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# Therapeutic schemes of denosumab in the treatment of giant cell tumor of bone - Protocol for a systematic review with meta-analysis

**Esquemas terapêuticos de denosumab no tratamento de tumor ósseo de células gigantes - Protocolo para uma revisão sistemática com metanálise**

**Regímenes terapéuticos de denosumab en el tratamiento del tumor óseo de células gigantes - Protocolo para una revisión sistemática con metanálisis**

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**Abstract**
The aim of this study is to evaluate the efficacy of different therapeutic regimens using denosumab in patients with giant cell tumor of bone (GCTB), regarding primary outcomes related to therapeutic response (lesion size, pain and function) and presentation to imaging exams, in addition to secondary outcomes related to age (in years) and tumor location, reduction or downgrade of surgical indication, local recurrence, presence of pulmonary metastases and therapeutic side effects. A systematic literature search will be carried out in the PubMed/MEDLINE, Embase (CAPES Journals), Science Direct/Elsevier, Scielo, Cochrane Library and clinical trial records (ClinicalTrials.gov and Registro Brasileiro de Ensaios Clínicos) databases; for exploration of grey literature, the Open Access Theses and Dissertations and the Biblioteca Digital Brasileira de Teses e Dissertações databases will be consulted. We will also conduct a "snowball" survey to identify additional eligible studies for full-text review. Two evaluators will select, extract and assess the risk of bias of the obtained data. If appropriate, a meta-analysis will be carried out, extracting data for the number of events and total patients to perform proportion meta-analysis using the R software, with the "meta" package (version 4.9–6), the "metaprop function" for aspect ratio data. The results of this review will provide convincing information on the efficacy of different therapeutic regimens using denosumab in GCTB, providing a reliable theoretical basis for the research that will follow.
**Keywords:** Bone neoplasms; Denosumab; Evaluation of results of therapeutic interventions; Giant Cell Tumor of Bone; Health teaching; Systematic review.

**Resumo**
O objetivo deste estudo é avaliar a eficácia de diferentes regimes terapêuticos utilizando denosumab em pacientes com tumor ósseo de células gigantes (TOCG), com relação a desfechos primários relacionados à resposta terapêutica

(tamanho da lesão, dor e função) e apresentação aos exames de imagem, e desfechos secundários relacionados à idade (em anos) e localização do tumor, redução ou rebaixamento da indicação cirúrgica, recorrência local, presença de metástases pulmonares e efeitos colaterais terapêuticos. Uma busca sistemática da literatura será realizada nas bases de dados PubMed/MEDLINE, Embase (Periódicos CAPES), Science Direct/Elsevier, Scielo, Cochrane Library e em registros de ensaios clínicos (ClinicalTrials.gov e Registro Brasileiro de Ensaios Clínicos); para exploração da literatura cinzenta, as bases de dados Open Access Theses and Dissertations e Biblioteca Digital Brasileira de Teses e Dissertações serão consultadas. Também realizaremos uma pesquisa de "bola de neve" para identificar estudos adicionais elegíveis para revisão completa do texto. Dois avaliadores selecionarão, extrairão e avaliarão o risco de viés dos dados obtidos. Se apropriado, será executada uma meta-análise, extraindo dados para o número de eventos e pacientes totais para realizar a meta-análise proporcional utilizando o software R, com o pacote "meta" (versão 4.9-6), a "função metaprop" para dados de proporção. Os resultados desta revisão fornecerão informações convincentes sobre a eficácia de diferentes regimes terapêuticos utilizando denosumab no TOCG, fornecendo uma base teórica confiável para a pesquisa que se seguirá.
**Palavras-chave:** Neoplasias ósseas; Denosumab; Avaliação de resultado de intervenções terapêuticas; Tumor de Células Gigantes do Osso; Ensino em saúde; Revisão sistemática.

