ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 06 | June - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

MANAGEMENT OF CENTRAL GIANT CELL GRANULOMA WITH DENOSUMAB THERAPY – A REVIEW OF LITERATURE

Maxillofacial Surgery

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ABSTRACT

A rare, intraosseous benign lesion, Central giant cell granuloma (CGCG) of the jaws occurs more commonly in young adults. It is rarely malignant, but can be locally aggressive causing disfigurement of the face by virtue of cortical expansion along with displacement of teeth, root resorption, and sensory nerve deficits. The most customary treatment has been surgical curettage and surgical resection with a margin of 0.5cm margins. Pharmacologic agents including intralesional corticosteroid injections such as triamcinolone acetonide and systemic treatment with calcitonin or interferon alfa-2a have also been successfully employed. CGCG is characterized by mononucleated, spindle-shaped neoplastic cells that over-express receptor activator of nuclear factor kB-ligand (RANKL) which can be targeted by Denosumab, a humanized monoclonal antibody, thus making it an effective antiresorptive agent and a novel method to treat conditions such as CGCG. This review deals with the basic understanding of CGCG along with it's management with an in-depth analysis on the utilization of Denosumab as a new management modality for the disease.

KEYWORDS

Central Giant Cell Granuloma, Denosumab, RANKL

INTRODUCTION

Central giant cell granuloma (CGCG) of the jaws is a rare, intraosseous benign lesion occurring more commonly in young adults. Jaffe[1] in 1953 introduced the term "giant-cell reparative granuloma" for the presumption of it being a non-neoplastic process and to distinguish it from the GCT of the extra-gnathic skeleton. Giant cell tumors show an aggressive clinical behavior with a high recurrence rate and a potential for metastasis. [2,3]

CGCGs of the jaws is rarely malignant, but can be locally aggressive causing disfigurement of the face by virtue of cortical expansion along with displacement of teeth, root resorption, and sensory nerve deficits[4,5]. Most cases of CGCG begin as painless expansion of the alveolar bone and may be first recognized as radiolucent areas within the bone which displace the surrounding structures, thus causing root resorption and cortical bone perforation [6,7].

The most customary treatment has been surgical curettage wherein surgical resection with 0.5cm margins is effective with a recurrence rate of 6% in one study [8] but with a compromise in the function and esthetics in certain cases. However, recurrence rates of 11 to 72% have also been reported. [5]

Since the past 2 decades, a number of non -surgical treatment options have been described.[5] These have the advantage of preventing, or at least minimizing the extensive and disfiguring surgical procedures which come with certain drawbacks of their own. Successfully applied pharmacologic agents include intralesional corticosteroid injections along with systemic treatment with calcitonin or interferon alfa-2a.[9-11]

Intralesional corticosteroid as a non -surgical treatment option for CGCG was introduced in 1988 wherein, complete resolution was seen in 6 weeks after 20 weekly injections [9]. 65% of the cases of CGCG showed complete resolution, whereas 35% of the cases did not respond or in turn behaved more aggressively, requiring further curettage or resection as reported by Marx and Stern[12]. Furthermore, recurrence was seen within 12 to 18 months of the initial therapy in a few cases.

Calcitonin receptors are expressed by multinucleated giant cells in CGCG and giant cell tumor of bone. This forms the basis of calcitonin therapy for CGCG.[13,14] Calcitonin inhibits osteoclast function. Pogrel et al. reported 8 out of 9 patients when treated with subcutaneous calcitonin injections, showed no decrease in the lesion size after 6 months of therapy, but showed complete resolution after 18 months.[15]

CGCG and giant cell tumor of bone (GCTB) are characterized by mononucleated, spindle-shaped neoplastic cells that over-express receptor activator of nuclear factor kB-ligand (RANKL) and recruit multinucleated, osteoclast like giant cells leading to bony destruction [16]. This discovery and subsequent understanding of the essential role of the receptor activator of nuclear factor kappa-B (RANK)/ RANKL/osteoprotegerin (OPG) pathway in bone biology has opened the door to new potential therapeutic targets.

