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Editorial

Management after first-line antiresorptive treatment for postmenopausal osteoporosis

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Drugs that inhibit bone resorption (bisphosphonates and denosumab) have been proven in vast 3- to 5-year randomized controlled trials to decrease the risk of vertebral, hip, and peripheral fractures in postmenopausal women with osteoporosis [1–5]. The optimal treatment duration, however, remains unclear. Whether treatment should be continued beyond the 3 to 5 years for which trial data are available is a crucial issue. The best monitoring strategy after treatment discontinuation also deserves investigation.

The scant data available on the fracture-preventing effectiveness of continuing antiresorptive agents beyond 3–5 years come from FLEX, which is the long-term extension of the Fracture Intervention Trial (FIT) of alendronate therapy for 4–5 years, and from extensions of the HORIZON-PFT (Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly-Pivotal Fracture Trial) and FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months) trial [6–8].

The unique design of FLEX [6] explains in part the scrutiny to which this trial is subjected in several publications. After a mean treatment-free interval of 1.9 years, a subgroup of volunteers who had completed FIT 1 or FIT 2 was allocated at random to double-blind treatment with alendronate (5 or 10 mg/day) or a placebo for 5 additional years. The subgroup was composed of 1099 women, i.e., 39% of the patients in FIT 1 and 2. Mean follow-up was 10 years (437 in the placebo group and 662 in the alendronate group). During the 5 years of additional treatment, the risk of clinical vertebral fractures was lower in the alendronate group than in the placebo group (relative risk [RR], 0.45; 95% confidence interval [95% CI], 0.24–0.85), whereas no significant differences occurred for non-vertebral fractures (RR, 1.0; 95% CI, 0.76–1.32) or morphometric vertebral fractures (RR, 0.86; 95% CI, 0.60–1.22) (Table 1). As shown in Table 2, the risk of new clinical vertebral fractures during the 5-year extension (i.e., between 5 and 10 years after FIT initiation) was associated with the femoral-neck *T*-score at initiation of the extension (i.e., 5 years after FIT initiation) and with the risk of clinical vertebral fractures during FIT (i.e., from FIT initiation to FIT completion 5 years later) [9]. The number needed (NNT) to treat to prevent one clinical vertebral fracture was computed in several subgroups defined based on baseline femoral-neck *T*-score and existence of prevalent clinical vertebral fractures. A *T*-score ≤ 2.5 at FLEX initiation was associated with a higher risk of vertebral fracture and a lower NNT, suggesting benefits from continued alendronate therapy in this subgroup. Moreover, patients with prevalent clinical vertebral fractures and a femoral-neck *T*-score ≤ -2 at FLEX initiation also had fewer clinical vertebral fractures if they continued alendronate therapy. Importantly, these conclusions apply only to alendronate, clinical vertebral fractures, and women having the profile seen in FLEX (about 70% with osteopenia and 65% without prevalent vertebral fractures at FLEX initiation). Finally, another post-hoc analysis suggests a beneficial effect of continued alendronate therapy on the risk of non-vertebral fractures in patients whose femoral-neck *T*-score was ≤ -2.5 at FLEX initiation.

Table 1
Incidence of fractures during FLEX.

Fractures	Placebo Number (%) ($n = 437$)	Alendronate Number (%) ($n = 662$)	Relative risk (95% CI)[a]
Vertebral			
Clinical	23 (5.3)	16 (2.4)	0.45 (0.24–0.85)
Morphometric	46 (11.3)	60 (9.8)	0.86 (0.60–1.22)
Clinical			
All	93 (21.3)	132 (19.9)	0.93 (0.71–1.21)
Non-vertebral	83 (19.0)	125 (18.9)	1.00 (0.76–1.32)
Hip	13 (3.0)	20 (3.0)	1.02 (0.51–2.10)
Forearm	19 (4.3)	31 (4.7)	1.09 (0.62–1.96)

95% CI: 95% confidence interval.
[a] After clinical adjustment and stratification.

In HORIZON-PFT [3], the efficacy of zoledronic acid (Z) in preventing osteoporotic fractures was evaluated in 7765 postmenopausal women with a mean age of 73 years. In the first extension [7], women who had received Z for 3 years were allocated at random to 3 additional years of Z (Z6, $n = 616$) or a placebo (Z3P3, $n = 617$). At randomization, mean age was 75.5 years, over 50% of patients had a femoral-neck *T*-score ≤ -2.5, and about 60% had one or more vertebral fractures. During the 3-year extension, the incidence of morphometric vertebral fractures was lower in the Z6 group than in the Z3P3 group (odds ratio [OR], 0.51; 95% CI, 0.26–0.95), whereas no significant differences occurred for clinical vertebral fractures (hazard ratio [HR], 1.81; 95% CI,

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Table 2
FLEX: Risk of clinical vertebral fractures and number needed to treat for 5 years to prevent one clinical vertebral fracture.

