



Beyond 2 Years, Oral Bisphosphonate Holiday Ups Broken Hip Risk

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MONTREAL, QUEBEC — Stopping oral bisphosphonate therapy for osteoporosis — taking a "drug holiday" — for 2 to 3 years appears to increase the risk of having a hip fracture compared with continuing therapy, new research indicates.

The findings come from a large study of Medicare claims data in older women who had been initiated mainly on oral alendronate (80%) and less often on oral risedronate (9%) or intravenous zoledronic acid (11%) and who took these therapies regularly for a few years before they stopped refilling their prescriptions.

However, within 2 years of stopping risedronate and alendronate there was a 30% to 50% relative increased risk of a hip fracture compared with continuing these therapies, but this was not seen with IV zoledronic acid, Kenneth Saag, MD, from the University of Alabama at Birmingham reported here at the American Society for Bone and Mineral Research (ASBMR) 2018 Annual Meeting.

The absolute difference in fracture rate was a "relatively modest (0.5 to 1/100 person-years)," he noted.

"The clinical implication," Saag said, "might be that a longer-term bisphosphonate drug holiday may not be appropriate for all patients, and a holiday from oral bisphosphonates — specifically alendronate and risedronate — in excess of 2 to 3 years may be undesirable."

To *Medscape Medical News*, Saag explained that "there are guidelines from the [ASBMR] suggesting that after 3 years of intravenous and 5 years of oral bisphosphonate, a holiday may be considered in selected individuals."

However, "we don't really know what to do after a drug holiday," he added. "That's the real unanswered question. And these data do inform that to some degree."

"The hip fracture is the one we worry about the most," he noted, "because of the increased morbidity and mortality, and that [outcome] we can ascertain particularly well using claims data."

Asked for her thoughts, session moderator Aliya Khan, MD, McMaster University, Hamilton, Ontario, told *Medscape Medical News* that guidelines recommend that

clinicians look at patients' fracture risks after they have been on therapy for 5 years, and "if the risk of fracture is high, we should look at switching to another drug; we should *not* give them a drug holiday. But if the fracture risk is low or moderate, then we could give them a drug holiday."

"A drug holiday is very helpful in people who have been on long-term bisphosphonates...more than 5 years," she added.

"But I think the important point [for clinicians] to remember," Khan stressed, "is that we should follow these people. Don't forget about them. Make sure that you are monitoring bone density and asking [patients] about fracture because if their bone density goes down or they have a fracture, they have to go right back on [osteoporosis-drug] therapy."

"A Major Question in the Bone Field Today"

Bisphosphonates remain the predominant class of drugs used to treat osteoporosis throughout the world, Saag noted, but "given concerns about rare side effects, particularly atypical femoral fracture, this idea of a bisphosphonate drug holiday — an intentional temporary or permanent discontinuation of therapy — is becoming increasingly common."

However, most data that support this practice come from extensions to large clinical trials such as the FLEX study, in which there were limited sample sizes, low statistical power, and poor generalizability (*J Clin Endocrinol Metab.* 2000;85:4118-4124).

According to Saag, "the benefits and risks of stopping [bisphosphonates] and optimal timing to restart remain unclear and constitute a major question in the bone field today." Therefore, he and his coauthors analyzed national Medicare data from 2005 to 2015 to investigate the rate of fractures following a bisphosphonate drug holiday in older women.

They identified 73,800 women aged 65 years and older who had been very compliant with initiated bisphosphonate therapy — they had 80% adherence for 3 years or more— before they stopped refilling prescriptions for a year or more, "presumably in some cases due to a drug holiday," Saag said.

They excluded patients who were taking other therapies for osteoporosis such as denosumab, estrogen, teriparatide, or calcitonin.

After a median follow-up of 2.7 years, 26,281 patients (35.6%) had stopped taking their bisphosphonate therapy for at least 12 months, and the remaining patients had continued taking it.

Participants in both groups had similar baseline characteristics.

Patients were a mean age of 79 years and about two-thirds were 75 years or older. About 18% had a history of a major fragility fracture, and about half had a Charlson comorbidity score of 1 or more.

Undoing All the Previous Good?

Patients who took a drug holiday from alendronate or risedronate, but not zoledronic acid, had a significantly increased risk of a hip fracture compared with their peers who continued these therapies.

Risk of Hip Fracture, Stopping Versus Continuing Bisphosphonate

Therapy	Discontinuation Time, Years	Adjusted HR (95% CI)*
Alendronate	> 1 to ≤ 2	1.3 (1.1 - 1.5)
Alendronate	> 2 to ≤ 4	1.3 (1.1 - 1.5)
Alendronate	> 4	1.8 (1.2 - 2.6)
Risedronate	> 1 to ≤ 2	1.5 (1.0 - 2.3)
Risedronate	> 2	1.6 (1.1 - 2.5)

*Adjusted for multiple variables.

The risk of hip fracture associated with temporarily or permanently stopping risedronate for more than a year appeared to be similar if not greater than the risk seen with stopping alendronate.

But there was no significant increased risk of hip fracture associated with stopping zoledronic acid, possibly because of different pharmacologic properties of drugs within this class.

Among patients taking alendronate, those who stopped taking it for more than 4 years had an 80% increase in hip fractures compared with those who continued taking it, which may have wiped out any previous benefit.

"If you look at the 53% relative risk reduction [of hip fractures] seen in the FLEX study," Saag said, this represents a "nearly undoing of the benefit that might have been achieved with previous use of alendronate."

Overall, stopping a bisphosphonate for more than 1 year was not associated with an increased rate of vertebral or wrist/distal radius fractures. But there was a significant increased risk of humerus fractures and a trend to an increased risk of pelvic fractures. Trial limitations included the fact that there was very little follow-up beyond 4 years; fractures were not confirmed with medical records; data such as bone mineral density by DXA was not available; and reasons for discontinuation of the bisphosphonates were unknown.

"Certainly, additional work is needed," Saag concluded, "with longer follow-up and larger numbers to better understand the longer-term effects of bisphosphonate discontinuation."

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