

Introduction

Bisphosphonates were first reported in the literature in the late 1960s and were initially used in patients for treatment of calcium metabolism. In the 1990s, bisphosphonates were approved for use in osteoporosis and have become the mainstay of treatment. However, concerns have recently been raised regarding long-term bisphosphonate use.

Background

Osteoporosis has an estimated prevalence of over 200 million people worldwide, impacting almost one-third of postmenopausal women in the United States and Europe.^(IOF, 2017) It is estimated that in these women, at least 40% will sustain a fragility fracture during their life. The estimated lifetime rate in men is 15 – 30 percent.^(IOF, 2017)

Considering the absence of absolute treatment guidelines and absolute durations of treatment, more recently, concerns have surfaced regarding long term safety of bisphosphonate use. Rare complications of long-term bisphosphonate treatment include atypical femoral fracture (AFF) and osteonecrosis of the jaw (ONJ). These safety issues coupled with residual post-treatment fracture risk reduction have resulted in temporarily suspending the bisphosphonate, also known as a drug holiday.

Risk of Atypical Femoral Fracture & Osteonecrosis of the Jaw

Some studies shown a twofold increased risk of AFF in patients treated with bisphosphonate use longer than 5 years.^(Anagnostis, et al, 2017) In many patients, the risk of AFF is outweighed by the benefits of bisphosphonate use.^(Tu, et al, 2018) In addition to long term use of bisphosphonates, risks for AFF include use of proton pump inhibitor, glucocorticoids, history of contralateral AFF, collagen disease and varus deformity.^(Toro, et al, 2016) ONJ is typically seen in oncology patients receiving high dose IV bisphosphonate treatment.^(Anagnostis, et al, 2017 & Jagpal&Saag, 2018) Dental co-morbidity and history are important in identifying risk for ONJ.^(Jagpal & Saag, 2018)

Drug Holiday

Drug holidays have been introduced to decrease the risk of AFF and ONJ. Some studies have suggested a lack of evidence for decreased risk for AFF during a drug holiday.^(Adams, et al, 2018 & Schilcher, et al, 2015) While a drug holiday of 5 years is commonly believed to be appropriate, the decision for initiating a drug holiday and the duration of the drug holiday must be individualized. Candid and balanced discussion with patients about the risks and benefits of temporarily discontinuing bisphosphonate therapy is critically important in patient centered shared decision making. Lifestyle modifications including weight-bearing exercise, supplemental calcium and reducing fall risk should be continued during the drug holiday. Periodic risk reassessment during the drug holiday is also vital so that bisphosphonate treatment can be reinstated if the patient's risk increases or bone mineral density declines.

Recommendations for bisphosphonate drug holidays			
Organization	Drug holiday	Risk assessment	BMD testing during drug holiday
American Society for Bone Mineral Research (2019) www.asbmr.org Consensus clinical recommendation	Reassess treatment with bisphosphonates after 3 to 5 years No specific drug holiday recommendation		No statement regarding testing during drug holiday
Endocrine Society & European Society of Endocrinology (2019) www.endocrine.org www.ese-hormones.org Guideline	After 5 years of oral treatment or 3 years of IV treatment, consider drug holiday up to 5 years in low to moderate risk women	Reassess fracture risk every 2 to 3 years during drug holiday	
American College of Physicians (2017) www.acponline.org Guideline	Recommends 5 years of osteoporosis treatment in women Appropriate treatment duration unknown		No statement
European Menopause and Andropause Society (2017) www.emas-online.org position statement	Drug holiday consideration after 5 years (alendronate or risedronate) or 3 years (zoledronate) in all treated patients Suggested recommendation for duration of drug holiday is 2 – 3 years (shorter with risedronate), but optimal duration is unknown	Reassess during drug holiday after 1 to 3 years	BMD, fall risk, age and smoking all part of risk assessment
American Association of Clinical Endocrinologists and American College of Endocrinology (2016) www.aace.com Guideline	Consider after 5 years of oral treatment in low to moderate risk patients, or 6 – 10 years in higher risk patients; 3 years after IV treatment in low to moderate risk patients or 6 years in higher risk patients Consider alternative medication treatment (raloxifene or teriparatide) during drug holiday for higher risk patients	Individualized assessment to resume bisphosphonates	

Adapted from DiGiulio, Loveless, Heider, Fagan and Porsche (2020)

Discussion

There is no evidence based optimal timing or duration for bisphosphonate drug holidays at this time. Bisphosphonate drug holiday may not be appropriate for all patients. Some patients may benefit from alternative osteoporosis treatment with raloxifene or teriparatide) during drug holiday. Treatment decisions must be individualized based on risk assessment which include bone mineral density, fracture risk, fall risk, co-morbidities, and bisphosphonate used.

References

- International Osteoporosis Foundation. Epidemiology. 2017. <https://www.iofbonehealth.org/epidemiology>. Accessed August 15, 2020
- DiGiulio M, Loveless T, Heider G, Fagan K, Porsche B. Bisphosphonate drug holidays: One size does not fit all. *The Nurse Practitioner*. 2020 Mar;45(3):50-55. <https://doi.org/10.1097/01.npr.0000605524.34681.e7>
- Pauline M. Camacho, Steven M. Petak, Neil Binkley, Bart L. Clarke, Steven T. Harris, Daniel L. Hurley, Michael Kleerekoper, E. Michael Lewicki, Paul D. Miller, Harmeet S. Narula, Rachel Pessah-Pollack, Vin Tangpricha, Sunil J. Wimalawansa, and Nelson B. Watts. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2016. *Endocrine Practice*: September 2016, Vol. 22, No. Supplement 4, pp. 1-42. <https://doi.org/10.4158/EP161435.0L>
- Anagnostis P, Paschou SA, Mintziori G, et al. Drug holidays from bisphosphonates and denosumab in postmenopausal osteoporosis: EMAS position statement. *Maturitas*. 2017;101:23-30.
- Tu KN, Lie JD, Wan CKV, et al. Osteoporosis: a review of treatment options. *P T*. 2018;43(2):92-104.
- Toro G, Ojeda-Thies C, Calabró G, et al. Management of atypical femoral fracture: a scoping review and comprehensive algorithm. *BMC Musculoskelet Disord*. 2016;17:227.
- Adams AL, Adams JL, Raebel MA, et al. Bisphosphonate drug holiday and fracture risk: a population-based cohort study. *J Bone Miner Res*. 2018;33(7):1252-1259.
- Schilcher J, Koeppen V, Aspenberg P, Michaëlsson K. Risk of atypical femoral fracture during and after bisphosphonate use. *Acta Orthop*. 2015;86(1):100-107.
- Jagpal A, Saag KG. How to use bisphosphonates safely and optimally. *Rheumatology (Oxford)*. 2018;57(11):1875-1876.
- Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2019;104(5):1595-1622.
- Quasem A, Forcica MA, McLean RM, Denberg TC. Clinical Guidelines Committee of the American College of Physicians. Treatment of low bone density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. *Ann Intern Med*. 2017;166(11):818-839.
- Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2014;25(10):2359-2381.
- Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2016. *Endocr Pract*. 2016;22(Suppl 4):1-42.
- Conley RB, Adib G, Adler RA, et al. Secondary fracture prevention: consensus clinical recommendations from a multistakeholder coalition. *J Bone Miner Res*. 2020;35(1):36-52.