Denosumab as a Treatment Alternative for Central Giant Cell Granuloma: A Long-Term Retrospective Cohort Study

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Purpose: Giant cell granuloma (GCG) of the jaw is a rare disease with high morbidity. Various treatment options have been discussed in the past. Since 2010, a pharmaceutical therapy with denosumab seems to have been successful for giant cell tumors of the femur. The authors hypothesized the equally successful use of denosumab for GCGs of the jaws.

Materials and Methods: In the present retrospective cohort study, 5 patients with large GCGs of the jaws were treated with denosumab with a follow-up of 25 to 49 months. Frequent clinical follow-ups and a radiologic follow-up were performed and systematically analyzed.

Results: All patients showed a curative treatment response and complete metabolic resolution of the GCGs under treatment with denosumab.

Conclusion: A brief review of the relevant literature and a detailed evaluation of current cases led to the conclusion that denosumab therapy should be considered a therapeutic option for large central GCGs of the jaws. The results of this study suggest denosumab is a successful treatment option. A treatment length no shorter than 12 months is recommended and monitoring of treatment response can be well managed by positron-emission tomographic computed tomography or magnetic resonance imaging.

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Central giant cell granuloma (CGCG) is defined by the World Health Organization as a rare disease consisting of predominantly giant cells causing bone destruction. This benign intraosseous lesion consists of cellular fibrous tissue that contains multiple foci of hemorrhage, aggregations of multinucleated giant cells, and occasionally trabeculae of woven bone. The fibroblastic background can vary in form, from a dense to a sparsely cellular background. Some mitotic figures can be seen but are not typical.

Jaffe[1] described these distinct benign lesions of the jaws as "giant cell reparative granulomas." Because these lesions do not disappear and are mostly progressive, the reparative part of the description was later abolished. Farhadi et al[2] described a higher level of mast cells in central giant cell lesions compared with peripheral lesions that could in part explain their more aggressive behavior. Giant cell lesions can be described as central or peripheral according to their localization. Central lesions are classically intrabony

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and peripheral lesions are often seen as reactive oral tumors.[3] CGCGs account for approximately 7% of all benign tumors of the jaws, affecting 1 in 1 million persons, and are common in younger women.[1] Most patients are younger than 30 years; however, children as young as 4 years can present with CGCG.[4,5] Although all parts of the facial skeleton can be involved, the anterior part of the mandible is usually affected. Patients might experience swelling and teeth can become mobile. Altered sensation also might feature in a smaller subset of patients.[6] Radiologically, lesions are relatively well-circumscribed areas of bone loss without a cortical border. Tooth resorption can be present in up to 13% of patients.[7]

CGCGs can vary in their clinical behavior and range from indolent, slowly expanding, and asymptomatic lesions to aggressive variants featuring rapid growth, pain, cortical destruction, root resorption, and tooth mobility, with the latter representing the more aggressive subtype.

The aggressive subtypes are mainly characterized by more aggressive clinical behavior, larger lesions at time of presentation, younger age at presentation, and poorer response to treatment.[4] Chuong et al[8] analyzed these 2 groups further and could differentiate between the 2 groups by the assessment of fractional surface area (FSA) occupied by giant cells and the relative size index (RSI), with recurrent lesions having increased RSI and FSA and aggressive lesions showing a higher RSI.

Radiologically, cortical expansion, cortical erosion, and the lack of a cortical border with root resorption are seen and retained teeth have been reported. Lesions might appear to be uni- or multilocular and might cross the midline. Size can range from small apical lesions to large, expansive, and destructive lesions. The level of osteolysis can vary from totally osteolytic to a mixed pattern of opacities and radiolucencies. Demarcation of lesions can range from well to poor; however, a cortical border is not present. Area of involvement can involve the maxilla and mandible, including the condyle and coronoid process, and the skull base.

Especially multiple CGCGs can be associated with different genetic conditions, such as Noonan syndrome, osteoglyphonic dysplasia,[9] neurofibromatosis type 1, and cherubism with a gene defect on chromosome 4p 16.3, which encodes the binding protein SH3 BP2,[4,7,10-12] and can be seen in combination with ossifying fibroma,[13] fibrous dysplasia,[14,15] and aneurismal bone cysts.[16]

Diagnosis is based on biopsy examination, in which the focal distribution of giant cells might surround hemorrhagic areas with a spindle cell matrix. Exclusion of primary and secondary hyperparathyroidism by serum calcium, phosphate, and parathyroid hormone levels is of paramount importance because brown tumors associated with hyperparathyroidism can cause identical histologic lesions.[12]

Treatment possibilities were initially limited to surgery alone. It was soon realized that many lesions also respond favorably to curettage and even spontaneous regression has been reported.[17] There are those who still advocate surgery, which can include segmental resections for aggressive subtypes.[18,19] Without doubt, aggressive surgery can cure CGCGs; however, the morbidity could be high and lead to severe esthetic and functional problems. Therefore, different pharmacologic treatment options have evolved in recent years to at least decrease the size of the lesions to avoid mutilating surgery; therefore, it is important to consider some effective nonsurgical solutions.