Femoral-neck *T*-score	Placebo Number (%) (*n* = 437)	Alendronate Number (%) (*n* = 662)	Risk difference (95% CI)	NNT
Overall population				
Any *T*-score	23/437 (5.5)	16/662 (2.5)	2.9 (0.3–5.4)	34
≤ –2.5	11/132 (9.3)	9/190 (4.5)	4.8 (0.8–9.2)	21
–2.5 to –2	9/126 (5.8)	3/185 (2.8)	3.0 (0.3–6.7)	33
> –2	3/179 (2.3)	4/282 (1.1)	1.2 (0.2–2.8)	81
No prevalent VFs				
≤ –2.5	6/75 (8.0)	4/109 (3.8)	4.2 (0.6–9.1)	24
–2.5 to –2	3/82 (3.0)	1/121 (1.4)	1.6 (0.2–5.0)	63
> –2	2/130 (1.8)	2/203 (0.9)	1.0 (0.1–2.6)	102
Prevalent VFs				
≤ –2.5	5/57 (11.1)	5/81 (5.3)	5.8 (0.8–12.1)	17
–2.5 to –2	6/44 (11.1)	2/64 (5.3)	5.8 (0.8–13.6)	17
> –2	1/49 (3.7)	2/79 (1.7)	2.0 (0.3–5.6)	51

Adapted from [9].
95% CI: 95% confidence interval; NNT: number needed to treat; VF: vertebral fracture.

0.53–6.2), hip fractures (HR, 0.9; 95% CI, 0.33–2.49), non-vertebral fractures (HR, 0.99; 95% CI, 0.7–1.5), and all clinical fractures (HR, 1.04; 95% CI, 0.71–1.54). A post-hoc analysis [10] identified three predictors of new morphometric vertebral fractures during the extension phase: baseline femoral-neck *T*-score ≤ –2.5 (OR, 3.3; 95% CI, 1.4–8.0; *P* = 0.008), baseline total-hip *T*-score ≤ –2.5 (OR, 4.01; 95% CI, 1.8–8.9; *P* = 0.0007), and new morphometric vertebral fractures during the 3-year extension (OR, 4.74; 95% CI, 1.3–16.7; *P* = 0.0156). The NNT to prevent one new morphometric vertebral fracture was 4 in patients with previous morphometric vertebral fractures and 17.5 in those with a femoral-neck *T*-score ≤ –2.5. In a second 3-year extension [11], the women who had taken Z for 6 years were allocated at random to Z (Z9, *n* = 95) or a placebo (Z6P3, *n* = 95). The number of incident fractures was too small to allow a statistical comparison of the two groups (Z9, *n* = 3; and Z6P3, *n* = 5). However, the similar time-course of bone mineral density (BMD) and bone turnover markers in the two groups does not support the administration of Z for 3 additional years after the first 6 years.

The 3-year FREEDOM randomized placebo-controlled trial [5] evaluated the ability of denosumab to prevent osteoporotic fractures in 7808 postmenopausal women with a mean age of 72.3 years. It was followed by a 4-year open-label extension [8], so that the total duration of denosumab therapy was 7 years in patients initially allocated to denosumab (long-term group, *n* = 2343) and 4 years in those initially allocated to the placebo (crossover group, *n* = 1731). The working hypothesis was that the decrease in non-vertebral fractures obtained after 3 years of denosumab in the main trial predicted a larger decrease after 4 years in the extension phase. In the crossover group, the risk of non-vertebral fractures during the 4th treatment year was decreased by 49% (rate ratio, 0.51; 95% CI, 0.32–0.82; *P* = 0.005) compared to the first 3 treatment years. In the long-term group, the fracture risk was lower by 25% (rate ratio, 0.75; 95% CI, 0.52–1.09; *P* = 0.127) during the 4th treatment year compared to the first 3 treatment years and by 21% (rate ratio, 0.79; 95% CI, 0.62–1.00; *P* = 0.046) during the 4-year extension phase compared to the first 3 treatment years. The decrease in the risk of non-vertebral fractures during the 4th year was statistically significant only in those women whose femoral-neck *T*-score was ≤ –2.5 (*n* = 778/4074) after 3 years of denosumab therapy (rate ratio, 0.37; 95% CI, 0.18–0.77; *P* = 0.008).

