Journal of Cranio-Maxillo-Facial Surgery 53 (2025) 2199–2209

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Review

Bisphosphonates – Boon or bane for oral and maxillofacial surgery? Anti-resorptive drugs and their potential role in dentistry and oral and maxillofacial surgery

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A B S T R A C T

Antiresorptive drugs such as bisphosphonates and denosumab are vital medications in the therapy of osteoporosis and in the treatment of cancer with osseous metastases. A rare but clinically relevant adverse effect is medication-related osteonecrosis of the jaw (MRONJ). This review outlines epidemiology, clinical features, diagnosis, treatment, and prevention of MRONJ. In addition, antiresorptives show promise in rare bone diseases relevant to oral and maxillofacial surgery, such as aneurysmal bone cysts, central giant cell granuloma, and diffuse sclerosing osteomyelitis. While early evidence indicates therapeutic benefit, further studies are needed to define safety and standardized protocols. Preventive dental care, patient education, and close interdisciplinary collaboration remain essential for optimal outcomes.

1. Introduction: Application of antiresorptive drugs

1.1. Introduction and objective

Anti-resorptive drugs (ARDs) such as bisphosphonates and denosumab inhibit osteoclastic activity, reduce bone turnover and are frequently used in patients suffering from osteoporosis and metastatic bone diseases. They increase quality of life of those patients by significantly preventing fractures and skeletal related events. On the downside, medication-related osteonecrosis of the jaw (MRONJ) is a clinically relevant and compound specific side-effect. Still, the enormous potential inhering AR drugs especially in reducing pain and preventing pathological fractures raises the question whether they might be suitable for the treatment of bone diseases in the maxillofacial area as well as in other parts of the human body.

This narrative review shows the enormous potential effects that can be anticipated from the use of AR drugs in certain bony diseases. AR drugs offer the possibility of effective new treatment strategies for patients with a variety of jaw bone disease.

As a matter of course, the risk of the development of MRONJ should be taken into account. The better understanding of the etiology of this disease lately led to promising preventive measurements, which should always be part of treatment protocols when AR drugs are in use.

1.1.1. History of anti-resorptive drugs

In the 1960s, in-vitro studies (Francis et al., 1969) and in-vivo-studies in dogs showed that parenterally administered pyrophosphates inhibit calcium phosphate crystal dissolution. The search for a substance with the same effect, but suitable for oral administration, led to the discovery of bisphosphonate. The biological effects of bisphosphonates were discovered 1968 (Fleisch et al., 1968). They inhibit osteoclastic activity and reduce bone turnover (Black et al., 2007;

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https://doi.org/10.1016/j.jcms.2025.10.003
Received 17 July 2025; Received in revised form 4 October 2025; Accepted 10 October 2025
Available online 3 November 2025

Fleisch, 2007; Cummings et al., 2009; Troeltzsch et al., 2012). Since metastatic bone diseases are frequently accompanied by hypercalcemia, bisphosphonates were introduced in the 1980s as an effective therapy to inhibit osteoclast activity and reduce bone resorption. (Lemaire, 1984).

In 2009 the human monoclonal antibody denosumab has been granted marketing authorization in the European Union and was FDA-approved in 2010 (Pageau, 2009). After subcutaneous application, this IgG2-*anti*-RANKL-antibody inhibits the activity of premature osteoclasts via interacting to the RANK/RANKL (Receptor Activator of Nuclear Factor κB Ligand)/OPG (Osteoprotegerin) pathway where it imitates the effects of osteoprotegerin (Troeltzsch et al., 2012).

As both various bisphosphonates and denosumab are used for comparable indications and show similar effects and side-effects, they are summarize as "antiresorptive drugs" (AR drugs) in this review.

1.1.2. Beneficial effects in orthopedics and oncology

Osteoporosis, osteogenesis imperfecta and several types of cancer, which either lead to metastatic bone disease (for example breast cancer, prostate cancer) or originate from bone marrow (multiple myeloma) are among systemic diseases associated with bone loss.

In patients suffering from **osteoporosis,** ARDs are frequently used to inhibit bone loss, to increase bone mineral density and thereby to reduce the risk of fractures (Fleisch, 2001; Cranney et al., 2002; Sambrook and Cooper, 2006; Dömötör et al., 2020).