Denosumab, a humanized monoclonal antibody targeting RANKL, developed for treatment of osteoporosis, is also a highly effective treatment for GCTB on the basis of large multicentric trials[17–19]. It is an effective antiresorptive agent and could be useful in the treatment of other skeletal diseases with excessive osteoclast activity, such as CGCG.

DENOSUMAB

Denosumab is a fully human monoclonal IgG2 antibody which has a high affinity and specificity for RANKL. RANKL is an essential cytokine in osteoclastic activity thereby promoting survival and activation of readily formed osteoclasts.[20] As a result, it possibly can be a target for novel therapies against bone diseases with excessive osteoclastic activity.

Mechanism Of Action

RANKL signaling has 3 main components.[20] (Fig 1A) The receptor, RANK, is expressed by a variety of cells such as osteoclasts and mononuclear preosteoclasts. The ligand, RANKL, is a member of the tumor necrosis factor family and is highly expressed by osteoblasts, periosteal cells, and osteocytes. A soluble decoy receptor, OPG, also expressed by osteoblasts, acts as a natural negative regulator of RANKL. Denosumab imitates the effect of OPG, inhibiting the RANK– RANKL interaction and, subsequently, the formation, activation, and survival of osteoclasts (Fig 1B).

The histopathological features of CGCG are well known but the fundamental understanding of the biological behavior is still lacking. Histopathology of biopsy specimens shows spindle-shaped stromal cells and characteristic multinucleated giant cells arranged in a fibroblastic stroma, with foci of hemorrhage.

Recently, the key components of RANKL signaling have been proven in CGCG.[21] The spindle-shaped mononuclear cells are osteoblast-like cells which aid osteoclast formation through the expression of RANKL.

The multi nucleated giant cells in CGCG have an osteoclastic phenotype and might be formed by monocyte/macrophage lineage. Both the osteoclast-like giant cells and their precursors express RANK. These features of CGCG tissue propose that the enrollment of osteoclast-like giant cells is related to the stromal expression of RANKL and that the giant cells are responsible for the osteolytic destructive behavior of the tumor. If so, therapeutic agents that inhibit this RANK–RANKL interaction, such as denosumab, could hypothetically control CGCG.

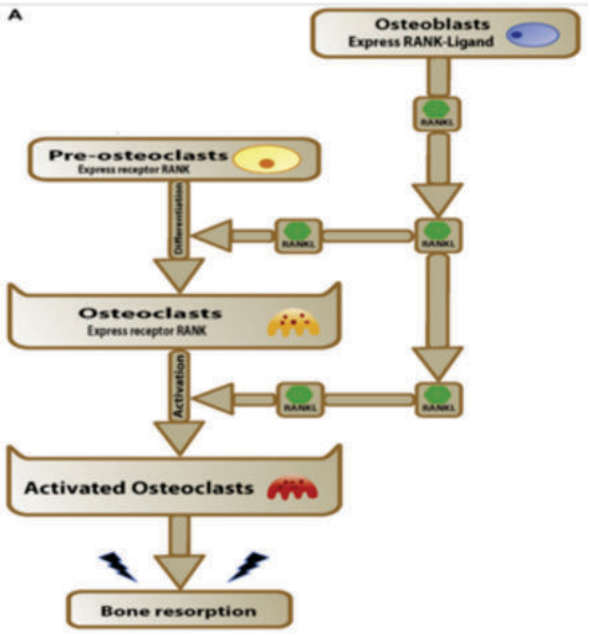

Fig 1A A simplified diagram of the receptor activator of nuclear factor kappa-B (RANK)–RANK ligand (RANKL) pathway. In central giant cell granuloma, it has been hypothesized that the formation of osteolytic osteoclast-like giant cells from its precursors is related to the spindle-shaped mononuclear cell expression of RANKL. Both the multinucleated giant cell and its precursors express RANK

Taken from: *Schreuder et al. Alternative Therapy for Aggressive CGCG. J Oral Maxillofac Surg 2014.*[22]