Intralesional steroid therapy has been advocated for many years and can be viewed as a benchmark therapy.[4,20] Recently, anti–bone resorptive human monoclonal antibody drugs, such as denosumab, have gained prominence in the therapy of osteoporosis, metastatic cancer, and central giant cell tumors.[21]

The purpose of this article is to describe the successful use of denosumab in 5 patients with large CGCGs of the jaws, with a follow-up of at least 25 months and a brief overview of the literature.

Materials and Methods

PATIENTS

The study design fulfilled the Declaration of Helsinki on medical research protocols and ethics. The local institutional review board permits the retrospective evaluation of 5 cases; furthermore, all cases were repeatedly discussed and the decision on treatment was made at an interdisciplinary tumor board.

At the Department of Craniomaxillofacial and Oral Surgery of the University Hospital of Zurich (Zurich, Switzerland), 5 patients with CGCG were treated with denosumab. The first of the 5 patients underwent different therapies before starting treatment with denosumab. The other 4 patients were almost immediately treated with denosumab as first-line treatment after the diagnosis of CGCG as made. All patients initially received 1 to 2 doses of intralesional corticosteroids. The patients are described in order of presentation at the hospital and their characteristics are presented in Table 1.

As baseline diagnostics, all patients underwent a biopsy examination, computed tomographic (CT) scanning, and positron-emission tomographic (PET) scanning and extended blood analysis focusing on calcium (Ca^{2+}), parathyroid hormone, and phosphate (PO_4) was performed.

Table 1. PATIENTS' CHARACTERISTICS

Case	Gender	Age at First Visit	Follow-Up (mo)	Total Applications, n	Relapse	Location
I	Male	3 yr 11 mo	39	15	No*	Maxilla and mandible
II	Female	18 yr 2 mo	49	15	No	Maxilla
III	Female	26 yr 1 mo	38	12	No	Anterior mandible
IV	Female	19 yr 10 mo	33	15	Yes	Anterior mandible
V	Male	22 yr 2 mo	25	14	No	Angle mandible

* At the jaw.

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CASE I

A boy born in July 2005 was referred at 4 years of age in July 2009 to the authors' department for non-eruption of teeth, oral pain, and multiple cystic lesions as shown on radiographs (Fig 1A).

Biopsy examinations of the lesions confirmed the presence of multiple CGCGs. In September 2009, curettage and intralesional steroid injection (ILSI) of the maxilla and mandibula were performed. For progressively expanding lesions, the patient was treated with subcutaneous (SC) calcitonin 70 and then 100 IU daily for 18 months. On clinical examination and by evaluation of cone-beam CT (CBCT) scan in December 2009, no tumor progression was detected; however, the patient had pain at night. Curettage of the maxilla and mandibula with ILSI was performed in June 2010, which was followed by 3 ILSIs every 2 months. In March 2011, the patient developed intracerebral hypertension (ICH) that was treated with acetazolamide. Therapy with calcitonin was stopped because of its possible contribution to ICH. Radiologic workup showed nonossifying lesions of the long bones and genetic analyses led to the diagnosis of osteoglyphonic dysplasia. The case was repeatedly discussed in an interdisciplinary tumor board and in May 2012 interferon-α (IFN-α) at a weekly dose of 180 μg (0.8/m^2 body surface) was started. Because of the poor response and distinct side effects, the therapy was discontinued after 3 months. Despite the previous extensive multimodal therapy, CGCG progression was detected in December 2013. Surgical curettage seemed risky for jaw fractures. Denosumab treatment was discussed as an option. There were reports (eg, by de Lange et al[22]) of children with giant cell tumors treated with denosumab. SC denosumab was given at a dose of 70 mg once a week for the first month and monthly thereafter. In addition, the boy received vitamin D (1,000 U/day) and calcium supplementation (500 mg/day). Clinical and radiologic follow-up showed an impressive response. The most recent CBCT scan from December 2015 showed good ossification of the jaws (Fig 1B) and PET-CT scan from September 2016 confirmed that there was no remaining metabolic activity.

Follow-up after the first denosumab application was 3 years 6 months (42 months). In total, the patient received curettage 4 times, 8 ILSIs, SC calcitonin 100 IU for 18 months, 12 doses of IFN-α 180 μg, and 15 doses of denosumab 70 to 100 mg.

CASE II

An 18-year-old woman was referred to the authors' department with a biopsy-confirmed diagnosis of a CGCG located in the right palate in May 2013 (Fig 2A). The patient noticed progressive swelling and mild pain during the previous 3 months. PET-CT scan showed a metabolic active process in the right maxilla. As initial treatment, ILSI was performed twice and the case was discussed at the tumor board. In May 2013, denosumab therapy was started with a loading dose of 120 mg. In September 2013, follow-up PET-CT scan showed no progression and no metabolic activity. In January 2014, because of sudden progressive pain, a debulking with ILSI was performed. The area of surgery showed delayed wound healing and slight infection. Pathological analysis did not show activity of the few remaining giant cells. The most recent CBCT scan from April 2017 (Fig 2B) showed a stable situation and no clinical relapse was detectable.

