Systematic review methods for meta-analysis of hip fracture rates, Figure 3

Figure 3 reports on an updated version of a systematic review published on-line:

Therapeutics Initiative. A Systematic Review of the Efficacy of Bisphosphonates. Therapeutics Letter Issue 83/ Sep – Oct 2011. Available at: http://www.ti.ubc.ca/letter83

Authors: Vijaya Musini, MD, DPH, MSc; Odie Geiger, PhD, Aaron Tejani, PharmD, Gautam Goel, Jennifer Shiu and Erica Wang

Therapeutics Initiative, Department of Anesthesiology, Pharmacology & Therapeutics, University of British Columbia, 2176 Health Sciences Mall, Vancouver BC V6T 1Z3; corresponding author: vijaya.musini@ti.ubc.ca

The aim of this systematic review was to examine whether use of bisphosphonates leads to clinically significant outcomes such as reduction in hip fractures, other symptomatic fractures and fragility fractures, and whether their safety profile, with regard to mortality and other adverse events supports their use in either primary and secondary prevention of osteoporosis.

This systematic review was carried out using Cochrane Review methods.[1] We reviewed randomized, placebo-controlled trials of at least one year duration for three bisphosphonate drugs commonly prescribed in North America: alendronate (Fosamax®), risedronate (Actonel®) and etidronate (Didronel®, Didrocal®).

The initial impetus for this review had been to update and extend three Cochrane systematic reviews on oral bisphosphonates for post-menopausal osteoporosis[2-4]; therefore zoledronic acid (Reclast®) was not included in the review, despite its availability as a treatment for osteoporosis in post-menopausal women. At a second stage, in order to provide a more complete overview of the available evidence on hip facture prevention with bisphosphonates available for this indication, for Figure 3 in the current article, trials assessing zoledronate were added to the review, based on the same inclusion criteria as in the initial systematic review.

Articles were identified through a structured search of Ovid MEDLINE and EMBASE. References indexed to the end of October 2011 were included. Standardized PICOS inclusion criteria (**P**opulation, **I**nterventions, **C**omparators, **O**utcomes and **S**tudy designs)[1] ~~(Higgins and Green, 2011)~~ were defined a priori as follows:

- The **population** studied was post-menopausal women. These were divided into primary prevention or secondary prevention based on study or study subgroup inclusion criteria. Primary prevention is defined as women without prior fragility fractures or vertebral compression; secondary prevention, women with prior fragility fractures or prior vertebral compression. Fragility fractures are defined as a low trauma fractures (e.g. equivalent to falls from a standing height or less); vertebral compression as a loss of vertebral height on x-ray (predefined thresholds differing in clinical trials). Vertebral compressions may be symptomatic or asymptomatic.

- The **intervention** of interest was use of alendronate, etidronate, risedronate or zoledronic acid, at any dose level.
- **Comparators** were either a placebo or no bisphosphonates, with or without a calcium + Vitamin D supplement. **Outcome** measures of interest were: all-cause mortality, total serious adverse events, hip fractures, vertebral fractures, wrist fractures, withdrawals due to adverse events (WDAE), total withdrawals, all-cause adverse events, radiographically detected asymptomatic vertebral fractures, and radiographically detected symptomatic vertebral fractures.
- **Study designs** were limited to randomized~~,~~ controlled studies of at least one-year duration.

References were identified as potentially relevant in initial title and abstract screening. Those considered potentially relevant were retrieved as full-text articles and examined by two reviewers, with any discrepancies identified and resolved by consensus, or if this was not possible, through adjudication by a third reviewer. Of 1498 initially identified references in combined searches, 77 met study inclusion criteria (41 alendronate; 14 risedronate; 19 etidronate; 3 zoledronate). Of these 77, 22 studies (reporting on 23 comparisons) included data on hip fracture rates and contributed to the analysis in Figure 3.[5-26]

Data were abstracted independently by two reviewers, cross checked, and then analyzed using the Cochrane collaboration's Review Manager version 5.2 software. Analyses of each of the drugs were independent, as there was no intention to determine relative effectiveness. Pre-planned subgroup analyses were carried out for primary prevention or secondary prevention, dependent on study participant inclusion criteria. Where data were not available separately for primary and secondary prevention, they were jointly analyzed (i.e. for two zoledronate trials).