**Resumen**

El objetivo de este estudio es evaluar la eficacia de diferentes regímenes terapéuticos que utilizan denosumab en pacientes con tumor de células óseas gigantes ósseo (TCGO), en relación con los resultados primarios relacionados con la respuesta terapéutica (tamaño de la lesión, dolor y función) y la presentación a las pruebas de imagen, y los resultados secundarios relacionados con la edad (en años) y la localización del tumor, la reducción o disminución de la indicación quirúrgica, recurrencia local, presencia de metástasis pulmonares y efectos colaterales terapéuticos. Se realizará una búsqueda sistemática de la literatura en las bases de datos PubMed/MEDLINE, Embase (Periódicos CAPES), Science Direct/Elsevier, Scielo, Cochrane Library y registros de ensayos clínicos (ClinicalTrials.gov y Registro Brasileiro de Ensaios Clínicos); para la exploración de literatura gris, Se consultarán las bases de datos Open Access Theses and Dissertations y Biblioteca Digital Brasileira de Teses e Dissertações. Dos evaluadores seleccionarán, extraerán y evaluarán el riesgo de sesgo de los datos obtenidos. Si procede, se realizará un metaanálisis, extrayendo datos para el número de eventos y el total de pacientes para realizar un metanálisis proporcional utilizando el software R, con el paquete "meta" (versión 4.9-6), la "función metaprop" para datos de proporción. Los resultados de esta revisión proporcionarán información convincente sobre la eficacia de diferentes regímenes terapéuticos que utilizan denosumab en el TOCG, proporcionando una base teórica confiable para la investigación que seguirá.
**Palabras clave:** Neoplasias óseas; Denosumab; Evaluación de resultados de intervenciones terapéuticas; Tumor Óseo de Células Gigantes; Enseñanza en la salud; Revisión sistemática.

## 1. Introduction

Giant cell tumor of bone (GCTB) constitutes a rare benign primary locally aggressive bone neoplasm which comprises approximately 5% of all bone tumors (Mendenhall et al., 2006, Deventer et al., 2022).

Histologically, GCTB is composed of reactive multinuclear osteoclast like giant cells expressing receptor activator of nuclear factor kappa-B (RANK) and of neoplastic mononuclear stromal cells expressing RANK ligand (RANKL) (van der Heijden et al., 2017, Deventer et al., 2022). GCTB affects an age group between 20 and 40 years, but it may occur at any age, with a slight predilection for females. The most frequent locations are the epiphysiometaphyseal segments of long bones around the knee (distal femur and proximal tibia), followed by distal radius (Catalan et al., 2006; Guedes et al., 2009, Deventer et al., 2022). This bone neoplasm is rarely located in the axial skeleton, and when this occurs, it predominantly affects the sacrum and iliac (de Mattos Brito Oliveira Viana et al., 2019). Metastatic dissemination of GCTB is rare, often around 1% (Balke et al., 2008; Guedes et al., 2009; Lazaretti et al., 2010, Deventer et al., 2022). GCTB may also present malignant transformation (Deventer et al., 2022).

Clinical manifestations of GCTB include pain, swelling, joint effusion and limited range of articular motion (Deventer et al., 2022), often sufficient to raise suspicion on a musculoskeletal tumor, although radiographic examination is the most common test to reveal it - radiographic examination of the affected segment establishes the basis of the imaging evaluation and is the method of choice in the initial assessment of primary bone tumors according to the Appropriateness Criteria of the American College of Radiology (ACR) (Guedes, Oliveira, de Melo, et al., 2021). Conventional, orthogonal radiographs

provide information regarding appearance, intraosseous extension, tumor matrix, and margins between the tumor and host bone (Guedes, Oliveira, Costa, et al., 2021). On radiographic examination, GCTB initially presents as an epiphysiometaphyseal, lytic, eccentric lesion with precise limits without reactional sclerosis, but when the diagnosis is neglected, progression can occur rapidly, with cortical disruption and soft tissue involvement, making the lesion extracompartmental (Guedes et al., 2009). Considering the characteristics of local aggressiveness and metastatic potential of this neoplasm, additional imaging tests (magnetic resonance imaging, computed tomography and bone scintigraphy) are required to evaluate local extension and to search to distant spread (metastases), followed by histological diagnosis (biopsy) (Guedes et al., 2021).

