# Non-osteoporotic Loss of Spinal Bone. Denosumab as a Therapeutic Tool and its Implications

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## ABSTRACT

**Background:** Denosumab is a human monoclonal antibody that acts against RANKL, inhibiting bone destruction mediated by osteoclasts, thus avoiding bone loss. For this reason, it is used in the treatment of osteoporosis as an antiresorptive and is authorized for the treatment of giant cell tumor and multiple myeloma. Our objective is to understand its indications and contraindications for the treatment of non-osteoporotic bone loss. **Materials and Methods:** A systematic review of English-language articles published between 2009 and 2023, using PRISMA criteria. Articles indicating or contraindicating the use of denosumab were considered for inclusion. **Results:** From a total of 4306 articles, 18 articles were analyzed, which showed consensus on the dose and controls with tomography and indicated or contraindicated the use of denosumab. **Conclusions:** Denosumab is recommended as a primary therapeutic option for unresectable spinal tumors, to prevent recurrences or to delay the formation of metastases from primary tumors or solid tumors, primarily breast, prostate, and lung, as well as for multiple myeloma spinal involvement. Denosumab is currently contraindicated in infectious lesions.

**Keywords:** Spine; non-osteoporotic bone loss; tumor; infection.

**Level of Evidence:** III

## Pérdida de stock óseo no osteoporótico en la columna. Denosumab como herramienta de tratamiento e implicancia

## RESUMEN

**Introducción:** El denosumab es un anticuerpo monoclonal humano que actúa contra el RANKL, inhibiendo la destrucción ósea mediada por los osteoclastos, así evitando la pérdida del stock óseo; por este motivo, se lo utiliza en el tratamiento de la osteoporosis como agente antiresortivo y está autorizado para el tratamiento del tumor de células gigantes y el mieloma múltiple. Nuestro objetivo fue conocer las indicaciones y contraindicaciones para la pérdida de stock óseo de causa no osteoporótica. **Materiales y Métodos:** Revisión sistemática de artículos en inglés publicados en el período 2009-2023. Se incluyeron artículos que indicaran o contraindicaran el uso del denosumab. **Resultados:** De un total inicial de 4306 artículos, se analizaron 18 artículos que mostraban consenso en la dosis y los controles con tomografía e indicaban o contraindicaban el uso del denosumab. **Conclusiones:** El denosumab está indicado como una buena opción de tratamiento preferente de tumores vertebrales primarios inoperables, para evitar recidivas o demorar las metástasis de tumores primarios o de tumores sólidos, principalmente de mama, próstata y pulmón, y para el compromiso vertebral del mieloma múltiple. El denosumab está contraindicado, por el momento, para las lesiones infecciosas.

**Palabras clave:** Columna; pérdida ósea no osteoporótica; tumor; infección.

**Nivel de Evidencia:** III

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## INTRODUCTION

Denosumab is a human monoclonal antibody that acts against the receptor activator of nuclear factor kappa B ligand (RANKL), which promotes osteoclastic activity through the RANK-RANKL interaction, thereby inhibiting osteoclast-mediated bone destruction.[1] For this reason, it is administered as a treatment for osteoporosis in doses of 60 mg, subcutaneously, every 6 months, associated with vitamin D and calcium. Increased osteoclastic activity is evident in many osteopenic disorders, including infections, Paget's disease, bone metastases or osteolytic primary tumors, and rheumatoid arthritis, which increase bone resorption and destruction.[2]

Since the second decade of this millennium, the U.S. Food and Drug Administration has approved the use of denosumab in patients with mature skeletons and giant cell tumors (GCT),[3] which has been validated by numerous oncological management guidelines, with a dose of 120 mg administered subcutaneously, monthly, along with vitamin D and calcium.[4] Its use in the management of aneurysmal bone cysts and chordoma is being studied as well.

The objective of this review was to determine the indications and contraindications to the use of denosumab in patients with bone loss of non-osteoporotic causes, specifically in those with primary spinal tumors or infections.

## MATERIALS AND METHODS

The study was conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA 2020).

