J Musculoskelet Neuronal Interact 2024; 24(4):332-335

Journal of Musculoskeletal and Neuronal Interactions JMNI

Cochrane Corner

Cochrane Rehabilitation
rehabilitation.cochrane.org

Which Bone-Modifying Agents Are Most Effective in Reducing Bone Loss in Women with Early and Locally Advanced Breast Cancer? - A Cochrane Review summary with commentary

Ekin Ilke Sen

Department of Physical Medicine and Rehabilitation, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

Keywords: Bisphosphonate, Bone Loss, Breast Cancer, Denosumab, Quality of Life

The aim of this commentary is to discuss from a rehabilitation perspective the Cochrane Review "Bone-modifying agents for reducing bone loss in women with early and locally advanced breast cancer: a network meta-analysis"[1] by Adams et al.[a], published by the Cochrane Breast Cancer Group. This Cochrane Corner is produced in agreement with *Journal of Musculoskeletal and Neuronal Interactions* by Cochrane Rehabilitation with views* of the review summary author in the "implications for practice" section.

Background

Breast cancer remains the most prevalent malignancy among women worldwide, with incidence rates continuing to rise[2]. Advancements in breast cancer management, particularly through enhanced screening, early diagnosis, and therapeutic interventions, have significantly improved survival rates. However, cancer related treatments, especially endocrine therapies, are associated with accelerated bone loss and an increased risk of fractures in pre- and postmenopausal women with breast cancer[3,4]. To mitigate these adverse effects on bone health, current therapeutic strategies have increasingly focused on the use of bone-modifying agents, such as bisphosphonates and denosumab[5].

Evidence indicates that antiresorptive drugs, including bisphosphonates and denosumab, effectively increase bone mineral density (BMD) in postmenopausal women with non-metastatic breast cancer undergoing aromatase inhibitor therapy[6]. A recent systematic review and network meta-analysis further suggests that denosumab, ibandronate, and risedronate significantly improve BMD compared to placebo in women receiving endocrine therapy for hormone-sensitive breast cancer[7]. However, despite these benefits, the evidence regarding fracture prevention remains inconclusive[6-8].

High quality evidence from individual patient data from randomized trials and meta-analyses demonstrate that adjuvant bisphosphonate therapy in early breast cancer

The author declares no conflicts of interest.

Corresponding author: Ekin Ilke Sen, Department of Physical Medicine and Rehabilitation, Istanbul Faculty of Medicine, Istanbul Uni-versity, Istanbul, Turkey
E-mail: ekinozgorgu@gmail.com

[a] This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2024, Issue 7, Art. No.: CD013451, DOI: 10.1002/14651858.CD013451.pub2. (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

* The views expressed in the summary with commentary are those of the Cochrane Corner author (different than the original Cochrane Review authors) and do not represent the Cochrane Library or Wiley.

significantly reduces the risk of bone recurrence and improves overall survival, with the benefits being particularly evident in postmenopausal women[9]. A clear ranking of all treatment options to identify the most effective drug for improving bone health is lacking.

Recently, a Cochrane Review by Adam et al.[1] critically examined the existing evidence on bone-modifying agents in women with early and locally advanced breast cancer using a network meta-analysis. The purpose of a network analysis is to determine whether a certain treatment is superior in terms of effectiveness and safety compared to other treatments. This is helpful when multiple treatments available have not been directly compared to one another in clinical trials.

Bone-modifying agents for reducing bone loss in women with early and locally advanced breast cancer: a network meta-analysis[1]

(Adams A, Jakob T, Huth A, Monsef I, Ernst M, Kopp M, Caro-Valenzuela J, Wöckel A, Skoetz N, 2024)

What is the aim of this Cochrane Review?

The aim of this study was to rank various bone-modifying agents by employing network meta-analyses to determine their effectiveness in minimizing BMD loss, improving quality of life, and preventing osteoporotic fractures, along with assessing potential adverse effects associated with these treatments in women with breast cancer without bone metastases.

What was studied in the Cochrane Review?

The population addressed in this review consisted of adult women aged 18 and older who had a confirmed diagnosis of early-stage or locally advanced breast cancer, including all non-metastatic stages. The interventions are bone-modifying agents, such as bisphosphonates and RANKL inhibitors. These interventions were compared both against each other and against placebo or no treatment. The primary outcome was the change in BMD, assessed through dual-energy X-ray absorptiometry scans or as reported in the trials if assessed differently, alongside quality of life, which was evaluated using validated generic and disease-specific questionnaires. Secondary outcomes included fracture rate, defined as the total number of any type of bone fractures occurring during and after treatment with bone-modifying agents (including both vertebral and non-vertebral fractures), overall survival, and adverse events such as osteonecrosis of the jaw and renal dysfunction.