Once diagnosed and properly staged, GCTB has indication of surgical treatment, whenever possible. Local control of the disease is paramount in reducing the possibility of recurrence and/or metastatic dissemination (lungs). Some authors have demonstrated that wide oncological resection decreases recurrence rates, however, this treatment modality may be associated with higher morbidity and functional deficit. Since most patients affected by this neoplasm are young adults, at their most productive age, and the fact that it is a tumor with a juxtarticular location, the objective of the treatment includes complete removal of the tumor and preservation of the function of the affected segment. Thus, the treatment by intralesional curettage (which preserves the joint), associated or not with local adjuvant treatment (electrofulguration, laser, instillation of absolute alcohol or phenol, or hydrogen peroxide) and filling with autologous, homologous, or heterologous bone graft, bone substitutes or polymethylmethacrylate is the most often accomplished (Baptista et al., 2001; Guedes et al., 2009; Sobti et al., 2016; van der Heijden et al., 2017, Lipplaa et al., 2019; Deventer et al., 2022).

The RANK/RANKL interaction is predominantly responsible for the formation and activation of giant multinuclear cells that behave, from the physiological point of view, in the same way as osteoclasts (van der Heijden et al., 2017), generating extensive bone resorption (Singh et al., 2015, Deventer et al., 2022). Denosumab is a human monoclonal antibody with strong affinity for RANKL, preventing RANK/RANKL binding and thus inhibiting bone resorption. This drug has been used in the treatment of osteoporosis, bone metastases, and, more recently, has become part of the therapeutic arsenal for GCTB, particularly in cases where it is considered unresectable or when there is indication for amputation or en bloc resection, as it allows local control and, eventually, more conservative surgical procedure (Catalan et al., 2006, Rutkowski et al., 2018, Deventer et al., 2022).

The therapeutic regimen that uses denosumab - a high-cost drug - for the treatment of GCTB is not yet a consensus in the literature. The used dose is usually of 120 mg every four weeks, but the number of doses and attack doses is not yet standardized, and the duration of treatment varies between studies, as well as between individuals in the same study, between four and 55 months (Luengo-Alonso et al., 2019). Lifelong treatment may be indicated in cases of pulmonary metastases and unresectable tumors.

The aim of this study is to evaluate the efficacy of different therapeutic regimens using denosumab in patients with giant cell tumor of bone (GCTB), regarding primary outcomes related to therapeutic response (lesion size, pain and function) and presentation to imaging exams, in addition to secondary outcomes related to age (in years) and tumor location, reduction or downgrade of surgical indication, local recurrence, presence of pulmonary metastases and therapeutic side effects.

## 2. Methodology

### *2.1 Protocol register*

This systematic review protocol was drafted under the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) (Moher et al., 2010; Page et al., 2021). This protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the record CRD42020190503.

### *2.2 Ethics*

Ethical approval will not be necessary for this systematic review, and the meta-analysis will not contain any private information on participants or violate their human rights.

### *2.3 Criteria for the included studies in the review*

#### *2.3.1 Types of studies*

We will include randomized, non-randomized or uncontrolled clinical studies and case series with at least 10 adult patients with GCTB, who have been treated with denosumab. Studies with languages other than English, Portuguese and Spanish will be excluded.

#### *2.3.2 Types of patients*

Adult patients (≥ 18 years old) without restriction of gender or ethnicity with GCTB, confirmed by anatomopathological study, will be included in this review.

#### *2.3.3 Types of outcome measures*

Response to treatment with denosumab, based on the adopted therapeutic regimen, regarding primary outcomes related to therapeutic response (lesion size, pain and function) and presentation to imaging exams, in addition to secondary outcomes related to age (in years) and tumor location, reduction or downgrade of surgical indication, local recurrence, presence of pulmonary metastases and therapeutic side effects.