Follow-up after the first denosumab application was 4 years 1 month (49 months). In total, the patient received 2 ILSIs (total, 15 mg), 15 doses of denosumab 120 mg, and 1 lesion debulking.

CASE III

A 26-year-old woman was referred with prediagnosed CGCG in the anterior mandible. The patient noticed a slowly progressive swelling of 1 year. CBCT scan showed an osteolytic process (Fig 3A). At the first visit in April 2014, ILSI with corticosteroid 10 mg was injected and repeated 2 weeks later. After presentation at the interdisciplinary tumor board in April 2014, denosumab therapy was started. Owing to nail problems, the patient refused the therapy with denosumab

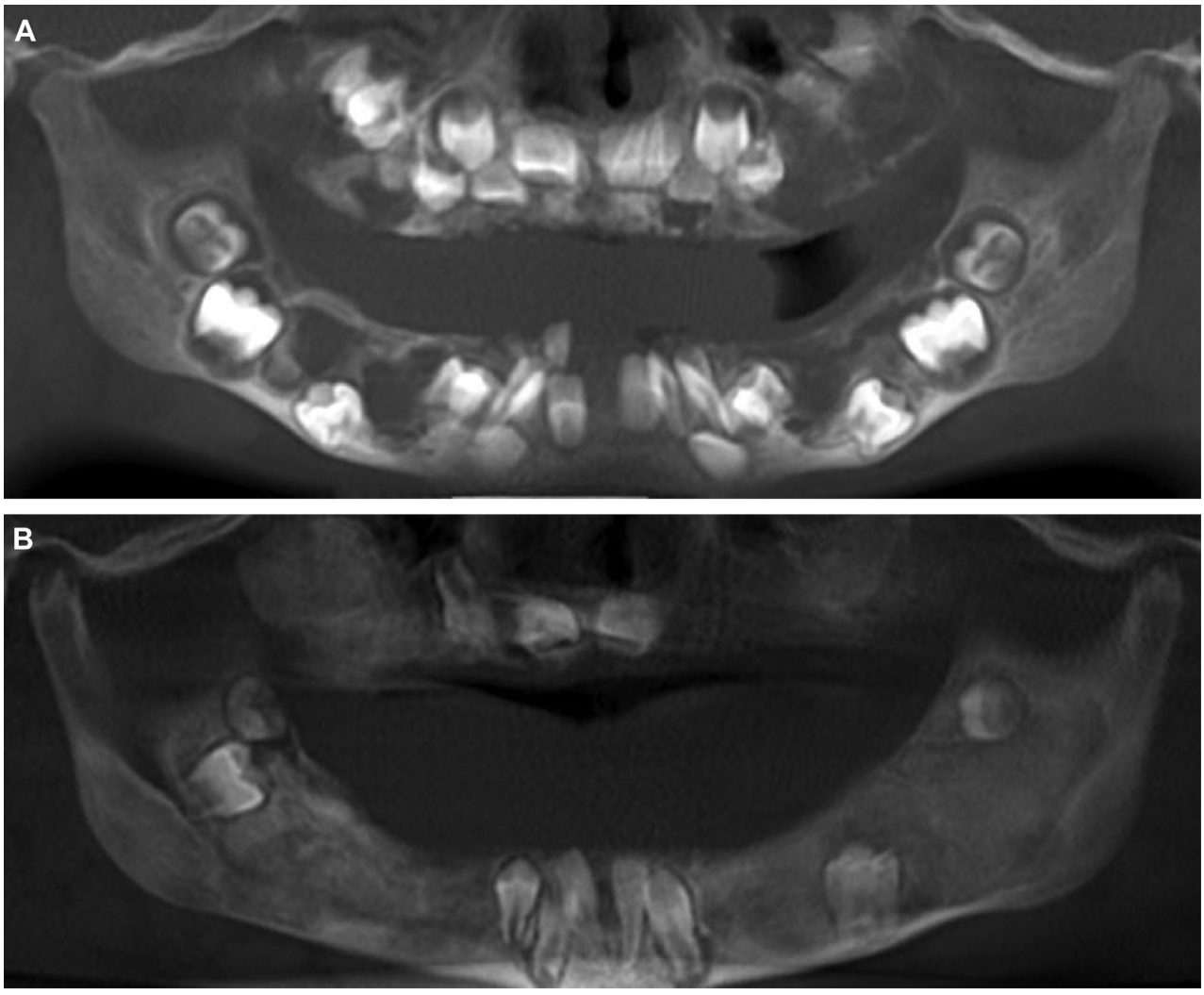

FIGURE 1. True-Pan cone-beam computed tomograms *A*, before and *B*, after 15 doses of denosumab.

