THE ENDOCRINE SOCIETY

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The Endocrine Society Recommends Patient-Centered Approach to Long-Term Bisphosphonate Use for the Treatment of Osteoporosis

A review of the May 2012 FDA Analysis

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Bisphosphonates are highly effective agents for the treatment of osteoporosis and prevention of fractures. Recently, concerns have been raised regarding the optimal exposure to these drugs because of long-term safety issues such as atypical femur fractures and osteonecrosis of the jaw although it is unclear what the relationship is between these rare events and bisphosphonate use.

In an article published in the New England Journal of Medicine's Perspective section on May 9, 2012 that received widespread media coverage, Whitaker and colleagues at the Food and Drug Administration (FDA) present data from three extension trials of commonly used bisphosphonates (alendronate, risedronate, and zoledronic acid) regarding the reduction in fracture risk beyond that shown in the initial 4-5 year registration trials of these drugs (1). Their analysis showed that stopping bisphosphonate therapy led to a modest decline in femoral neck bone density in the first 1-2 years following cessation of treatment with stabilization thereafter. Lumbar spine BMD continued to increase despite therapy being discontinued. The FDA found similar rates of overall vertebral and non-vertebral fracture rates in those treated up to 10 years compared to those who were switched to placebo during the extension phase in all three trials, thus raising concern regarding the benefit of long-term bisphosphonate therapy for osteoporosis.

However, an accompanying Perspective in the same issue of the New England Journal of Medicine by Black and colleagues parses out the data for vertebral and non-vertebral fracture risk separately rather than using a composite of both fractures together (2). Their rationale for doing so was based on the different pathogenesis and responses to treatment at these sites. Black and colleagues found benefit for continuation of bisphosphonate therapy in some higher risk subgroups, particularly with respect to prevention of vertebral fractures.

Despite differences in methodology employed in the two papers, the FDA and Black analyses agree on many points. Both note that the few extension trials looking at long-term bisphosphonate use are limited by problems with statistical power, selection bias, sample size, and timing issues. They agree that bisphosphonates may be safely discontinued in some patients without compromising therapeutic gains. Both also agree that decisions to continue treatment must be based on individual assessment of risks and benefits and on patient preference. Moreover, both papers state that not all bisphosphonates are alike, so recommendations to discontinue bisphosphonates should be based on the specific drug.

Black et al. go on to provide a therapeutic algorithm for clinicians based on the current limited evidence summarized as follows:

> 1) Patients with bone density T-scores of -2.5 or lower at the femoral neck after 3 to 5 years of treatment are at the highest risk for vertebral fractures and appear to benefit most from continuation of bisphosphonates.
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> 2) Patients with an existing vertebral fracture and T-scores up to −2.0 may also benefit from continued therapy.

3) Patients with femoral neck T-scores above −2.0 have low risk of vertebral fractures and are unlikely to benefit from continued treatment after 3-5 years.

The Endocrine Society is concerned that a superficial reading of the FDA analysis will result in an inappropriate abandonment of bisphosphonates for both short- and long-term use in patients with osteoporosis. Therefore, the Society urges its members to engage in a patient-specific dialogue about the appropriateness of long-term bisphosphonate use. Furthermore, healthcare professionals should follow the package insert's recommendations when prescribing bisphosphonates. Patients should continue taking their medication unless advised to stop by their health care provider. The Society supports continued research in this area to better clarify the short- and long-term benefits, and risks of bisphosphonates and other drugs used in patients with osteoporosis.

For questions, please contact Stephanie Kutler, Director of Government Affairs, at skutler@endo-society.org.

1. Whitaker M., Guo J., Kehoe T., Benson G. 10.1056/NEJMp1202619
2. Black D.M., Bauer D.C., Schwartz A.V., Cummings S.R., Rosen C.J. 10.1056/NEJMp1202623