### *2.4 Search strategy*

A systematic literature search will be carried out in the PubMed/MEDLINE, Embase (using CAPES Journals), Science Direct/Elsevier, Scielo and Cochrane Library, as well as in clinical trial records (ClinicalTrials.gov and Registro Brasileiro de Ensaios Clínicos - ReBEC) databases without temporal restrictions in the search strategy. For exploration of grey literature, the Open Access Theses and Dissertations and the Biblioteca Digital Brasileira de Teses e Dissertações databases will be consulted. We will also conduct a "snowball" survey to identify additional studies by researching the reference lists of publications eligible for full-text review to retrieve unidentified studies in the survey.

In the bibliographic survey, the Medical Subject Headlings (MeSH) controlled vocabulary, as well as the Embase Subject Headings (Emtree) and the Descritores em Ciências da Saúde (DeCS) will be adopted, being grouped and/or crossed with the Boolean operators "OR" and "AND", as shown in Table 1. The reference lists of the included articles will be evaluated to identify unidentified studies.

### *2.5 Data screening and extraction*

The databases searches will be performed and imported into EndNote® software, a bibliographic reference management program, which will remove duplicates automatically and allow manual inspection to identify possible remaining copies. After removal, an evaluator will export the results to the Rayyan (Ouzzani et al., 2016) selection management web application, so that, independently, two evaluators will select the papers by titles and abstracts, identifying possibly eligible studies for full reading. All study selection procedures were based on the PRISMA flowchart (Figure 1). In cases of divergence, the evaluators will discuss about the study inclusion. If no agreement is achieved, a third evaluator will be requested to make the tiebreak.

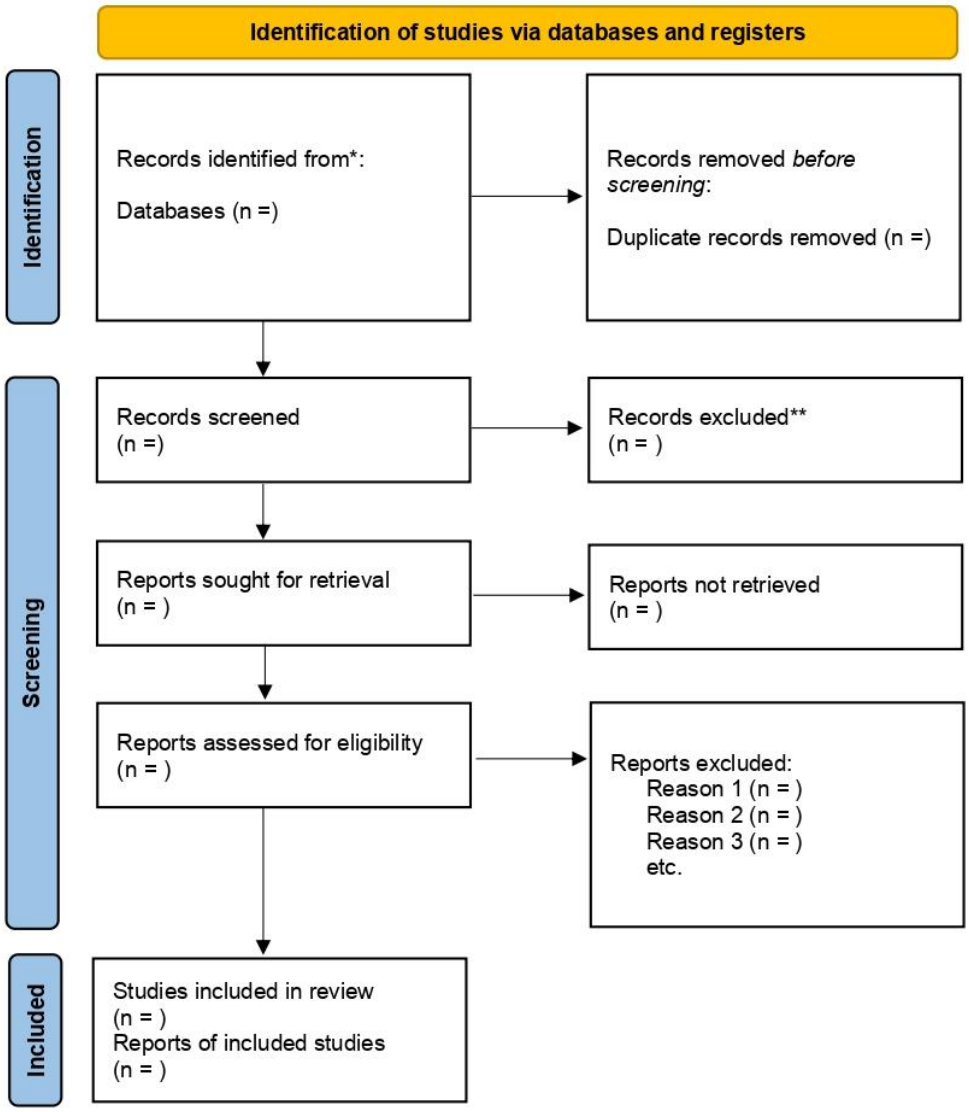
**Table 1.** Database search strategy.