Regarding **osteogenesis imperfecta**, pharmacological treatment with growth hormones and anti-resorptive drugs has become the third main pillar of symptomatic treatment besides surgical (e.g. intramedullary rodding surgical techniques) and non-surgical treatment (e.g. physiotherapy) (Åström and Söderhäll, 2002; Antoniazzi et al., 2006; Esposito and Plotkin, 2008)' Nitrogen-containing bisphosphonates, such as pamidronate, enhance trabecular bone complexity and exert beneficial effects on condylar trabecular bone. (Pantoja et al., 2022; Speiser et al., 2005).

In patients with **metastatic bone diseases**, AR drugs are the therapy of choice. They decrease both bone resorption and new osteoclastic lesions, significantly prevent fractures and other skeletal related events and improve quality of life of those patients by alleviating pain (Berenson et al., 1996; Schwartz and Kagan, 2002; Wajda et al., 2025).

1.1.3. Side effects of anti-resorptive drugs

Medication-related osteonecrosis of the jaw (MRONJ) is a serious side-effect in the therapeutic use of AR drugs (Troeltzsch et al., 2012). The majority of MRONJ cases occurred in patients receiving intravenous administrations of nitrogen-containing bisphosphonates due to metastatic bone lesions. Underlying malignant diseases are predominantly breast cancer, multiple myeloma and prostate cancer. Less frequenty, MRONJ has also been reported in patients suffering from osteoporosis and receiving oral or intravenous anti-resorptive drugs such as bisphosphonates, Denosumab or antiangiogenic drugs (Marx, 2003, Ruggiero et al., 2022; Bamias et al., 2005; Otto et al., 2011a,b; Otto et al., 2011a,b; Al-Sabbagh et al., 2015). Dental infection, teeth extraction and poor oral hygiene are main risk factors for the development of MRONJ (Pichardo et al., 2020; Hasegawa et al., 2017; Coropciuc et al., 2023). Since then, this pathogenesis model has not only advanced our understanding of MRONJ but has also provided preventive strategies, particularly through the eradication of local infections in the jawbone. (Otto et al., 2010). Supporting this, a retrospective study compared the pH levels of MRONJ patients with those of a healthy control group. The acidic group exhibited a markedly higher occurrence of MRONJ (95 %) compared to the alkalotic group (60 %) and the control group (76.9 %)(Kim et al., 2019; He et al., 2020).

While a non-exposed variant of the disease has also been recognized (Kishimoto et al., 2019; Nicolatou-Galitis et al., 2019) MRONJ usually presents itself as gingival ulceration with necrotic bone exposure in the oral cavity. In the course of the disease, spontaneous severe pain, purulent drainage, extra-oral fistula and pathological fractures occur, with consequent significant reduction in quality of life (Eguchi et al., 2017). Further progression of the condition can lead to tooth loss and necrosis of entire sections of the jaw bone, including pathological fractures of the mandible (Poxleitner et al., 2017).

Fig. 1 shows an extensive case of MRONJ of a woman treated with zoledronate (4 mg) for three years due to breast cancer.

Consequently, many OMF (oral maxillofacial) surgeons and dentists fear the pernicious side effects of AR drugs. Due to the complication of MRONJ, the beneficial effects of bisphosphonates are sometimes forgotten, even in the field of oral and maxillofacial surgery.

1.1.4. Beneficial effects of bisphosphonates in dentistry and OMFS

1.1.4.1. Bisphosphonates for diagnostic use. Since the 1960s bisphosphonates offer undoubted benefit and are of high value for diagnostics of bony diseases.

While radiography shows anatomic changes in bones, bone scintigraphy offers the possibility to assess the activity of bone metabolism. Technetium 99m-labelled Bisphosphonate-derivates are used as standard markers in bone scintigraphy. The bisphosphonates diffuse to the extravascular space and lead to incorporation of the complex to viable bone. Areas of increased tracer uptake therefore correlate with high bone metabolism.

Thus, bone scintigraphy is highly useful for the diagnosis of bony metastases, temporomandibular dysfunction, osteonecrosis of the jaw, osseous inflammatory diseases such as osteomyelitis and rare diseases such as Paget's disease and diffuse sclerosing osteomyelitis (Hino et al., 2005; Coutinho et al., 2006; Roca et al., 2013).