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after 4 applications in July 2014. In October 2014, the patient had progressive pain and clinical bone expansion was noted on radiographs. Surgical superficial curettage and ILSI were performed in November 2014, with poor wound healing postoperatively. PET-CT scan from March 2015 confirmed progressive osteolysis and denosumab was restarted in April 2015 at 120 mg/month. Follow-up in November 2015 showed more ossification and a better clinical situation (Fig 3B). In February 2016, another PET-CT scan showed considerably improved mineralization of the bone with no remaining metabolic activity. Clinical examination in December 2016 was unremarkable, except for neuropathic pain in the right mental area that responded well to decompression of the mental nerve.

Follow-up after the first denosumab application was 3 years 2 months (38 months). In total, the patient received 3 ILSIs, 12 doses of denosumab 120 mg, and 1 surgery.

CASE IV

A 20-year-old woman was referred in September 2014 with the diagnosis of CGCG in the anterior mandibular area (Fig 4A). At the first visit she received an ILSI of 10 mg. Two weeks later the patient received the first dose of denosumab 120 mg after her case was presented at the interdisciplinary tumor board. After the loading dose of 120 mg 3 times every 2 weeks, the patient received denosumab 120 mg/month for 1 year. Follow-up with several CBCT scans and 2 PET-CT scans showed continuing mineralization of the CGCG lesions (Fig 4B). Clinical examination findings in September 2016 were within normal limits; however, PET magnetic resonance imaging (MRI) in November 2016 showed an asymptomatic increase in metabolic activity. Therefore, the denosumab therapy was restarted in November 2016 with complete metabolic response as confirmed by a PET-CT scan in June 2017.

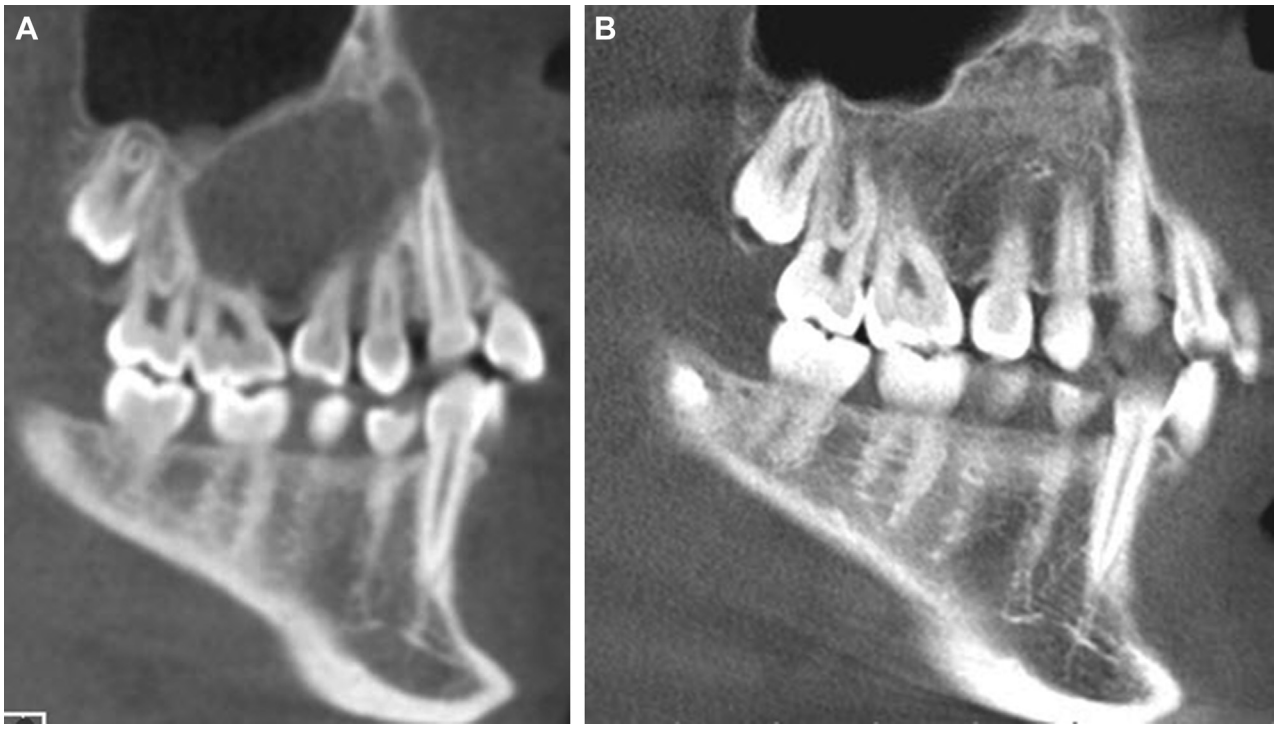

FIGURE 2. Sagittal cone-beam computed tomographic views *A*, before and *B*, after 15 doses of denosumab.

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Follow-up after the first denosumab application was 2 years 9 months (33 months). In total, the patient received 1 ILSI and 15 doses of denosumab 120 mg.

CASE V

A 22-year-old man presented with a rapidly progressive swelling in the right mandible in October 2014 (Fig 5A). Biopsy examination confirmed the presence of a CGCG. The patient received 3 ILSIs (total, triamcinolone acetonide 30 mg; Kenacort, Bristol-Myers Squibb, New York, NY®). Therapy with denosumab started in November 2014 with 3 120-mg loading doses and monthly doses for 1 year. Radiologic and clinical follow-up showed complete resolution of the osteolysis. The last consultation was in November 2016 (Fig 5B).