| **Databases** | **Estrategy** |
|---|---|
| Medline via Pubmed | #1 - "Giant Cell Tumor of Bone"[Mesh] OR osteoclastoma<br>#2 - "Denosumab"[Mesh] OR (Xgeva) OR (AMG 162) OR (Prolia)<br>#3 - #1 AND #2 |
| Scielo | #1 - "Giant Cell Tumor of Bone" OR "Tumor Óseo de Células Gigantes" OR "Tumor de Células Gigantes do Osso" OR Osteoblastoma<br>#2 - Denosumab OR Xgeva OR AMG 162 OR Prolia OR Denosumabe<br>#3 - #1 AND #2 |
| Embase | #1 - 'osteoclastoma'/exp OR (giant AND cell AND tumor AND of AND bone) OR (giant AND cell AND tumor, AND bone) OR (giant AND cell AND tumour AND of AND bone) OR (giant AND cell AND tumour, AND bone) OR (polyostotic AND osteoclastoma)<br>#2 - 'denosumab'/exp OR (amg AND 162) OR amg162 OR amgiva OR prolia OR xgeva<br>#3 - #1 AND #2 |
| Science direct | #1 - ("Giant Cell Tumor of Bone" OR osteoclastoma) AND (Denosumab OR Xgeva OR AMG 162 OR Prolia) |
| Cochrane library | #1 – MeSH descriptor: [Giant Cell Tumor of Bone] explode all trees<br>#2 – osteoclastoma<br>#3 – #1 OR #2<br>#4 – MeSH descriptor: [Denosumab] explode all trees<br>#5 – Xgeva<br>#6 - AMG 162<br>#7 - Prolia<br>#8 - #4 OR #5 OR #6 OR #7<br>#6 - #3 AND #8 |
| Clinicaltrial.gov | **#1** - (Giant Cell Tumor of Bone OR osteoclastoma) AND (Denosumab OR Xgeva OR AMG 162 OR Prolia) |
| Registro brasileiro de ensaios clínicos | **#1 -** (Giant Cell Tumor of Bone OR osteoclastoma) AND (Denosumab OR Xgeva OR AMG 162 OR Prolia) |
| Open access theses and dissertations | **#1** – ("Giant Cell Tumor of Bone" OR osteoclastoma) AND (Denosumab OR Xgeva OR AMG 162 OR Prolia) |
| Biblioteca digital brasileira de teses e dissertações | **#1** – ("Giant Cell Tumor of Bone" OR osteoclastoma) AND (Denosumab OR Xgeva OR AMG 162 OR Prolia) |

Source: Authors.