2. AR drugs - therapy in oral and maxillofacial surgery

2.1. Rare diseases of maxillofacial bone

2.1.1. Paget's disease of bone (PDB)

Paget's disease of bone or osteitis deformans is a monostotic or polyostotic disease characterized by focal areas of increased bone turnover, bone hypertrophy, and abnormal bone structure. It can be associated with bone pain and deformity, but is often asymptomatic. Other complications involve osteoarthritis, pathological fracture, bone deformity, deafness, and nerve compression syndromes. The objective of treatment is to minimize bone pain (Delmas and Meunier, 1997; Ralston et al., 2008; Rendina et al., 2024).

Pagetic bone generally responds well to anti-resorptive therapy: it reduces bone turnover, improves bone pain and morphology (Lyles et al., 2001; Ralston et al., 2019; Cook and Wall, 2021).

In the maxillofacial area, the upper jaw is more often affected by PDB than the lower jaw [44]. Deformation of maxillofacial bones can lead to facial disfigurement.

Fassio et al. reported a case of PDB in the mandible of a 22-year old patient, that was treated with 100 mg of intravenous neridronate on two consecutive administrations, leading to pain improvement (Smith and Eveson, 1981; Fassio et al., 2016). Campolongo et al. reported a case of a 72-year old patient without pain but newly developed malocclusion and prognathism who was treated with zoledronate and showed normal bone acitivity afterwards (Campolongo et al., 2018).

Another interesting case wasby Reid et al., (2016), in which a 75-year old woman suffering from PBD involving the skull received alendronate, but did not tolerate the ARD therapy. Due to the severe symptoms and the high levels of ALP, denosumab 60 mg has been injected subcutaneously. As a result, the ALP levels dropped rapidly with regression of clinical symptoms (Reid et al., 2016).

2.1.2. SAPHO-syndrome

The SAPHO syndrome is an acronym for the most common symptoms: synovitis, acne, pustulosis, hyperostosis and osteitis (Chamot