A systematic literature search of full articles in English was carried out in the PubMed, LILACS and SciELO databases, using the MeSH terms: Bone loss NOT osteoporotic AND Spine AND Denosumab AND Tumor OR Infection. Duplicates, unpublished studies, books, letters, and other documents were excluded. Publications between January 2009 and March 2023 were included.

We selected laboratory studies, randomized clinical trials, systematic and narrative reviews, and case reports that justified or contraindicated the use of denosumab for patients with bone loss related to spinal tumors or infections.

Within the inclusion criteria, we selected relevant studies on the use of denosumab for the treatment of bone defects associated with a bone tumor or spinal infection in humans, which justified or contraindicated its use, dosage, and controls.

Articles related to the management of osteoporosis or traumatic fractures and post-surgical bone defects were excluded.

## RESULTS

The initial search yielded 4306 articles in PubMed and three in LILACS from 2009 to 2023.

A second review was conducted after reading the titles and abstracts of each, after which 70 studies were selected and 18 of them were included for final data analysis (Figure).

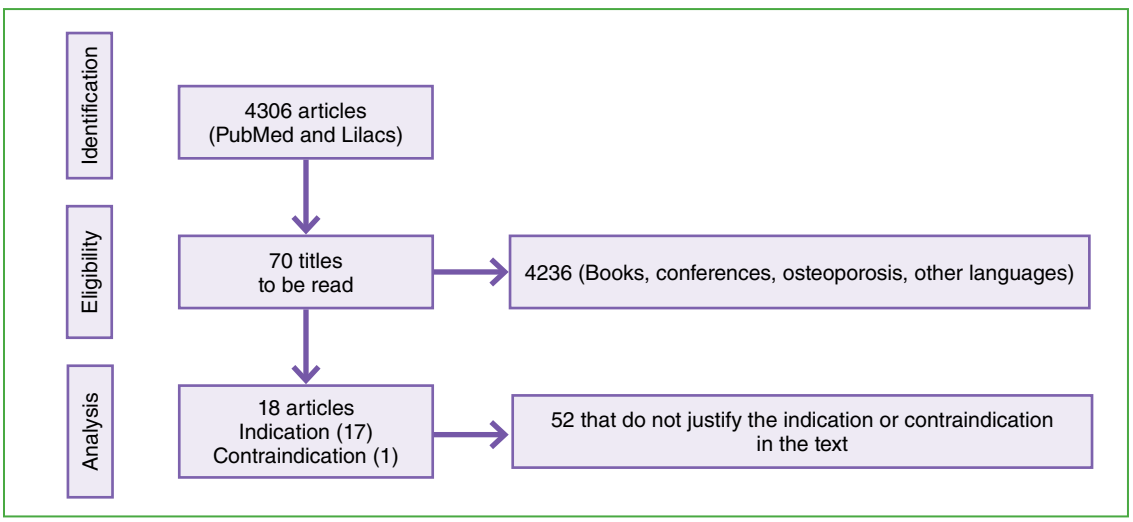


**Figure.** PRISMA 2020 flowchart.

Since 2013, the *Food and Drug Administration* has authorized the use of denosumab in patients with tumors, such as unresectable, relapsed or metastasized GCTs, and therefore it is now a consensual tool.[4] The dose is 120 mg/month, administered subcutaneously along with vitamin D (400 IU/month) and calcium (500 mg/day). For a loading dose, 120 mg/week is suggested for the first month.[3-8] There is no consensus on the duration of treatment, although it is at least 12 months.[4] In patients with large tumors,[1] it can be administered for six months to reduce size and facilitate resection, and thereafter to decrease recurrence,[3,9] as well as in those cases where the morbidity of resection does not warrant surgery.[9]

In cases of aneurysmal bone cyst, it is administered in the same way as for GCT, for unresectable or recurrent cases.[10-13]

In 2017, Kushlinskii et al.[14] pointed to the possibility of use for chordoma recurrences.

The administration of denosumab to patients with metastases from solid tumors, mainly breast, prostate, and lung,[15-22] such as multiple myeloma lesions, is safe and cost-effective.[23,24]

Its administration to patients with bone loss due to an infectious process has been investigated. In a literature review, Ohnishi et al.[2] contraindicated denosumab for this condition (Table).