Study quality was assessed using the Cochrane risk of bias tool, assessing risk as low, unclear or high on seven dimensions (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias). Risk ratios and 95% confidence intervals between intervention and comparison groups were the principal summary measure evaluated in meta-analyses.

References

1 Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

2 Wells GA, Cranney A, Peterson J, Boucher M, Shea B, et al. (2008a) Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev: (1) CD004523.

3 Wells GA, Cranney A, Peterson J, Boucher M, Shea B, et al. (2008b) Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev: (1) CD003376.

4 Wells GA, Cranney A, Peterson J, Boucher M, Shea B, et al. (2008c) Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database Syst Rev: (1) CD001155.

5 McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344:333-40.

6 Ascott-Evans BH, Guanabens N, Kivinen S, et al. Alendronate prevents loss of bone density associated with discontinuation of hormone replacement therapy: a randomized controlled trial. Arch Intern Med 2003;163:789-94.

7 Chailurkit LO, Jongjaroenprasert W, Rungbunnapun S, et al. Effect of alendronate on bone mineral density and bone turnover in Thai postmenopausal osteoporosis. J Bone Miner Metab 2003;21:421-7.

8 Chesnut CH 3rd, McClung MR, Ensrud KE, et al. Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. Am J Med 1995;99:144-52.

9 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(24):2077-82.

10 Leung JY, Ho AY, Ip TP, et al. The efficacy and tolerability of risedronate on bone mineral density and bone turnover markers in osteoporotic Chinese women: a randomized placebo-controlled study. Bone 2005;36:358-64.

11 Li Y, Zhang Z, Deng X, et al. Efficacy and safety of risedronate sodium in treatment of postmenopausal osteoporosis. J Huazhong Univ Sci Technolog Med Sci 2005;25:527-9.

12 Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995;333(22):1437-43.

13 McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. N Engl J Med 2006;354:821-31.

14 Murphy MG, Weiss S, McClung M, et al. Effect of alendronate and MK-677 (a growth hormone secretagogue), individually and in combination, on markers of bone turnover and bone mineral density in postmenopausal osteoporotic women. J Clin Endocrinol Metab 2001;86:1116-25.

15 Pols HA, Felsenberg D, Hanley DA, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low

bone mass: results of the FOSIT study. Fosamax International Trial Study Group. Osteoporos Int 1999;9:461-8.

16 Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356(18):1809-22.

17 Lyles KW, Colon-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007;357(18):1799-809.

18 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(9041):1535-41.

19 Cecilia D, Jodar E, Fernandez C, et al. Effect of alendronate in elderly patients after low trauma hip fracture repair. Osteoporos Int 2009;20:903-10.

20 Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999;282(14):1344-52.

21 Lyritis GP, Tsakalakos N, Paspati I, et al. The effect of a modified etidronate cyclical regimen on postmenopausal osteoporosis: a four-year study. Clin Rheumatol 1997;16:354-60.

22 Montessori ML, Scheele WH, Netelenbos JC, et al. The use of etidronate and calcium versus calcium alone in the treatment of postmenopausal osteopenia: results of three years of treatment. Osteoporos Int 1997;7:52-8.

23 Qin L, Choy W, Au S, et al. Alendronate increases BMD at appendicular and axial skeletons in patients with established osteoporosis. J Orthop Surg Res 2007;2:9.

24 Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000;11:83-91.

25 Storm T, Thamsborg G, Steiniche T, et al. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990;322(18):1265-71.

26 Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med 1990;323:73-9.