Osteoporos Int (2013) 24:1927–1928
DOI 10.1007/s00198-013-2294-9

LETTER

Efficacy of osteoporosis therapies in a network meta-analysis with indirect comparisons: many concerns for new tools of evidence synthesis?

F. Catalá-López · G. Sanfélix-Gimeno · A. Tobías · I. Hurtado · J. Sanfélix-Genovés · S. Peiró

Received: 25 September 2012 / Accepted: 7 January 2013 / Published online: 14 February 2013

Dear Editor,

We have read with great interest the paper by Freemantle et al. [1] on an indirect and mixed-treatment comparison meta-analysis (a new evidence synthesis tool also called, "network meta-analysis") of trials evaluating the comparative efficacy of osteoporosis therapies. In their paper, the authors conclude that their network meta-analysis "showed denosumab to be more effective than strontium ranelate, raloxifene, alendronate, and risedronate in preventing new vertebral fractures".

Network meta-analysis or mixed-treatment comparisons refer to the same methodological framework that combines direct and indirect evidence across a network of trials to infer about the comparative effectiveness of competitive (alternative) treatments. The main assumptions which underlines these methods are the transitivity (if treatment A is better than B and B is better than C, then A is assumed to be better than C) and consistency (agreement between direct and indirect evidence) [2, 3]. In this regard, Freemantle et al. implicitly assumed that all antiosteoporotic therapies in the direct comparisons have similar efficacy to those in the indirect comparisons, which is not easy to sustain and verify with the available information in their paper.

Primary analyses evaluating new vertebral fractures (see Table 1 and Fig. 1 in the web appendix) showed that the direct meta-analysis comparing multiple antiosteoporotic therapies only considered placebo-controlled trials but not head-to-head comparisons against active therapies (e.g. strontium ranelate, raloxifene, alendronate, risedronate, teriparatide, and so on). Along these analyses, denosumab was evaluated exclusively in a single placebo-controlled trial (relative risk [RR]=0.32; 95 % confidence interval=0.26–0.41) sponsored by the drug manufacturer [4] and was the largest (with 3,933 women enrolled in the denosumab group) and the most recent trial included in the analyses. Because of the absence of denosumab-active comparator trials in the networks and the considerable influence of the single denosumab trial [4], the use of network meta-analysis including mixed-treatment comparisons may not be appropriate. As such, consistency evaluation in the networks (defined as a disagreement between direct and indirect evidence for the same comparison) did not seem feasible (although the authors argued that "in the mixed-treatment comparison of each comparator with placebo, the RR for new vertebral fractures were consistent with those obtained directly from the meta-analyses (Table 1)" which is obviously somewhat misleading).

On the other hand, trials on antiosteoporotic therapies have been conducted over different time periods (e.g.

Related correspondence can be found at doi 10.1007/s00198-013-2297-6 and doi 10.1007/s00198-013-2299-4.

F. Catalá-López
Division of Pharmacoepidemiology and Pharmacovigilance, Spanish Medicines and Healthcare Products Agency (AEMPS), Madrid, Spain

F. Catalá-López (✉) · G. Sanfélix-Gimeno · I. Hurtado · J. Sanfélix-Genovés · S. Peiró
Centro Superior de Investigación en Salud Pública (CSISP), Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO), Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC), Valencia, Spain
e-mail: ferran_catala@hotmail.com

A. Tobías
Institute of Environmental Assessment and Water Research (IDAEA), Spanish Council for Scientific Research (CSIC), Barcelona, Spain

trials on oral biphosphonates have been primarily published in the late 1990s) explaining why there are different amounts of evidence owing to variations in characteristics of patients (women with differences in risk factors for osteoporotic fractures), different supplementation exposures (e.g. calcium and vitamin D), screening procedures, outcome assessments or treatments compliance across trials. This implies looking at the distribution of potential confounders across all treatment comparisons when the body of evidence permits [2, 3].

Finally, indirect treatment comparisons based on single trials or based on disparate comparisons are of doubtful relevance and need to be interpreted cautiously by clinicians and researchers, especially in a field-at-large influenced by commercial third parties and with well-known potential risk of sponsorship biases.

References

1. Freemantle N, Cooper C, Diez-Perez A, Gitlin M, Radcliffe H, Shepherd S, Roux C (2012) Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: a meta-analysis. Osteoporos Int. doi:10.1007/s00198-012-2068-9
2. Salanti G (2012) Indirect and mixed-treatment comparison, network, or multiple treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res Syn Meth. doi:10.1002/jrsm.1037
3. Catalá-López F, Tobías A (2012) Clinical evidence synthesis and network meta-analysis with indirect-treatment comparisons. Med Clin (Barc). doi:10.1016/j.medcli.2012.09.013
4. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S, Adami S, Zanchetta J, Libanati C, Siddhanti S, Christiansen C, FREEDOM Trial (2009) Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 361(8):756–765, Erratum in: N Engl J Med. 2009;361(19):1914