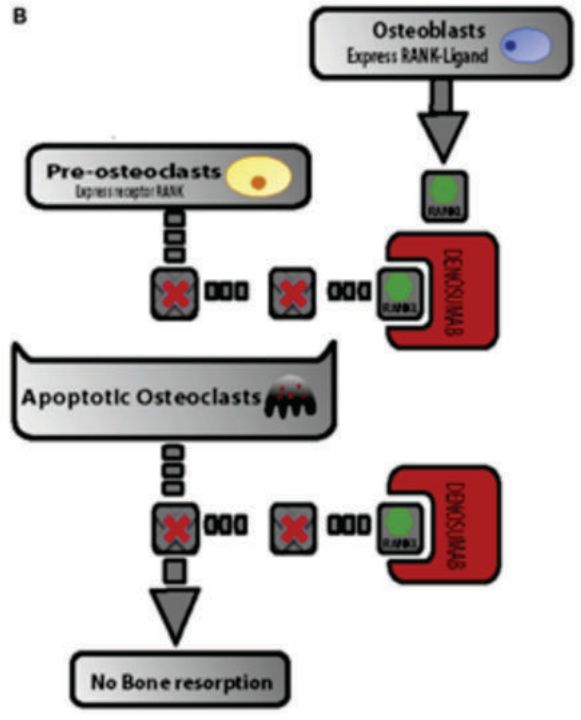

Fig 1B. The same diagram graphically showing the site of interaction of denosumab. By binding to RANKL, denosumab inhibits osteoclast formation, function, and survival. Thus, it decreases bone resorption and increases bone mass and strength in cortical and trabecular bone.

Taken from: *Schreuder et al. Alternative Therapy for Aggressive CGCG. J Oral Maxillofac Surg 2014.*[22]

TREATMENT REGIMEN

Since it is less aggressive then GCTB, the treatment protocol involves administration of Denosumab in a subcutaneous 120 mg monthly initial dosing with no loading dose. The subsequent dosing interval is then customized depending on treatment response at regular 3-monthly clinical, biochemical and radiological assessment (orthopantomograms for mandibular lesions, cone beam computed tomography for maxillary lesions).

Customized treatment should follow a standardized protocol, i.e., stepwise increase in dose interval to 120 mg 2-monthly, 3-monthly and 6-monthly, when ossification and/or decrease in size is observed over at least two consecutive reviews (Fig. 2). Additional course(s) of denosumab should be considered if there is any recurrence following completion of initial course of therapy.

This less aggressive treatment approach reduces the lesion size and achieves intralesional ossification while avoiding the side effects of potent anti-resorptive therapy, in particular Osteonecrosis of the Jaw, given the location of disease. Clinical and radiological reviews should be continued 3–6-monthly following denosumab cessation to monitor recurrence.

TREATMENT OUTCOME

Multiple phase III studies have suggested that denosumab is more effective than the bisphosphonate, zoledronic acid, in treating patients with skeletal metastases from breast cancer, prostate cancer, and multiple myeloma.[24-26]