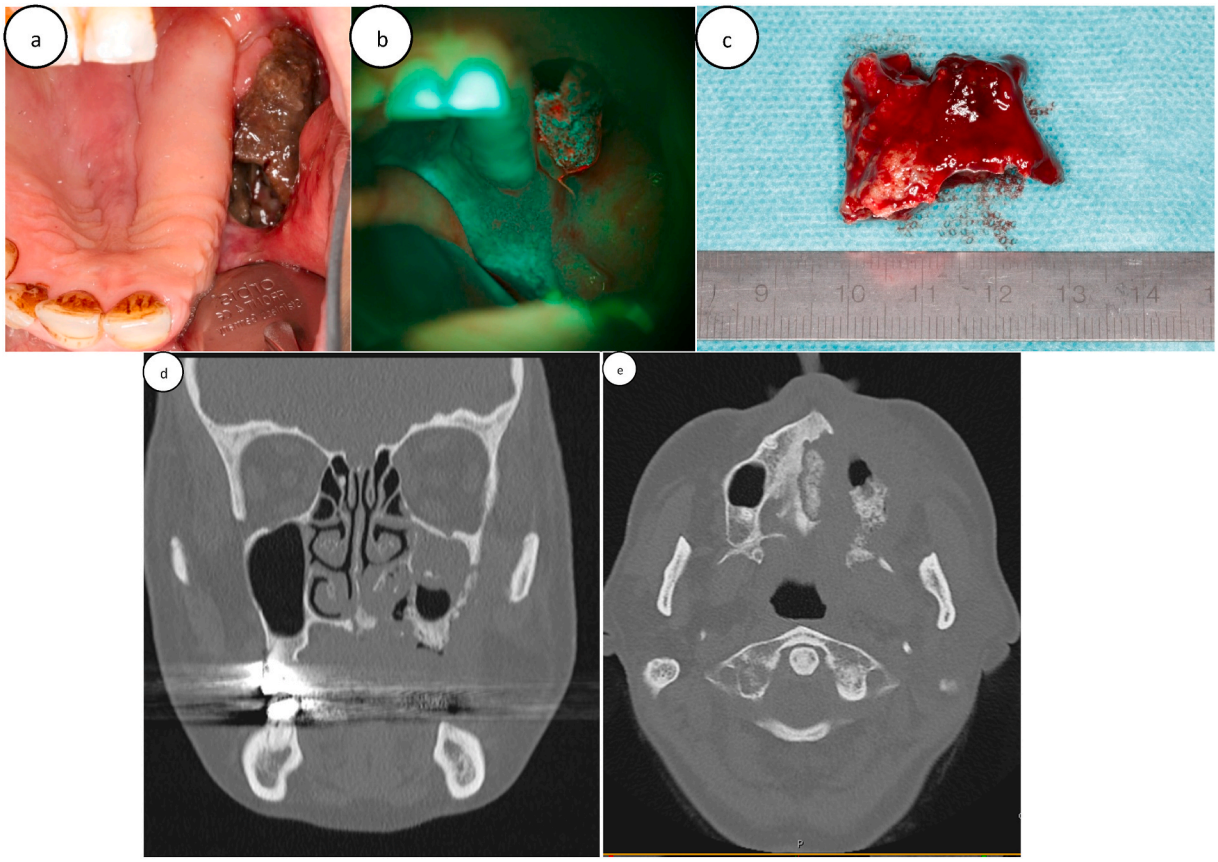

Fig. 1. (a–c). Extensive case of MRONJ in a 64-year-old patient treated with zoledronate due to osseous metastasized breast cancer a) Preoperative intraoral photograph showing a large, well-demarcated area of exposed necrotic bone in the posterior mandible. The lesion is surrounded by inflamed mucosa, indicating chronic infection and compromised local healing, characteristic of stage 3 MRONJ b) Intraoperative image taken under fluorescence illumination using a certified fluorescence lamp. Fluorescence-guided bone surgery was utilized to accurately identify and delineate necrotic bone from surrounding viable tissue. The necrotic bone appears as a non-fluorescent (dark) area, while vital bone demonstrates a green autofluorescence, enabling targeted and minimally invasive removal of devitalized structures c) Sequester after resection d) Coronal image demonstrating a bony sequestrum in the right maxilla e) Axial image demonstrating a bony sequestrum in the right maxilla. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

et al., 1987). The symptoms neither necessarily occur all nor simultaneously (Suei et al., 2005). This contributes to the ongoing debate on whether diffuse sclerosing osteomyelitis (DSO), described earlier by various authors, represents a manifestation of SAPHO syndrome or constitutes a distinct entity (Björkstén et al., 1978; Kahn et al., 1994; Garcia-Marin et al., 1996; Eyrich et al., 1999; Fleuridas et al., 2002; Suei et al., 2005). 1–10 % of SAPHO syndrome patients experience mandibular lesions, which are often extensive (Nguyen et al., 2012).

Conservative treatment of SAPHO syndrome is often recommended (Zemann et al., 2011; Zemann et al., 2011), to provide relief from the at times debilitating pain associated with SAPHO syndrome.

Since 2004, multiple case reports have documented the potential benefits of antiresorptive drug therapy in patients with SAPHO syndrome (Amital et al., 2004; Kopterides et al., 2004; Ichikawa et al., 2009; Amital et al., 2004, Kopterides et al., 2004, Ichikawa et al., 2009) as they lead to a reduction of pain and improvement in function and well-being (Kerrison et al., 2004). However, to date no generally accepted treatment strategy exists as the majority of reports are limited to anecdotal cases or small case series.

Still, a survey conducted in 2020 among 78 physicians of a wide geographic representation showed that treatment approaches were overall similar among the rheumatology and dermatology communities, including non-steroidal anti-inflammatory drugs (76.6 %), conventional DMARDs (Disease-modifying anti-rheumatic drugs, 57.1 %), anti-TNF biologic therapy (75.3 %) and bisphosphonates (48.1 %). European and Middle East responders reported a significantly more common use of bisphosphonates (63.6 %, n = 7 and 62.5 %, n = 15, respectively) compared to Japanese responders (n = 11, 39.3 %) (Furer et al., 2020; Winter et al., 2025 recommended intravenous treatment as second-line treatment in patients with SAPHO syndrome.

2.1.3. *Diffuse sclerosing osteomyelitis (DSO)*

As noted above, diffuse sclerosing osteomyelitis may manifest as a component of SAPHO syndrome or arise as an isolated condition. Clinically, it is characterized by the triad of recurrent severe pain, facial swelling, and trismus. (Matharu et al., 2020).

