

## Cochrane Corner



# What are the efficacy and safety of bisphosphonates and RANK-ligand-inhibitors for men with prostate cancer and bone metastases? - A Cochrane Review summary with commentary

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**Keywords:** Bisphosphonates, Cochrane, Denosumab, Metastasis, Rehabilitation

The aim of this commentary is to discuss from a rehabilitation perspective the Cochrane Review "Bisphosphonates or RANK-ligand-inhibitors for men with prostate cancer and bone metastases: a network meta-analysis"<sup>1</sup> by Jakob et al.<sup>2</sup>, published by Cochrane Urology Group. This Cochrane Corner is produced in agreement with the Journal of Musculoskeletal and Neuronal Interactions by Cochrane Rehabilitation with views\* of the review summary author in the "implications for practice" section.

## Background

Prostate cancer is among the leading causes of cancer-related death in men<sup>2</sup>. Despite improvements in both its detection at early stages as well as effectiveness of available interventions, metastatic progression remains a main determinant of morbidity and mortality, with a survival rate of less than 30%<sup>3,4</sup>. Bone metastases are common in

affected men, with a prevalence of 80% in prostate cancer deaths<sup>2</sup>. The androgen deprivation therapy (ADT), that is widely used in this population, increases the risk of skeletal fragility by decreasing bone mineral density up to 5% per year<sup>5</sup>. In this context, anti-osteoporotic drugs, particularly agents reducing bone resorption, are commonly used for managing bone involvement in patients with prostate cancer. Bisphosphonates (BPs) and denosumab, a receptor activator of nuclear factor kappa B ligand (RANKL)-inhibitor, are the most used antiresorptive agents<sup>6</sup>. Zoledronic acid, the most potent among BPs, and denosumab have been approved by the international regulatory agencies (i.e., FDA and EMA) for prostate cancer patients with bone metastases.

This network meta-analysis is relevant for rehabilitation because provides supporting evidence for the pharmacologic treatment options in the context of management strategies of bone involvement and its consequences on functioning of people with advanced prostate cancer. This is a main topic for

The author declares no conflicts of interest.

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<sup>a</sup> This summary is based on a Cochrane Review previously published in the Cochrane Database of Systematic Reviews 2020, Issue 12. Art. No.: CD013020. DOI: 10.1002/14651858.CD013020.pub2. (see [www.cochranelibrary.com](http://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.



all physiatrists, considering the huge disability burden and poor quality of life associated with the occurrence of bone metastases in these men<sup>7</sup>.

## Bisphosphonates or RANK-ligand-inhibitors for men with prostate cancer and bone metastases: a network meta-analysis

(Jakob T, Tesfamariam YM, Macherey S, Kuhr K, Adams A, Monsef I, Heidenreich A, Skoetz N, 2020)<sup>1</sup>

### What is the aim of this Cochrane review?

The aim of this Cochrane Review is to investigate the efficacy and safety of BPs and denosumab as ancillary intervention for patients with prostate cancer and bone metastases.

### What was studied in the Cochrane review?

The population addressed in this review consisted of adults with a confirmed diagnosis of prostate cancer and bone metastases, irrespective of disease stage or type of therapy (hormone-sensitive or castrate-refractory patients). The interventions studied were BPs or denosumab. The interventions were compared with each other (including the comparisons between different BPs) or versus placebo. The primary outcomes studied were the proportion of participants with pain response as defined in the trials, adverse events including renal impairment (creatinine elevation and renal failure) and osteonecrosis of the jaw (ONJ). The secondary outcomes were skeletal-related events (SREs) with or without hypercalcemia, including total number of SREs, pathological fractures, spinal cord compression, bone radiotherapy, bone surgery; overall survival/mortality; quality of life; further adverse events, including grade 3 to 4 adverse events overall, according to the Common Terminology Criteria for Adverse Events (CTCAE) or as defined in the trial, hypocalcemia, fatigue, diarrhea, and nausea.

### Search methodology and up-to-dateness of the Cochrane review?

The review authors searched for studies that had been published up to 23 March 2020 in several databases, including Embase, MEDLINE, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), and Database of Abstracts of Reviews of Effects (DARE), trial registers (WHO International Clinical Trials Registry Platform; EU Clinical Trials Register, US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov, UMIN clinical trial registration), and abstract proceeding of relevant meetings of the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO), and the Multinational Association

of Supportive Care in Cancer (MASCC). The GRADE system has been used to assess the certainty of the evidence for the main outcomes.

### What are the main results of the Cochrane review?

The review included 21 trials for the quantitative analysis and 25 trials for the qualitative synthesis.