**Table.** Indication or contraindication of denosumab in patients with non-osteoporotic bone defects.

| Authors (year) | Use | Condition | Control | Evidence |
|---|---|---|---|---|
| Chawla et al. (2013) | Yes | GCT | CT | III |
| Ford et al. (2013) | Yes | Metastasis of any type of tumor | CT | III |
| Sun and Yu (2013) | Yes | Metastasis of any type of tumor | CT | III |
| Sohn et al. (2014) | Yes | Metastasis of any type of tumor | CT | III |
| Ng et al. (2014) | Yes | GCT | CT | II |
| Skubitz et al. (2015) | Yes | ABC | CT | III |
| Dubory et al. (2016) | Yes | GCT & ABC | CT | II |
| Kumar et al. (2017) | Yes | GCT | CT | III |
| Roitman (2017) | Yes | GCT | CT | II |
| van der Heijden et al. (2017) | Yes | GCT | CT | III |
| Kurucu et al. (2018) | Yes | ABC | CT | IV |
| Kushlinskii et al. (2017) | Yes | Chordoma | CT | II |
| Way (2018) | Yes | GCT | CT | III |
| Raje et al. (2018) | Yes | MM | CT | III |
| Rusin (2019) | Yes | GCT | CT | IV |
| Bukata et al. (2021) | Yes | GCT | CT | IV |
| Bazán et al. (2020) | Yes | GCT | CT | III |
| Diel et al. (2020) | Yes | Breast, prostate, and lung metastases | CT | II |
| Stopek (2020) | Yes | Metastasis of any type of tumor | CT | III |
| Lanari et al. (2021) | Yes | ABC | CT | IV |
| Ohnishi et al. (2021) | No | Infection | CT | II |
| Chen et al. (2021) | Yes | Metastasis of any type of tumor and MM | CT | II |
| Cadieux et al. (2022) | Yes | MM | CT | III |
| Li et al. (2022) | Yes | Small cell metastases from lung cancer | CT | III |
| Li et al. (2022) | Yes | Metastasis of any type of tumor | CT | II |

Use: Yes = indicated, No = contraindicated; GCT = giant cell tumor; ABC = aneurysmal bone cyst; MM = multiple myeloma.

## DISCUSSION

Vertebral tumors have a very low frequency and make up 4% of all spinal tumors.[25] Currently, the use of denosumab for the initial treatment and recurrence of tumor conditions, in addition to infectious diseases, is being discussed; additionally, it may be a therapeutic alternative for tumors located in areas of difficult surgical access.[10]

In 2013, the Food and Drug Administration approved denosumab for the treatment of skeletally mature adults and adolescents with unresectable GCTs or the potential for severe morbidity due to resection. In 2017, the Clinical Practice Guidelines in Oncology (NCCN Guidelines®) also recommended the administration of denosumab in cases of axial lesions (spine, pelvis and sacrum) and metastatic lesions.[3] Short-term (six-dose) preoperative administration of denosumab to patients with unresectable or recurrent GCT improved clinical symptoms, decreased tumor size, and increased tumor density. The changes in the tumors, in turn, simplified the manipulation of the tumor for removal and subsequently reduced the local recurrence of resection surgery.[3] In a prospective multicenter series of five patients with spine GCT, the following radiographic findings were observed after treatment with denosumab: tumor size decreased by at least 10% and tumor calcification was a consistent finding in all patients; in addition, a stronger pseudocapsule was observed during surgery.[26] A systematic review concluded that denosumab is indicated for patients with advanced GCT in the sacrum. The goals are to achieve local control and create an optimal surgical situation. It is recommended to administer a dose of 120 mg, subcutaneously, every 7 days, for the first month and then administer it every 4 weeks, for 2.5 to 13 months. After the use of denosumab, resection surgery should encompass the entire original tumor to reduce the risk of recurrence.[4] When the resection is without tumor-free margins, the risk of recurrence is much higher. Although studies are needed to confirm the following theory, in patients with GCT who do not receive a neoadjuvant, this risk of recurrence after resection surgery is greater when the dose of denosumab as an adjuvant is decreased or discontinued, which is controlled once the dose of 120 mg/month is restarted.[9] Denosumab may be used as a stand-alone treatment in patients with GCT.[27] In a published case of an 18-year-old woman, complete histologic remission was achieved after treatment with denosumab, histopathologic analysis of the surgical specimen revealed absence of GCT cells.[28] Over the past five years, the development of denosumab as adjuvant therapy in patients with GCT has had a profound impact on the surgical resection of this tumor. The ability to reduce tumor size and induce consolidation through cortical bone formation has facilitated both intralesional and total en bloc spondylectomy of affected vertebrae and improved its effectiveness.[29] Further research will be required to determine the efficacy and safety of denosumab as a stand-alone long-term treatment for GCT, as there is currently no consensus on its appropriate duration.[29,30] Denosumab therapy has had effects on bone and surrounding tissues, including a case report of a 58-year-old female patient with GCT in the lumbar spine, in whom histopathologic findings of sections resected after 10 courses of denosumab revealed the presence of RANK-positive cells around bone tissue.[31]