Typically, DSO is diagnosed based on the combination of anamnestic information (recurrent severe episodes of pain, swelling and trismus), absence of fistula formation or suppuration in clinical examination, the tendency of localized increasing sclerotic bone formation and no bacterial colonisation in microbiological testing (Otto et al., 2018).

Former treatment protocols such as steroid or analgesic medication and corticotomies showed poor to frustrating outcome results. Therefore, in the early 2000s several research groups tested promising therapy options for the treatment of DSO with bisphosphonates (Montonen et al., 2001; Soubrier et al., 2001; Sugata et al., 2003; Compeyrot-Lacassagne et al., 2007; Yamazaki et al., 2007; Kuijpers et al., 2011).

Montonen et al. evaluated the pain reduction in 10 patients with DSO who were treated with clodronate (a non-nitrogen-containing bisphosphonate) or placebo in the mid 1990s, detecting a statistically significant lower pain intensity in the clodronate group 6 months after treatment (Montonen et al., 2001).

Kuijpers et al. concluded, that bisphosphonate infusions can lead to long-lasting pain-free intervals and are a promising treatment alternative after treating seven patients.

Our Munich-based research group treated eleven patients with DSO with single-shot infusions of ibandronate (6 mg), which was well tolerated and resulted in distinct, long lasting improvement in subjective pain levels based on VAS scores. Furthermore, no side effects have been observed, and in particular there has been no case of MRONJ. Additionally, bone scintigraphy records displayed less inflammatory activity of the affected areas in the mandible using (Otto et al., 2015).

In 2018, our research group successfully treated DSO of the left mandible in a 64-year old woman with two subcutaneous injections of 60 mg denosumab. The administration led to a decrease of VAS pain levels from 9 to 1 within 7–10 days after the first, and from 5 to 6 to 0–1 within 7 days after the second injection. Also, Hallmer et al., 2018 reported about two DSO cases treated with denosumab, which resulted in significant pain relief in both patients (Otto et al., 2015; Weinstein, 2006; Frank et al., 2024).

Summarized, not only the bisphosphonate ibandronate, but probably also denosumab treatment may offer a promising treatment option for attaining stable, pain-free conditions in patients suffering from DSO.

Effects of ibandronat in a 25-year old patient, treated due to DSO in our department, is shown in Fig. 2.

2.1.4. Fibrous dysplasia (FD)

Fibrous dysplasia is a benign monostotic or polyostotic disease with predilection of long bones, ribs and craniofacial skeleton. It might occur solely or associated with McCune-Albright-Syndrome (MAS) (Burke et al., 2017).

FD is caused by a mutation in the GNAS1-gene leading to replacement of normal bone with fibrous tissue and abnormal bone presented as woven bone (Florez et al., 2016). Symptoms may vary from asymptomatic local lesions to severe bone deformity which can lead to facial deformation (Ricalde and Horswell, 2001). Facial deformity is the primary reason for seeking treatment and might even lead to nerve compression and sensory loss (Menon et al., 2013; Chapurlat et al., 2004).

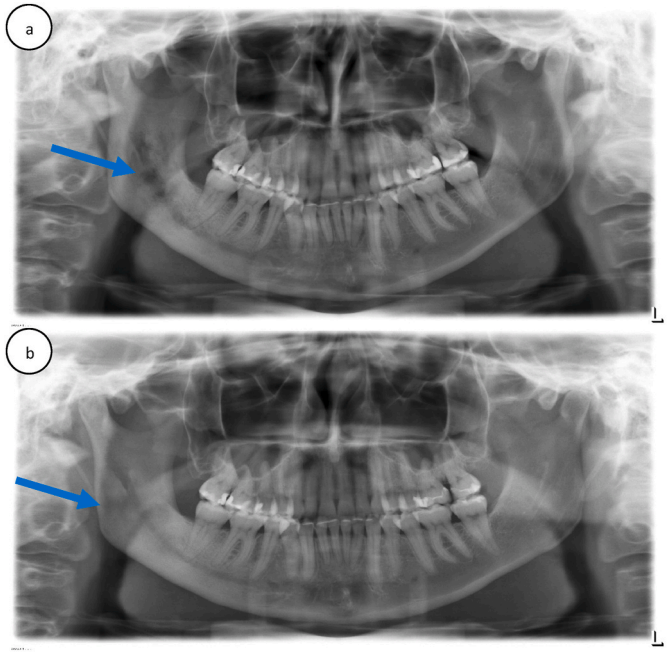

Fig. 2. Panoramic radiograph of a 25-year old female patients with DSO left side a) Patient before administration of ibandronate 6 mg in an acute pain episode (osteolytic remodeling zones and blurred nerve canal) b) Patient 6 months after administration of one dose ibandronate 6 mg (reduced bone remodeling zones and increased sclerotic areas).