Follow-up after the first denosumab application was 2 years 1 month (25 months). In total, the patient received 3 ILSIs and 14 doses of denosumab 120 mg.

Discussion

Any therapeutic intervention should have as few side effects as possible with the best chance of long-term cure. There is no current consensus on the correct management of central giant cell lesions, with most of the literature consisting of smaller case series. Surgery, from resection to conservative curettage, has been advocated, with the latter having a major risk of recurrence in larger lesions. Morbidity can be high because surgery usually entails aggressive curettage and even segmental resection, often leading to loss of teeth in tooth-bearing areas. Lesions are usually mono-focal, as in 4 patients in this case series, but can be multifocal in rare cases and mostly associated with rare genetic aberrations, such as Noonan syndrome, or as described in the rare condition of osteoglyphonic dysplasia.[23,24] Medical treatments including intralesional corticosteroids, calcitonin therapy, IFN-α, and bisphosphonates have been described. Intranasal calcitonin spray as maintenance therapy has shown marked benefits in preventing recurrence after surgical curettage.[4,25,26]

In this retrospective cohort study, intralesional corticosteroids were used during the initial phases of treatment to allow time for consideration at the interdisciplinary tumor board. Positive responses and even cure have been reported in some case series.[20] The authors' experience is that progressive calcification prohibits adequate access to the deeper part of the lesions after several injections, especially in larger lesions; thus, this method of therapy with a curative intent is reserved for smaller lesions.

Denosumab is a monoclonal antibody that binds to receptor activator of nuclear factor-κB (RANK) ligand (RANKL). RANK is expressed on the surface of precursors to osteoclasts (ie, pre-osteoclasts). RANK is activated by RANKL and promotes the maturation