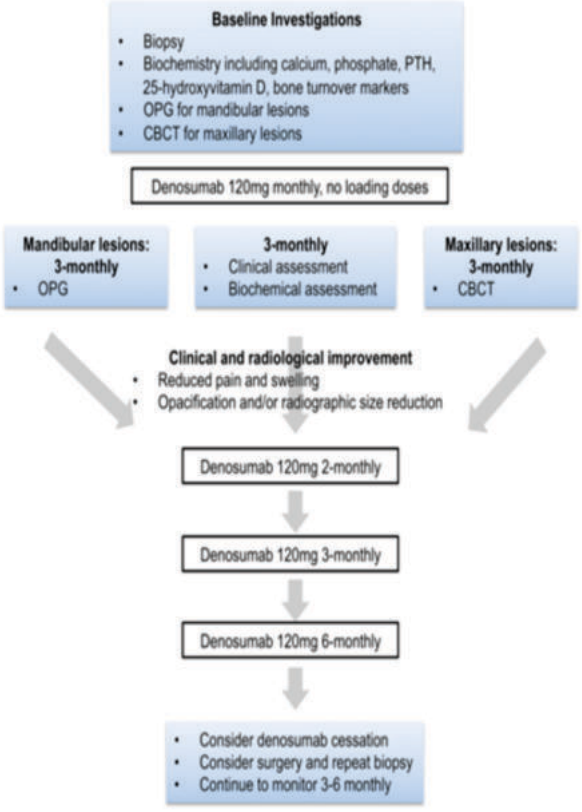

Fig 2: Proposed denosumab treatment and monitoring regimen for central giant cell granuloma to achieve treatment response while minimising risk of adverse effects of therapy and radiation exposure. PTH parathyroid hormone, OPG orthopantomogram, CBCT cone beam computed tomography

Taken from*: Y. J. J. Rhou et al. Clinical and Radiologic Response of Central Giant Cell Granuloma to Denosumab*[23]

Paper published by the American Association of Oral and Maxillofacial Surgeons specifically addressing medication-related osteonecrosis of the jaws has emphasized that, in contrast to bisphosphonates, RANKL inhibitors such as denosumab do not bind to bone and their effects on bone remodelling are mostly diminished within 6 months of treatment cessation.[27]

Taken from*: Y. J. J. Rhou et al. Clinical and Radiologic Response of Central Giant Cell Granuloma to Denosumab* [23]

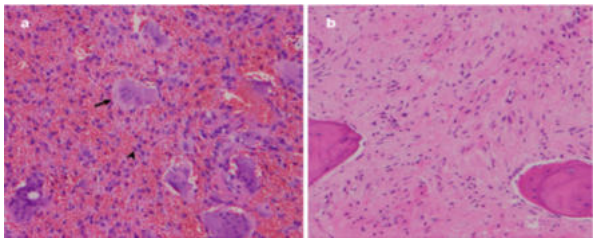

Fig 3: Histopathology of central giant cell granuloma lesion prior to denosumab therapy, demonstrating multinucleated giant cells (arrow) and mononucleated, spindle-shaped cells (arrowhead) (a) and histopathology of lesion following two courses of denosumab, in which giant cells are no longer seen.

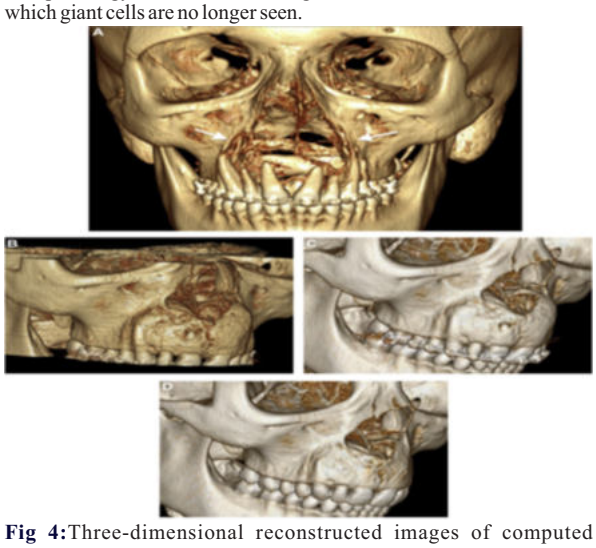

Fig 4: Three-dimensional reconstructed images of computed tomography scans showing A, the destructive expansive osteolytic lesion in the anterior maxilla before treatment and bony demarcation of the lesion due to reformation of the cortex B, after 6 months of treatment and C, at cessation of therapy. D, This result was stable at 1 year after treatment with even slightly more regression.

Taken from: *Schreuder et al. Alternative Therapy for Aggressive CGCG. J Oral Maxillofac Surg 2014* [22]

CONCLUSION

Y. J. J. Rhou et al[23] support the superior efficacy of denosumab as a targeted therapeutic option compared to other modalities by showcasing response in all patients, including failure after other therapies. A longer treatment duration with denosumab (at least 12 doses), the need for a definitive surgical plan following neoadjuvant therapy with denosumab to reduce surgical morbidity, and closer longitudinal follow-up may be required for larger CGCG lesions of the aggressive subtype.

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