Beside surgical treatment ever since the 1990s, the use of various bisphosphonates to inhibit osteoclast activity in FD patients was discussed to decrease pain, lower fracture risk and improve function. Several studies showed good results for pain reduction for patients with facial and non-facial FD (Weinstein, 1997; Chapurlat et al., 1997; Benhamou et al., 2014; de Boysson et al., 2015). In case of non-response to bisphosphonates, the monoclonal antibody tocilizumab might be an alternative (Boyce et al., 2014). On the other hand, high dose alendronate (40 mg daily) did not improve pain in a controlled trial (DiCaprio and Enneking, 2005; Kim et al., 2023).

The treatment of craniofacial fibrous dysplasia (CFFD) aims to prevent functional loss (especially hearing and vision), arrest or reduce physical disfigurement, prevent secondary deformity and minimize long-term morbidity from CFFD and its treatment (Javaid et al., 2019; Couturier et al., 2017; Wentworth et al., 2025).

For CFFD, a case study of Courturier et al. showed stable conditions for two and favourable evolution for three of five patients treated with intravenous pamidronate Within one to six months following the start of treatment, the patient's headache and vestibular symptoms had subsided. (Chronopoulos et al., 2018).

The consensus statement from the FD/MAS (McCune-Albright-syndrom) international consortium 2019 proposed pamidronate and zoledronate for persistent, moderate to severe pain as defined by VAS score of >3/10. If pain reduction through bisphosphonate treatment is justified after initial dosing (which may consist of several doses),subsequent intervals should be determined based on the patient's need for analgesia and their response to previous doses. Dose intervals should be progressively extended over time. Additionally, the FD/MAS Consortium advises that alternative antiresorptive therapies, including denosumab, be administered exclusively in specialized centers, given the limited data on appropriate dosing, efficacy, and safety (Couturier et al., 2017).

Despite their use, the effectiveness of bisphosphonates in modulating disease activity, especially concerning lesion size and progression, remains uncertain.[74]. Further studies are needed to determine their ability to increase local bone density or prevent complications. Summarized, a medico-surgical approach depending on severity of FD, extension of lesion and symptoms seems to be favourable (Berenson et al., 1996; Black et al., 1996; Cvjetinovic et al., 2020; Francis, 1969; Francis and Briner, 1973; Hong et al., 2020).

2.1.5. Osteoradionecrosis (ORN)

Osteoradionecrosis of the jaw is a severe chronic disease and a dangerous complication of irradiation in head and neck cancer (Ewing, 1926). It was first described by Ewing 1926; Chrcanovic et al., 2010). ORN predominantly affects the mandible, an area of reduced blood supply, and may lead to pain, fistula formation, pathological fractures, and sequestration of the affected bone (Epstein et al., 1984).

ORN exhibits substantial heterogeneity in terms of classification and treatment approaches; nevertheless, the majority of cases are eventually treated by surgical excision of necrotic bone (Notani et al., 2003; Delanian et al., 2005; Oh et al., 2009; Jacobson et al., 2010; Reuther et al., 2003). Nevertheless, conventional surgical management of ORN frequently yields suboptimal results, and complete resolution is achieved in only a minority of cases (Delanian et al., 2005; Vozenin-Brotons et al., 2003).

The exact pathomechanisms inducing ORN are still to be analysed. Tissue hypoxia and its downstream effects have long been hypothesized as the primary underlying mechanism.A new theory proposes that radiation induces fibroatrophic mechanisms including free radical formation, endothelial dysfunction, inflammation, microvascular thrombosis, fibrosis and remodeling and finally bone and tissue necrosis. Consequently, ORN might be caused by radiation-induced fibrosis (Delanian et al., 2011; Delanian and Lefaix, 2004).

