

Continuing alendronate for an additional 5 years maintained bone mineral density in postmenopausal women

Black DM, Schwartz AV, Ensrud KE, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA*. 2006;296:2927-38.

Clinical impact ratings: GIM/FP/GP ★★★★★☆ Endocrinology ★★★★★☆ Geriatrics ★★★★★☆ Rheumatology ★★★★★☆

QUESTION

In postmenopausal women with low bone mineral density (BMD) who had been receiving daily alendronate for a mean of 5 years, what is the effect of continuing alendronate treatment for 5 years compared with discontinuing it?

METHODS

Design: Randomized placebo-controlled trial (Fracture Intervention Trial [FIT] Long-term Extension [FLEX]).

Allocation: Unclear allocation concealment.*

Blinding: Blinded (clinicians, participants, data collectors, and outcome assessors).*

Follow-up period: 5 years.

Setting: 10 clinical centers in the United States.

Patients: 1099 postmenopausal women (mean age 73 y, 97% white) who had low femoral neck BMD (< 0.68 g/cm²) and had been allocated to alendronate (5 mg/d for 2 y and 10 mg/d thereafter) in FIT. Exclusion criteria were total hip BMD < 0.515 g/cm² (T score < -3.5) or total hip BMD lower than that at FIT baseline.

Intervention: Alendronate, 5 mg/d (*n* = 329); alendronate, 10 mg/d (*n* = 333); or placebo (*n* = 437). All participants received calcium, 500 mg/d, and vitamin D, 250 U/d.

Outcomes: Total hip BMD. Secondary outcomes included BMD at femoral neck, trochanter, lumbar spine, and forearm and of the total body; fracture incidence; and adverse events.

Patient follow-up: 83% (intention-to-treat analysis).

MAIN RESULTS

A prespecified pooled analysis of groups taking either 5 or 10 mg/d of alendronate showed that 5 additional years of alendronate maintained total hip BMD compared with a decrease with placebo (Table). Continuing treatment with alendronate also maintained BMD at the femoral neck, trochanter, and lumbar spine, and of the total body (Table). Continuing alendronate led to fewer clinical vertebral fractures, but groups did not differ for all clinical fractures or morphometric ver-

tebral fractures (Table). Groups did not differ for serious adverse events.

CONCLUSION

In postmenopausal women with low bone mineral density (BMD) who had been receiving daily alendronate for a mean of 5 years, continuing treatment of alendronate for 5 years maintained BMD.

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*See Glossary.

Continuing alendronate for 5 years vs placebo after 5-year treatment with alendronate in postmenopausal women†

Outcomes	Pooled alendronate‡	Placebo	Mean difference (95% CI)	
Total hip BMD (%)	-1.02	-3.38	2.36 (1.81 to 2.90)	
Femoral neck BMD (%)	0.46	-1.48	1.94 (1.20 to 2.68)	
Trochanter BMD (%)	-0.08	-3.25	3.17 (2.49 to 3.84)	
Lumbar spine BMD (%)	5.26	1.52	3.74 (3.03 to 4.45)	
Total body BMD (%)	1.01	-0.27	1.28 (0.70 to 1.86)	
Forearm BMD (%)	-1.19	-3.21	2.01 (1.35 to 2.68)	
			RRR (CI)	NNT (CI)
Clinical vertebral fractures	2.4%	5.3%	55% (15 to 76)	35 (25 to 126)
Any clinical fractures	20%	21%	7% (-21 to 29)	Not significant
Morphometric vertebral fractures	9.8%	11%	14% (-22 to 40)	Not significant

†BMD = bone mineral density. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from control event rates and relative risks in article.

‡Data from groups taking 5 or 10 mg/d of alendronate were pooled.

COMMENTARY

The appropriate duration of bisphosphonate therapy for postmenopausal osteoporosis or low BMD has been a topic of debate for some time (1). Concerns regarding medication costs, the theoretical risk for oversuppression of bone turnover, and recent reports of jaw osteonecrosis associated with bisphosphonate use have led clinicians to question whether it would be prudent to discontinue therapy once an osteoporotic patient has been treated for some time (2).

Answering the question of how long to treat is difficult. The logistics of any clinical trial lasting several years are complex. Thus, the results of the FLEX trial may be the best data clinicians ever have to try to answer this question.

Patients allocated to placebo in FLEX had a slight decrease in hip and spine BMD and an increase in bone turnover markers. Although clinical spine fractures were increased in the placebo group, overall clinical fractures and morphometric spine fractures were not. These data tend to affirm that bisphosphonate therapy for 5 years is adequate for fracture prevention in many patients with low BMD following menopause.

But in which patients would it be appropriate to withdraw therapy? Subgroup analysis in FLEX did not identify any trends for greater benefit in those with lower BMD or prevalent vertebral fracture at study baseline. However, the absolute risk for both clinical vertebral and non-vertebral fractures was greatest in patients with those known fracture risk factors. On the basis of this finding, the authors appropriately conclude that women at high risk for clinical vertebral fracture, such as those with very low BMD or previous vertebral fracture, may benefit from prolonged therapy beyond 5 years. Furthermore, patients in FLEX were monitored for decrease in BMD. Thus, prudent follow-up of BMD, and perhaps bone turnover markers, would be appropriate in those in whom therapy is discontinued.

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References

1. Stewler GJ. *N Engl J Med*. 2004;350:1172-4.
2. Delmas PD. *Curr Opin Rheumatol*. 2005;17:462-6.