The review results about the comparison of antiresorptive agents versus placebo in castration sensitive and castration resistant prostate cancer patients with bone metastases show that:

- Zoledronic acid probably makes little or no difference in terms of proportion of patients with pain response compared to placebo with a risk ratio (RR) of 1.46 [95% confidence interval (CI) 0.93-2.32] and with responses in 386 vs. 265 per 1000 in groups (4 RCTs, 1013 patients, follow-up 5-12 months; moderate certainty of evidence). No data are available about this outcome for denosumab.
- Zoledronic acid probably increases the risk of renal impairment compared to placebo (RR 1.63, 95%CI 1.08-2.45; 202 vs. 124 per 1000 patients with renal impairment; 6 RCTs, 1769 patients, follow-up 5-36 months; moderate certainty of evidence). Denosumab has not been considered for this outcome, since zero events were reported.
- Zoledronic acid probably makes little or no difference in terms of ONJ risk compared to placebo (RR 1.88, 95%CI 0.73-4.87; 23 vs. 12 per 1000 cases of ONJ; 4 RCTs, 3006 patients, follow-up 5-24 months; moderate certainty of evidence)
- Denosumab increases the risk of ONJ compared to placebo (RR 3.45, 95%CI 1.06-11.24; 42 vs. 12 per 1000 cases of ONJ; 4 RCTs, 3006 patients, follow-up 5-24 months; high certainty of evidence).
- Zoledronic acid as well as denosumab may reduce the risk of SREs compared to placebo (RR 0.84, 95%CI 0.72-0.97 and RR 0.72, 95%CI 0.54-0.96, respectively; 12 RCTs, 5240 patients, follow-up 5-60 months; low certainty of evidence).
- Zoledronic acid as well as denosumab probably make little or no difference in terms of mortality risk compared to placebo (RR 0.90, 95%CI 0.80-1.01 and RR 0.93, 95%CI 0.77-1.11, respectively; 13 RCTs, 5494 patients, follow-up 12-60 months; moderate certainty of evidence).
- For quality of life, insufficient reporting did not allow network meta-analysis.

### What did the authors conclude?

The authors concluded that zoledronic acid probably makes little or no difference on pain and mortality, and probably increases the risk of renal impairment in patients with prostate cancer and bone metastases when compared to placebo. On the other side, this drug may reduce the SREs and probably makes little or no difference on the risk of ONJ in the same population. Also, denosumab may reduce SREs, but this drug increases the risk of ONJ in these patients.

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

The skeleton is often the first site for metastasis in most prostate cancer patients. The occurrence of bone metastases may be a cause of poor functioning and quality of life in affected men with relevant consequences in terms of chronic pain, pathological fractures, spinal cord compression, and hypercalcemia<sup>8</sup>.

Bone metastases increase the production of RANKL by osteoblasts that activate RANK on pre-osteoclasts to enhance differentiation and growth of osteoclasts, major players of bone loss<sup>9</sup>. On the other side, BPs induce apoptosis of these by altering intracellular biochemical pathways<sup>10</sup>. Furthermore, BPs seem to inhibit cancer-related pathogenic events, such as self-seeding, angiogenesis, macrophages recruitment, whereas denosumab modulate invasion and migration of cancer cells expressing RANK<sup>11,12</sup>.

The use of antiresorptive drugs, particularly zoledronic acid and denosumab, in these patients is supported by the evidence of their efficacy in reducing SREs, such as pathologic fractures, with potentially relevant implications for rehabilitation in terms of conservative approaches to both prevention of these events and to chronic pain. Indeed, avoiding the occurrence of SREs is crucial for both patients and clinicians considering that these complications require surgery and/or radiation therapy resulting in increasing morbidity and mortality<sup>13</sup>. However, unmet needs remain, particularly about pain management with antiresorptive drugs as well as the role of these agents in the context of therapeutic exercise for prostate cancer patients. According to the lack of data reported in this network meta-analysis, the role of denosumab in modulating pain response in this population should be investigated, considering mounting evidence about this topic in patients with bone fragility and osteoporotic fractures<sup>14-18</sup>. This drug seems to modulate pain by reducing osteoclast-mediated acidification thus hindering acid-sensitive nociceptor stimulation (mechanism shared with BPs), through a negative modulation of NF- $\kappa$ B, via RANK/RANKL inhibition to reduce neuroinflammation and chronic pain, by improving bone microarchitecture, through a rapid stabilization of the fracture site, and by reducing bone edema<sup>19-21</sup>. Denosumab might be a resource also for counteracting muscle wasting, that is commonly observed in advanced cancer patients. Indeed, RANK is expressed on myotubes and myocytes and its genetic deletion has selective benefits for fast twitch muscle fiber. Moreover, OPG/RANK/RANKL pathway modulates sarcoplasmic reticulum Ca<sup>2+</sup>-ATPase (SERCA) that regulates calcium fluxes within sarcoplasmic reticulum<sup>22</sup>. These mechanisms might positively affect muscle function, with potential benefits on fall prevention<sup>23</sup>.

Evidence regarding safety concerns about zoledronic acid and denosumab for patients with advanced prostate cancer should be carefully considered to avoid serious adverse events, such as renal failure or ONJ, respectively<sup>1</sup>.

Finally, in the multidisciplinary approach to people with bone metastasis<sup>24</sup> it should be further investigated the role of antiresorptive drugs in combination with other treatment options, including surgical procedures.

### Acknowledgements

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

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