This inspired a new treatment: the concept of antioxidant and

antifibrotic treatment of fibro-atrophy - PENTOCLO, a combination of pentoxifylline, α-tocopherol and clodronate, a non-nitrogen containing bisphosphonate (McLeod et al., 2012; Fromigué and Body, 2002). Therapy involving pentoxifylline and tocopherol (PENTO) has been described earlier (McLeod et al., 2012).

Unlike other bisphosphonates, clodronate has been shown to stimulate osteoblast function and promote bone formation (Rivero et al., 2017).

The Delanian group in France has published several studies on PENTOCLO treatment, demonstrating its effectiveness compared with placebo and single-agent therapies for radiation-induced trauma at other body sites, as well as for mucosal and bone healing, with significant symptom improvement (McLeod et al., 2012; Delanian and Lefaix, 2004).

In their 2011 study, 54 patients were treated with a combination of pentoxifylline, tocopherol, clodronate, prednisone and ciprofloxacin. The treatment led to a reduction of local pain, fistula, osteitis and trismus and improved overall prognosis (McLeod et al., 2012).

However, Rivero et al. urged that "although there are some promising studies on the use of PENTOCLO in ORN management, many have come from a single research group to date. Histopathologic and biologic research on the molecular level for ORN with RIF (Radiation induced fibrosis) should be executed in a well-designed animal experimental model."(Jaffe and Lichtenstein, 1942).

Summarized, for cancer survivors suffering from ORN, the PENTOCLO regimen offers a potentially supportive therapy (Shaw et al., 2025).

If randomized trials confirm all these findings, the described PENTOCLO protocol might not only be used as a standard treatment option for ORN but may also be used to prevent ORN.

2.2. Use of antiresorptive drugs in odontogenic tumors of the jaw

2.2.1. Treatment of aneurysmal bone cyst (ABC)

Aneurysmal bone cyst is described as a rare lesion of the long bones (Dormans et al., 2004) and may already be very extensive at initial diagnosis. Similarly, the aneurysmal bone cyst is associated with a high recurrence rate and although it is a benign lesion of the jawbone, operations can be extensive (Maximen et al., 2022). Due to the histopathological similarities of aneurysmal bone cysts and central giant cell granulomas, several studies using denosumab as conservative treatment in aneurysmal bone cyst are described in literature (Dürr et al., 2019; Dürr et al., 2019 reviewed 6 patients with ABC in critical anatomical locations treated with denosumab (Kurucu et al., 2018). One patient suffered from recurrence and the others stayed stable. Due to severe rebound hypercalcemia months after discontinuation of denosumab, the authors state that denosumab may be an adjuvant treatment option, but should be used carefully to avoid severe side effects. Another evaluation of 9 cases showed reduction of pain and volume reduction up to 82 % in medium follow-up of 15 months (Pan and Boyce, 2021). However, the clinical use of denosumab is impacted by side effects related to post-discontinuation rebound, particularly in children. The use of denosumab in ABC should be considered carefully and should preferably be used in anatomically critical localizations (De Lange et al., 2007; Wang et al., 2023). After the application of denosumab a sealing infusion with bisphosphonates should be applied to avoid rebound effects.

2.2.2. Central giant cell tumor (CGCG)

CGCG is a rare benign lesion of the jaw with unknown etiology and accounts for about 7 % of all lesions of the jaw (Kaffe et al., 1996). It occurs preferentially in children and young people, with the female sex being particularly affected (Austin et al., 1959). Trauma or reactive reactions after tooth extraction are discussed in the literature as the pathophysiological cause (Chuong et al., 1986). Depending on the course of the disease, two types can be distinguished: the aggressive type and the non-aggressive type. Chuong et al., 1986 already described the aggressive type with a size >5 cm, root resorptions, rapid growth, breakthrough of the cortical bone and with a high risk of recurrence after surgical removal (Chrcanovic et al., 2019). Multiple lesions are often associated with Noonan syndrome or cherubism. Differentially, hyperparathyroidism must always be considered, which can be diagnosed by endocrinological diagnostics. The overall recurrence rate in osteoclastic giant cell granulomas is 26.3 % (Adami et al., 2019). 3D imaging is recommended in all cases. Therapeutically, different concepts described in the literature exist:

Conservative treatment includes pharmacologic agents such as calcitonin, corticosteroids, or alpha-interferon.