Little scientific evidence has been published about patient monitoring after the discontinuation of a first course of osteoporosis drug therapy. A post-hoc analysis of data from FLEX [12] showed that, of the 437 placebo-treated women (including 150 with vertebral fractures), 82 experienced one or more clinical fractures after the 1st year of follow-up. Factors associated with the occurrence of clinical fractures were older age and lowest tertile femoral-neck and total-hip *T*-scores (vs. the other two tertiles pooled) at inclusion into FLEX. Clinical fractures were predicted neither by the changes after 1 year in bone turnover marker values (urinary collagen 1 crosslinked *N*-telopeptide and serum bone alkaline phosphatase) nor by those in femoral-neck or total-hip BMD.

Thus, published data indicate that the appropriate course of action after an initial period of antiresorptive drug therapy in patients with postmenopausal osteoporosis depends on several factors, including the drug used (alendronate, zoledronic acid, or denosumab), hip *T*-scores (at the femoral-neck and/or total-hip), incident vertebral fractures and, probably, other factors, such as age. Women whose femoral-neck *T*-score is ≤ –2.5 after 3 years of zoledronic acid or 5 years of alendronate are at highest risk for new vertebral fractures and should therefore receive continued antiresorptive therapy. Another situation warranting continued therapy is the occurrence of at least one vertebral fracture during initial alendronate therapy with a *T*-score ≤ –2. With denosumab, the decrease in the risk of non-vertebral fractures is largest in women whose femoral-neck *T*-score is ≤ –2.5 after 3 years of treatment, who should therefore receive continued denosumab therapy.

French recommendations about the management of postmenopausal osteoporosis issued in 2012 suggest the use of pragmatic criteria [13]. The antiresorptive agent can be stopped after 5 years (3 years for zoledronic acid) in women who meet the following criteria: no fractures during treatment, no new risk factors, no significant BMD decline and, in the event of a severe osteoporotic fracture, a femoral-neck *T*-score > –2.5 at completion of the initial treatment period.

Because most studies used an open-label design and failed to collect information on fractures, there is insufficient evidence at present to recommend a specific drug rotation strategy after an initial period of antiresorptive therapy. Nevertheless, BMD and bone turnover marker data are available. When considering a switch from a bisphosphonate, denosumab or teriparatide (in patients with two or more vertebral fractures) are better candidates than another bisphosphonate (intravenously or orally). The DATA trial found no benefits from switching from denosumab to teriparatide [14]. No BMD data after switching from denosumab to a bisphosphonate are available.

Further work is needed to put osteoporosis treatment into sharper focus, in particular by determining the hip *T*-score target of the initial antiresorptive drug treatment. Another crucial issue is the best monitoring strategy for patients who are taken off antiresorptive therapy. Atypical femoral fractures and osteonecrosis of the jaw, although rare, may be more common with long-term antiresorptive drug exposure. Consequently, a careful risk/benefit

ratio evaluation is mandatory when considering treatment continuation.

Disclosure of interest

The author declares that he has no competing interest.

References

[1] Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535–41.
[2] Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077–82.
[3] Black DM, Delmas PD, Eastell R, et al. HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809–22.
[4] Lyles KW, Colón-Emeric CS, Magaziner JS, et al. HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007;357:1799–809.
[5] Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361:756–65.
[6] 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;24:2927–38.
[7] Black DM, Reid IR, Boonen S, et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res 2012;27:243–54.
[8] Ferrari S, Adachi JD, Lippuner K, et al. Further reductions in nonvertebral fracture rate with long-term denosumab treatment in the FREEDOM open-label extension and influence of hip bone mineral density after 3 years. Osteoporos Int 2015;26:2763–71.
[9] Black DM, Bauer DC, Schwartz AV, et al. Continuing bisphosphonate treatment for osteoporosis – for whom and for how long? N Engl J Med 2012;366:2051–3.
[10] Cosman F, Caulin F, Eastell R, et al. Who is at highest risk for new vertebral fractures after 3 years of annual zoledronic acid and who should remain on treatment? J Bone Miner Res 2011;26:1248 [Abstract].
[11] Black DM, Reid IR, Cauley JA, et al. The effect of 6 versus 9 years of zoledronic acid treatment in osteoporosis: a randomized second extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Miner Res 2015;30:934–44.
[12] Bauer DC, Schwartz A, Palermo L, et al. Fracture prediction after discontinuation of 4 to 5 years of alendronate therapy: the FLEX study. JAMA Intern Med 2014;174:1126–34.
[13] Briot K, Cortet B, Thomas T, et al. 2012 update of French guidelines for the pharmacological treatment of postmenopausal osteoporosis. Joint Bone Spine 2012;79:304–13.
[14] Leder BZ, Tsai JN, Uihlein AV, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet 2015;386:1147–55.

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