Search methodology and up-to-dateness of the Cochrane Review

The review authors conducted a comprehensive search for studies published up until January 17, 2023, across multiple databases, including the Cochrane Breast Cancer Group's Specialized Register, CENTRAL, MEDLINE, Embase, the World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov, without imposing any language restrictions.

What are the main results of the Cochrane Review?

The review included 47 studies with a total of 35,163 participants, of which 34 studies involving 33,793 participants were eligible for quantitative synthesis (network meta-analysis). These 34 trials, encompassing eight different treatment options, were connected within a network, thereby enabling a comprehensive ranking of all treatment options. The main findings from the network meta-analysis for each pairwise comparison between the interventions and no treatment/placebo are as follows:

- Zoledronic acid is likely to result in a modest increase in BMD (T-score -0.45; MD 0.89, 95% CI 0.62 to 1.16; moderate certainty), while ibandronate may also offer a slight increase (T-score -0.77; MD 0.57, 95% CI -0.05 to 1.19; low certainty) compared to no treatment/placebo (T-score -1.34). Risedronate appears to have little to no impact (T-score -1.08; MD 0.26, 95% CI -0.32 to 0.84; low certainty), and the evidence for alendronate is highly uncertain (T-score 2.36; MD 3.70, 95% CI -2.01 to 9.41; very low certainty) when compared to no treatment or placebo. Other treatments, such as clodronate, denosumab, and pamidronate, lacked sufficient data for inclusion in the network meta-analysis, and therefore their effects could not be adequately assessed. Considering the relevant confidence intervals and the certainty of estimates, no definitive top-ranked drug was identified.
- There were no apparent differences in quality of life scores between different bisphosphonates and placebo. The three studies available did not provide sufficient data for quantitative or network meta-analysis.
- Ibandronate and clodronate significantly reduce the overall number of fractures (RR 0.57, 95% CI 0.38 to 0.86; RR 0.60, 95% CI 0.39 to 0.92, respectively; high certainty evidence) compared to no treatment/placebo. Denosumab and zoledronic acid probably reduce fractures slightly (RR 0.73, 95% CI 0.52 to 1.01; RR 0.79, 95% CI 0.56 to 1.11, respectively; moderate certainty of evidence), while the effect of risedronate is unclear (RR 0.56, 95% CI 0.15 to 2.16; low certainty of evidence) compared to no treatment/placebo. However, pamidronate likely increases the risk of fractures (RR 1.52, 95% CI 0.75 to 3.06; moderate certainty of evidence) compared to no treatment/placebo.
- As previously noted, systematic reviews of individual participant data have shown that bisphosphonates provide a survival benefit in postmenopausal women, which has been used in international clinical practice guidelines. However, in this network meta-analysis, the authors analysed data by combining both pre- and post-menopausal women. By combining both cohorts, survival estimates were similar for denosumab, ibandronate and zoledronic acid (HR 0.95, 95% CI 0.77 to 1.17; HR 0.91, 95% CI 0.69 to 1.21; HR

1.06, 95% CI 0.83 to 1.34; HR 0.93, 95% CI 0.76 to 1.14, respectively, low certainty), and no treatment/placebo.

- The incidence of osteonecrosis of the jaw is a rare side effect of bone modifying agents, occurring in the range of 0.6% to 2.5% in the adjuvant setting. As expected, denosumab (25 per 1000; RR 24.70, 95% CI 9.56 to 63.83; moderate certainty), ibandronate (6 per 1000; RR 5.77, 95% CI 2.04 to 16.35; moderate certainty), and zoledronic acid (9 per 1000; RR 9.41, 95% CI 3.54 to 24.99; moderate certainty) likely increase the incidence of osteonecrosis of the jaw compared to no treatment/placebo (1 per 1000). Clodronate may also increase the risk of osteonecrosis of the jaw (3 per 1000; RR 2.65, 95% CI 0.83 to 8.50; low certainty) compared to no treatment/placebo. In terms of ranking treatment options, clodronate may lower the risk of osteonecrosis of the jaw compared to zoledronic acid (RR 0.28, 95% CI 0.13 to 0.61; moderate certainty) and denosumab (RR 0.11, 95% CI 0.02 to 0.48; moderate certainty) while ibandronate may reduce the small risk of osteonecrosis of the jaw when compared to denosumab (RR 0.23, 95% CI 0.06 to 0.96; moderate certainty).
- Denosumab and clodronate are more effective than ibandronate in reducing the risk of renal impairment (RR 0.40, 95% CI 0.19 to 0.88; RR 0.44, 95% CI 0.20 to 0.96, respectively; moderate certainty of evidence). Ibandronate (RR 1.98, 95% CI 1.01 to 3.88; moderate certainty) and zoledronic acid (RR 1.49, 95% CI 0.87 to 2.58; moderate certainty) are likely increase the risk of renal impairment compared to no treatment/placebo.

How did the authors conclude?