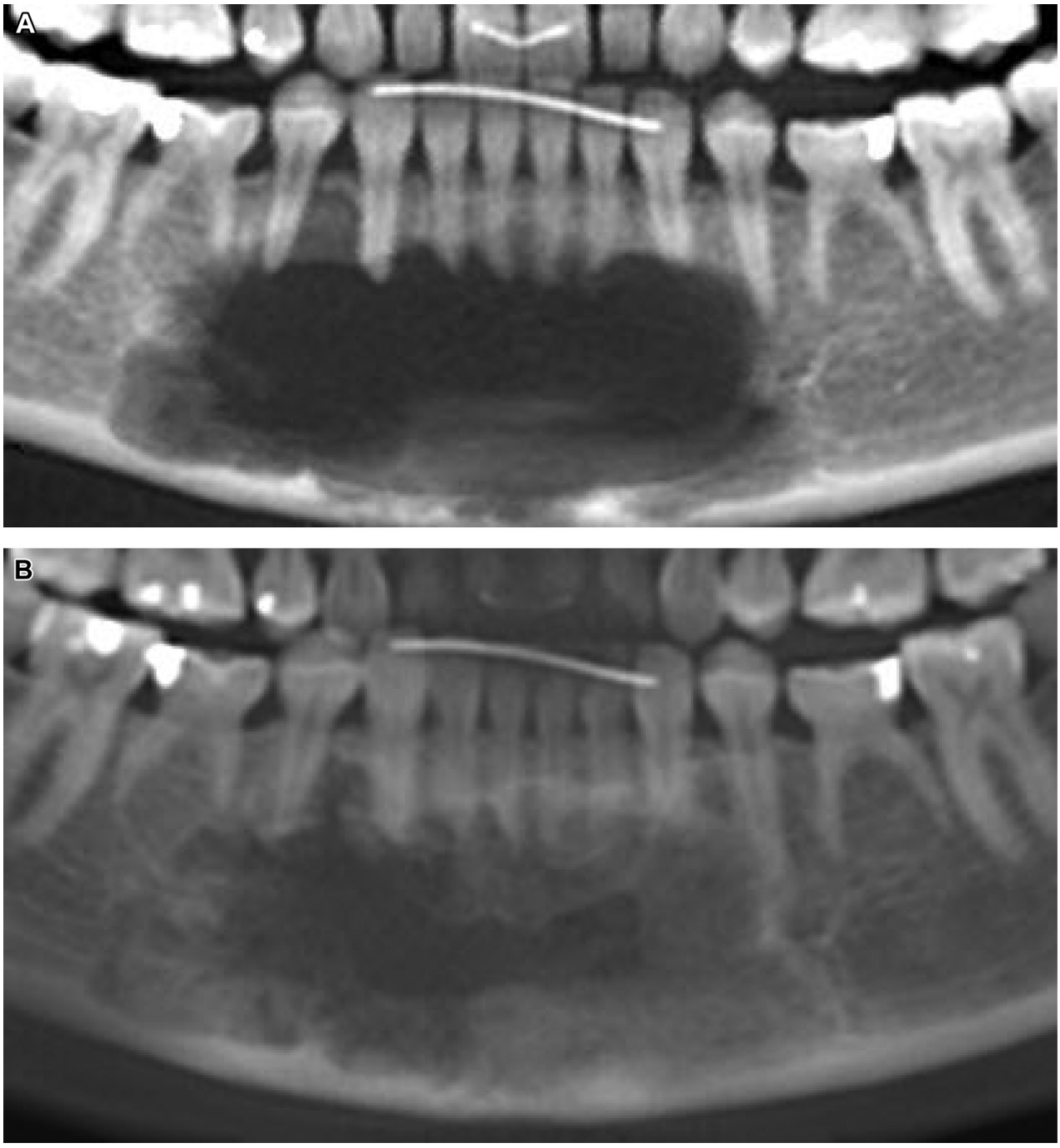

FIGURE 3. True-Pan cone-beam computed tomograms *A*, before and *B*, after 12 doses of denosumab.

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process of osteoblasts from pre-osteoblasts. By binding to RANKL, denosumab inhibits this important maturation process of osteoclasts and thus the osteolytic process. In osteoporosis, the RANKL inhibitor is decreased and thus denosumab simulates the effect of the RANKL inhibitor, leading to increased mineralization (Fig 6).[27]

Denosumab was successfully used in patients with giant cell tumors of the bone. In 2010 Thomas et al[28] published the first data on the use of denosumab in unresectable giant cell tumors of the long bones in an open-label phase 2 study in which 30 of 37 patients showed tumor response. In 33 of 37 patients, adverse events were noted, of which pain in the extremities was the most common. Because CGCG is histologically identical to and probably has a similar metabolic mechanism as its more aggressive long bone counterpart, the application of denosumab to CGCG of the

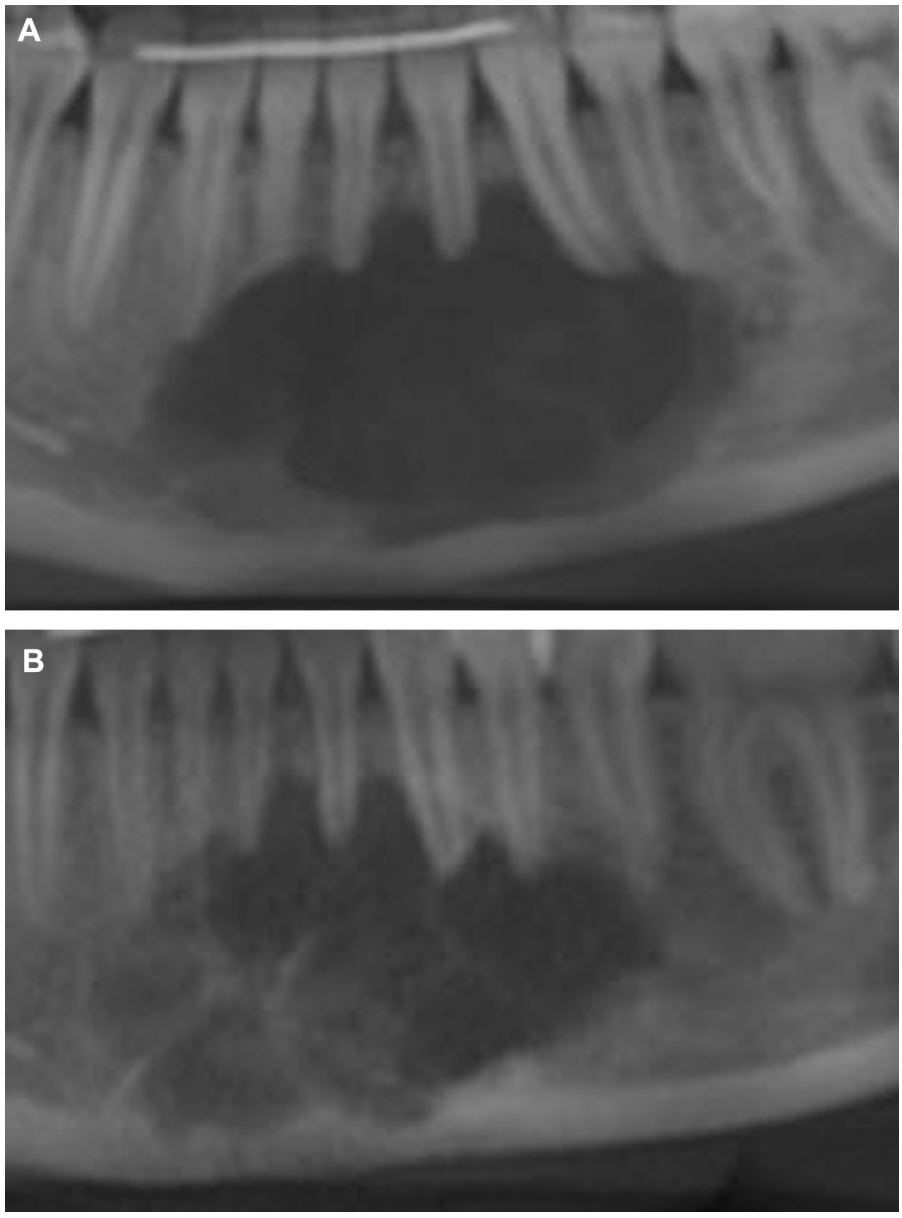

FIGURE 4. True-Pan cone-beam computed tomograms *A*, before and *B*, after 15 doses of denosumab.