Denosumab is a therapeutic option available for recurrences, unresectable or intralesionally resected aneurysmal bone cysts. Clinical and radiological results of calcification and remission of the tumor lesion have been observed.[10]

Denosumab is useful in the management of bone tumors, such as chordomas. In one study, 12 chordomas out of a total of 199 primary bone tumors were evaluated, with determination of RANK and RANKL. Chordoma has high RANK and low RANKL levels, making the use of denosumab possible.[14]

Some drugs to treat osteoporosis are considered potentially therapeutic for bone loss secondary to infection, as they are given for bone loss in other diseases. Agents for osteoporosis include anabolics (teriparatide, romosozumab) and antiresorptives (bisphosphonates, denosumab, and romosozumab).[2] Denosumab is a human monoclonal antibody against RANKL that inhibits the differentiation of osteoclast precursors into mature osteoclasts. However, since its receptor, RANK, is also expressed by monocytes/macrophages and dendritic cells, it highlights the importance of this pathway in the development and maturation of the immune system. This means that there is no evidence for the administration of denosumab to patients with active infection, as it has been shown that it could increase the deficiencies of the immune system to fight these infectious processes. Therefore, denosumab may worsen the infection when administered to patients with pyogenic osteomyelitis, although it is effective for suppression of osteolysis.[2] Further studies are also needed to clarify the efficacy of denosumab in the treatment of this condition.

Long-term use of denosumab is not harmless and complications or adverse events have been reported, such as osteonecrosis of the jaw (6%), hypocalcemia (5%), and atypical femur fractures (4%). Calcium and vitamin D supplementation is recommended, in addition to radiological monitoring of the jaw.[30,32] Osteonecrosis is more frequent in the lower jaw than in the upper jaw and not in other bones, this is due to its embryonic origin (ectomesenchymal origin), its vascular irrigation, and bone remodeling, which are altered by different drugs, such as denosumab at high doses, but especially in patients receiving bisphosphonates.[33] A dental diagnosis should be made to differentiate infectious processes from osteoradionecrosis associated with head and neck radiation therapy, especially in patients with dental trauma due to loose dental prostheses.[33]

Tumor recurrence has been reported after discontinuation of this drug. We report the case of a 25-year-old man with C2 GCT who underwent surgical resection and was treated with long-term denosumab and discontinued the drug. Discontinuation of denosumab resulted in rapid recurrence of the tumor. There is still no consensus on the dosage and duration of denosumab treatment after GCT resection.[34] In conclusion, the efficacy and safety profiles of denosumab in patients with GCT of the spine, including the sacrum, appear to be consistent with those of denosumab in the general population with GCT and in other advanced bone neoplasms, such as aneurysmal bone cyst, chordoma, and bone metastases. The results of the analysis suggest that treatment with denosumab is potentially useful for patients with GCT of the spine, including the sacrum.[5,35]

## CONCLUSIONS

Denosumab is indicated because it is a good preferential treatment option for unresectable primary vertebral tumors, it is a good option to avoid recurrences or to delay metastases of primary tumors or solid tumors, mainly of the breast, prostate and lung, and for the vertebral involvement of multiple myeloma. Denosumab would be contraindicated, for the time being, in patients with infectious lesions.

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