The authors highlighted the challenges in determining the top-ranked bone-modifying agent and emphasized the importance of conducting more direct comparisons, particularly between denosumab and bisphosphonates, to better evaluate the balance between efficacy and safety in managing bone loss in this population.

What are the implications of the Cochrane evidence for practice in rehabilitation?

This review[1] provides a contemporary appraisal of recent literature on the effectiveness of bone-modifying agents in preventing bone loss, reducing fracture risk, and addressing adverse events in women with early and locally advanced breast cancer. Bone-modifying agents, including bisphosphonates and denosumab, have demonstrated efficacy in reducing bone loss and lowering the risk of fractures, which is crucial in rehabilitation settings aimed at maintaining or improving physical function and mobility. However, there remains a lack of consensus on the most effective agent to improve bone health and quality of life[8]. In line with this, the Cochrane review found no clear optimal choice among bone-modifying agents in the network meta-analysis. As such, the rankings for each outcome should be interpreted with caution, as no single agent emerged as superior across all outcomes.

Moreover, rehabilitation professionals must carefully consider both the benefits and potential adverse effects, such as osteonecrosis of the jaw, when incorporating these treatments into patient care plans. The incidence of adverse effects and additional risk factors should also be evaluated. For instance, in cancer patients, where bisphosphonates are used to prevent cancer treatment-induced bone loss, decrease skeletal-related events, and reduce the risk of bone metastases, the reported incidence of osteonecrosis of the jaw ranges from 0.7% to 8% when used for bone metastases, and from 0% to 1.8% when administered as adjuvant treatment[10,11]. In particular, the Number Needed to Treat (NNT) alongside the Number Needed to Harm (NNH), serves as an important tool for clinicians to assess and compare the efficacy of these drugs, aiding in more evidence-based and patient-centered treatment decisions.

Given these considerations, it is essential that future studies prioritize reporting critical outcomes and conduct head-to-head comparisons of all potential agents to provide a comprehensive understanding and validate these findings.

Acknowledgements

The author thanks Cochrane Rehabilitation and Cochrane Breast Cancer Group for reviewing the contents of the Cochrane Corner.

References

1. Adams A, Jakob T, Huth A, Monsef I, Ernst M, Kopp M, et al. Bone-modifying agents for reducing bone loss in women with early and locally advanced breast cancer: a network meta-analysis. Cochrane Database Syst Rev 2024;7(7):CD013451.
2. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74(3):229-263.
3. Hadji P, Aapro MS, Body JJ, et al. Management of Aromatase Inhibitor-Associated Bone Loss (AIBL) in postmenopausal women with hormone sensitive breast cancer: Joint position statement of the IOF, CABS, ECTS, IEG, ESCEO IMS, and SIOG. J Bone Oncol 2017;7:1-12.
4. Waqas K, Lima Ferreira J, Tsourdi E, Body JJ, Hadji P, Zillikens MC. Updated guidance on the management of cancer treatment-induced bone loss (CTIBL) in pre- and postmenopausal women with early-stage breast cancer. J Bone Oncol. 2021;28:100355.
5. Takahashi S. Management of cancer treatment-induced bone loss (CTIBL) in patients with breast cancer or prostate cancer. J Bone Miner Metab 2023;41(3):307-316.
6. Bassatne A, Bou Khalil A, Chakhtoura M, Arabi A, Van Poznak C, El-Hajj Fuleihan G. Effect of antiresorptive therapy on aromatase inhibitor induced bone loss in postmenopausal women with early-stage breast cancer: A systematic review and meta-analysis of randomized

controlled trials. Metabolism 2022;128:154962.
7. Nicolopoulos K, Moshi MR, Stringer D, Ma N, Jenal M, Vreugdenburg T. The clinical effectiveness of denosumab (Prolia®) in patients with hormone-sensitive cancer receiving endocrine therapy, compared to bisphosphonates, selective estrogen receptor modulators (SERM), and placebo: a systematic review and network meta-analysis. Arch Osteoporos 2023;18(1):18.
8. de Sire A, Lippi L, Venetis K, Morganti S, Sajjadi E, Curci C, et al. Efficacy of Antiresorptive Drugs on Bone Mineral Density in Post-Menopausal Women With Early Breast Cancer Receiving Adjuvant Aromatase Inhibitors: A Systematic Review of Randomized Controlled Trials. Front Oncol 2022;11:829875.
9. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 2015;386(10001):1353-1361.
10. Yarom N, Shapiro CL, Peterson DE, Van Poznak CH, Bohlke K, Ruggiero SL, et al. Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline. J Clin Oncol 2019;37(25):2270-2290.
11. Anastasilakis AD, Pepe J, Napoli N, Palermo A, Magopoulos C, Khan AA, et al. Osteonecrosis of the Jaw and Antiresorptive Agents in Benign and Malignant Diseases: A Critical Review Organized by the ECTS. J Clin Endocrinol Metab 2022;107(5):1441-1460.