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jaws was inevitable. Because CGCG is much rarer than its long bone tumor counterpart, only single or small number case series with limited follow-up are available for comparison (Table 2).[21,26,29-32]

The normal protocol for denosumab therapy of CGCG is similar to that of giant cell tumors. Usually, a loading dose of 120 mg with an additional 120 mg on days 8 and 15 and then every 4 weeks. This regime was followed for 1 year in these patients, except for a dose-adapted protocol for the pediatric patient (case I). All patients had extensive lesions, with a lower probability to respond to ILSI.

When evaluating treatment responses, most patients showed a full clinical response after a treatment period of 1 year. One patient showed early relapse (case III) related to treatment refusal after 4 doses of denosumab. Six months after the cessation of treatment, PET-CT scan showed renewed metabolic activity and the patient agreed to restart the therapy and continued therapy for another 8 months. Since completing the therapy, she has been free of recurrence for 22 months. Case IV showed recurrence approximately one year after cessation of treatment, with complete metabolic response after 7 months of renewed treatment with denosumab. Patients' characteristics are presented in Table 1.

The results from this case series should be interpreted with caution. First, all patients received ILSIs

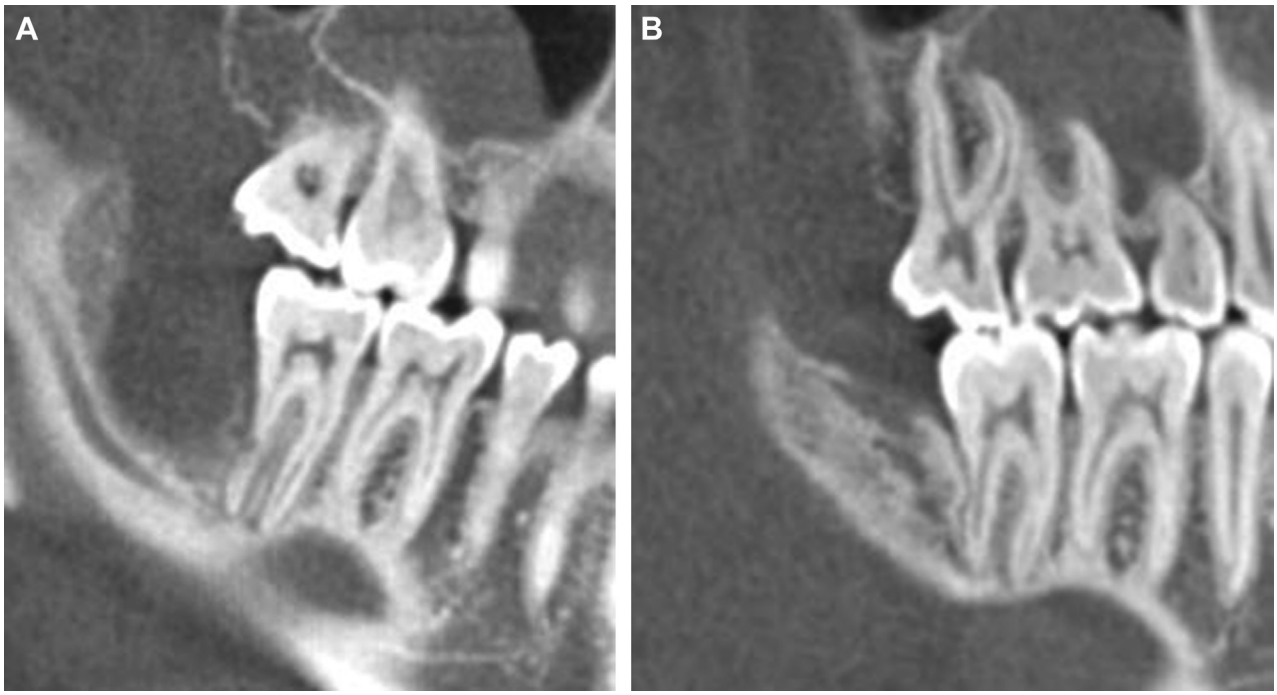

FIGURE 5. Sagittal cone-beam computed tomographic views *A*, before and *B*, after 15 doses of denosumab.

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of triamcinolone acetonide (Kenacort). Most patients only received 2 to 4 injections; however, case I received multiple injections, with moderate to no response. In the authors' experience, the treatment response cannot be attributed to the ILSI (Kenacort) because the number of injections was too small to expect a full response from these extensive lesions. Second, 3 patients had previous or concurrent surgical interventions. In case I, repeated surgery was performed before denosumab therapy; in cases II and III, surgery was indicated for pain after approximately 6 months of denosumab therapy, despite good response to treatment. It is important to note that the surgery was not undertaken with curative intent.