The data will be extracted and tabulated in spreadsheet using Microsoft® Excel® (Microsoft Corporation, 2019). These data will include the number, age, gender and location of the tumor of the study participants; author, year, place of publication, among other related aspects; therapeutic adopted regimens (dose, intervals between doses, treatment duration, etc.); and outcomes (therapeutic response, adverse effects, local recurrence, lung metastases, etc.). To avoid bias in the extraction process, two evaluators will perform the extractions independently; the agreement of the extraction will be calculated by Cohen's kappa coefficient (κ). In case of lack or insufficiency of data, the corresponding author of the respective article will be contacted for obtaining it; if this is not possible, the incomplete study will be removed.

**Figure 1.** The research flowchart.




**Source:** Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., McGuinness, L. A., … Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical research ed.), 372*, n71. https://doi.org/10.1136/bmj.n71

### *2.6 Risk of bias (quality) assessment*

The risk of bias in the selected studies will be judged independently by two evaluators. The evaluation of the quality of the studies will be carried out by the tool developed by the National Institutes of Health (NIH) (NIH, 2022); the checklist consists of 12 questions - each study will be reviewed answering 'yes', 'no', 'not determined', 'not applied' or 'unreported'.

### *2.7 Statistical analysis*

#### *2.7.1 Data analysis and processing*

Quantitative synthesis will be performed if the included studies were sufficiently homogeneous. Homogeneity will be evaluated similarly to the study design, population and statistics directed to the studies.

Meta-analyses will be conducted, if appropriate, extracting data for the number of events and total number of patients to perform proportion meta-analysis using the R software, with the "meta" package (version 4.9-6), the "metaprop" function for

aspect ratio data. We will present combined results of proportion with respective confidence intervals (CI) of 95% by the inverse variance method with a random effects model, using the derSimonian-Laird estimator for τ2. The data will be adjusted by Freeman-Tukey's double arc transformation and the confidence intervals will be calculated by the Clopper–Pearson method for individual studies. Heterogeneity will be evaluated using the $I^2$ statistic, being considered $I^2$ <50% low heterogeneity, ≥50% substantial heterogeneity, and >75% high heterogeneity (Higgins et al., 2011).

#### *2.7.2 Analysis of subgroups or subsets*

We will make subgroups analyses, structured around the characteristics of the intervention (dosage, duration, attack dose), population (cohorts...). Visual inspection will be adopted using the funnel plot with contour to assess the risk of publication bias, if the analyses have 10 studies included (Higgins et al., 2011).

## 3. Results and Discussion

We plan to present the results further in a final systematic review and, if possible, a meta-analysis, as described above in the Methodology section.

### *3.1 Why it is Important to do this Review*

The scientific literature about the efficacy of different therapeutic regimens using denosumab in patients with GCTB has not yet been widely investigated. To the best of our knowledge, no systematic review or meta-analysis has been conducted in this context.

The purpose of this protocol is to design a systematic review of level I evidence to ascertain the data.

## 4. Final Considerations

This systematic review protocol was designed to comprehensively contribute to the literature on the efficacy of different therapeutic regimens using denosumab in patients with GCTB. We plan to identify, critically appraise, summarize and provide the certainty about the best, currently available evidence on the subject in question.

The study findings will be published in the form of a dissertation and a systematic review with, if possible, a meta-analysis. This work is linked to the master's degree of Bruno Garcia Barreto (Medical Sciences Pos-Graduate Program, Holy House of Mercy of São Paulo Medicine Faculty), under the orientation supervision of Claudio Santili, MD, PhD (Advisor), and Alex Guedes, MD, MSc, PhD (Co-Advisor) with a scientific, economic, and social impact.

This work will bring the benefit of informing about the efficacy of different therapeutic regimens using denosumab in patients with GCTB, providing important data that will support future research and assist in possible therapeutic measures.

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