and Asia.

Patients: 7765 postmenopausal women (mean age 73 y) with a bone mineral density T score ≤ -2.5 at the femoral neck, with or without vertebral fractures, or with a T score ≤ -1.5 and ≥ 2 mild or 1 moderate vertebral fracture. Women were grouped as stratum 1 ($n = 6113$) if they were not taking any other osteoporosis drug or stratum 2 ($n = 1652$) if they were already taking 1 of a prespecified list of osteoporosis drugs. Exclusion criteria included previous use of parathyroid hormone or sodium fluoride, use of anabolic steroids or growth hormone within 6 months, use of corticosteroids within 12 months, and previous use of strontium.

Intervention: 15-minute intravenous infusion of zoledronic acid, 5 mg ($n = 3889$), or placebo ($n = 3876$) at baseline, 12 months, and 24 months. All patients received daily oral calcium (1000 to 1500 mg) and vitamin D (400 to 1200 IU).

Outcomes: Vertebral fractures (in stratum 1) and hip fractures (both strata). Secondary outcomes included nonvertebral fractures, clinical fractures, and all adverse events.

Patient follow-up: 84% (99.6% in the intention-to-treat analysis).

MAIN RESULTS

The zoledronic acid group had fewer vertebral and hip fractures than the placebo group

(Table). The zoledronic acid group had a higher incidence of overall adverse events and serious atrial fibrillation, but groups did not differ for the incidence of stroke (Table).

CONCLUSION

In postmenopausal women with osteoporosis, a yearly intravenous infusion of zoledronic acid prevented fractures.

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*See Glossary.

Zoledronic acid vs placebo in women with osteoporosis at 3-year-follow-up†

Outcomes	Zoledronic acid	Placebo	RRR (95% CI)	NNT (CI)
Vertebral fracture (stratum 1)	3.3%	11%	70% (62 to 76)	14 (13 to 15)
Hip fracture	1.4%	2.5%	41% (17 to 58)	98 (69 to 236)
Nonvertebral fracture	8.0%	11%	25% (13 to 36)	38 (26 to 72)
Any clinical fracture	8.4%	13%	33% (23 to 42)	24 (19 to 34)
Stroke	2.3%	2.3%	1.4% (-32 to 26)	Not significant
			RRI (CI)	NNH (CI)
Any adverse event	95.5%	93.9%	1.7% (0.6 to 2.8)	62 (38 to 161)
Serious atrial fibrillation	1.3%	0.5%	149% (50 to 316)	129 (82 to 276)

†Abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from data in article.

COMMENTARY

Black and colleagues are correct when they conclude that annual infusion of a bisphosphonate "may provide a promising approach" to reducing osteoporosis-related fractures. Their industry-sponsored study documents reduced vertebral, nonvertebral, and clinical fractures, including the most important outcome, hip fracture. Although hip fracture had a relative risk reduction of 41%, this represents an absolute reduction of only 1.1%, translating to a number needed to treat of 98 women to prevent 1 hip fracture. The reduction in fractures is roughly similar to that achieved by other oral bisphosphonates. If compliance with a once-yearly infusion is improved over weekly or monthly oral bisphosphonate treatment and cost is reduced, clinicians will welcome this addition to their treatment choices.

Concern has been raised about long-term use of bisphosphonates. This concern relates to the observation that bisphosphonates remain in bone long past deposition, increasing bone density without increasing bone volume. It is unknown whether these drugs, by reducing the resorption half of the resorption-deposition cycle of bone metabolism, will result in the unintended consequence of increased brittleness or incapacity to repair microcracks (1) (recall the now-discredited fluoride treatment for osteoporosis).

New alternatives to bisphosphonates in clinical trials include monoclonal antibodies that reduce osteoclast-mediated bone resorption (as do the bisphosphonates) and calcimimetic drugs that block parathyroid hormone-mediated bone metabolism (not the mechanism of postmenopausal osteoporosis). Some products in development may stimulate osteoblasts and osteocytes to increase bone formation and strength (2).

The greater challenge, though, is more mundane. Despite explicit, conservative guidelines (3), widespread screening for osteoporosis is not being accomplished. And prevention of falls, the ultimate cause of hip fracture, still begs for adequate intervention.

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References

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