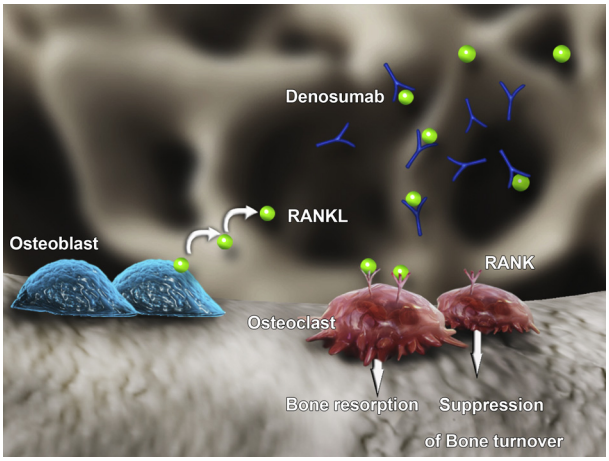

FIGURE 6. Denosumab binding RANKL. RANK, receptor activator of nuclear factor-κB; RANKL, receptor activator of nuclear factor-κB ligand.

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Side effects during treatment were not noted, except for case II showing poor wound healing after explorative surgery and some transient nail changes in case III. Poor wound healing during denosumab therapy is to be expected because osteoclast activity is inhibited, thus intervening in the normal reparative process of bone.[33,34] Poor wound healing in case II could be viewed as stage II medicine-related osteonecrosis of the jaws (MRONJ) directly associated with the surgical intervention during denosumab therapy.[35]

Pain during denosumab therapy was noted in 2 patients (cases II and III). This is a well-known phenomenon in denosumab therapy of CGCTs of the long bones.[8] A possible explanation might be the active mineralization process with possible pressure on sensate nerves. These patients were free of pain after treatment (after superficial curettage in case II and after decompression of the mental nerve in case III).

Naturally, the use of denosumab is questioned because the risk of MRONJ is a well-known complication of the use of denosumab and bisphosphonates or other related antiresorptive drugs. MRONJ is not commonly seen in younger patients but can have a negative effect on healing as described previously.[36,37]

Table 2. LITERATURE OVERVIEW OF CURRENT EXPERIENCE

	n	Location	Previous Therapy				Success With Denosumab	Follow-Up Time (mo)	Dosage		
			Curettage	ILSI	Calcitonin	INF-α			mg	Frequency	Span (mo)
O'Connell et al[27]	1	Maxilla	No	Yes	No	No	Yes	35	120	Every 3 mo	12
Naidu et al[29]	2	Mandible	No/no	No/yes	No/no	No/no	Yes	24/15	120	Monthly	18/9
Schreuder et al[30]	1	Maxilla	No	No	Yes	Yes	Yes	24	120	Monthly	12
Gupta et al[31]	1	Mandible	No	Yes	Yes	No	Yes	18	120	Monthly	6
Rostetter et al[21]	1	Mandible	No	Yes	No	No	Yes	25	120	Monthly	15

Abbreviations: ILSI, intralesional steroid injection; INF-α, interferon-α.

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Duration of denosumab therapy and monitoring of response remain open questions. In this study, PET-CT or MRI was used and correlated with the metabolic response. CBCT and CT are probably less sensitive, although the increase of mineralization is an undisputed sign of treatment response. The use of PET-CT has been well established for central giant cell tumors of the long bones.[38,39] In 2 patients who had biopsy examinations, negative giant cell activity was associated with notable loss of metabolic activity, as measured on previous PET scans.

Treatment was not stopped until complete cessation of metabolic activity. The shortest treatment period was 12 months. Even for the more common long bone tumor, there are no guidelines for length of treatment.[40] Based on their limited experience, the authors recommend a minimum treatment of 12 to 18 months, because relapse can occur with shorter treatment regimens (as in case III). After cessation of denosumab treatment, careful follow-up is necessary to find recurrences that can occur years later.

Because denosumab is a systemic drug with systemic effects, it should be used with caution and not in smaller lesions that can be treated with minimal morbidity using surgery ILSI or calcitonin. In this case series, all patients presented with large lesions, most of which exhibited aggressive growth.

The combination of denosumab therapy with other drugs, such as intranasal calcitonin, and possibly surgery might increase treatment response, but no study on such treatment has been published. Consideration also should be given to maintenance therapy with a lower dose of denosumab or intranasal calcitonin; however, there is very little evidence in this regard. Schreuder et al[41] elucidated the benefit of pharmacologic agents during long-term follow-up.

Despite the early, albeit limited, use of ILSI in all patients, denosumab was successfully used with curative intent in 5 patients with large or multiple CGCGs of the jaws in whom surgical intervention would have led to serious morbidity. Denosumab therapy should be considered a therapeutic option for large CGCGs of the jaws. A treatment length no shorter than 12 months is recommended and monitoring of treatment response can be well managed using PET-CT or MRI.

Acknowledgments

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