Surgical intervention is another therapeutic option. Large post-resection defects may require reconstruction with osteomyocutaneous flaps, for instance using fibula or scapula grafts. Likewise, drug therapy with the RANK-ligand inhibitor Denosumab, which represents the standard of care for osteoporosis,can be considered as an alternative treatment (Choe et al., 2021; Choe et al., 2021 treated six children with CGCG with denosumab and suggest denosumab to be a favourable treatment option (Pogrel, 2020). Another case series observed calcification and regression of clinical symptoms with denosumab administration, but no size regression of the tumor (Rhou et al., 2022). On the other hand, a long-term follow-up study of six years reported high incidence of recurrence (50 %) in this patient group (Camarini and de Souza Tolentino, 2022). A systematic review of treatment options in CGCG came to the conclusion, that antiresorptive therapy in CGCG can lead to reduced tumor size (Reichenberger et al., 2012). In a phase II trial, Hassing et al. (2025a,b) demonstrated that monthly intralesional low-dose denosumab (≥8 injections) resulted in a complete remission rate of approximately 78 % and a low recurrence rate in patients with CGCG.

2.2.3. Cherubism

Cherubism of the jaw is a rare autosomal dominant disorder. Clinically, it is characterized by symmetrical expansion of the mandible, which usually begins before puberty and can recede self-limitingly after puberty (Machado et al., 2017). Symptoms can range from asymptomatic swelling to disfiguring bone deformities that can lead to pain. The concerned locus was mapped to chromosome 4p16 and a mismatch mutation in the gene encoding the adapter protein *SH3PB2* (SH3-domain binding protein 2) has been identified (Bar et al., 2020). Different therapeutic approaches exist and include conservative observational, surgical or pharmacological treatment (Bird et al., 2011). Based on the fact that CGCG responds very well to denosumab and that it is known that osteoclasts in cherubism are very sensitive to the RANKL receptor, a possible therapeutic approach with denosumab is conceivable. Only case reports and case series are availabe. Bar et al., 2020 report about two cases of cherubism in childhood treated with denosumab and positive effects (Bar et al., 2020).We can also report about a case of a 12 years old girl suffering from cherubism. After several surgical attempts to control the symptoms, the patient finally received denosumab.

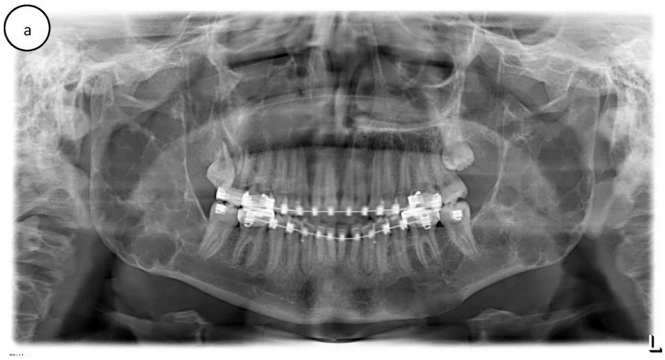

Fig. 3. Patient with Cherubism Panoramic radiograph with typical bony expansion of the mandible and osteolysis zones.

Panoramic radiographs of this patient are shown in Fig. 3. As cherubism is a very rare disease, there are only very few case reports on the use of antiresorptive drugs in this patient population. Further studies with a higher number of patients are to get a valid insight about the effect of AR in cherubism.

2.3. Antiresorptive therapy in oncology

2.3.1. Multiple myeloma (MM)

With an annual incidence of 60–70 cases per million, Multiple Myeloma is one of the most common hematologic malignancies (Smith and Yong, 2013; Bolzoni et al., 2013). MM cells are located in the bone marrow of the whole skeleton and produce mediators that stimulate osteoclasts (Epstein et al., 1987) and therefore can cause severe osteoclastic lesions, including cases in the orofacial region. In more than 10 % of the affected patients, the first manifestation of the disease occurs in maxillofacial or, even more frequently, in the mandibular bone (Witt et al., 1997; Theodorou et al., 2003; Stoopler et al., 2007; Locke and Morgan, 2012). To prevent skeletal related events, MM-associated osteoclastic lesions should be treated with antiresorptive drugs.

Fig. 4 shows the panoramic radiography and PET-CT of a 67-year old patient with a prominent osteolytic MM lesions of the mandible. As shown in Fig. 4 the root of tooth 47 is severly resorbed. In this case, the patient was treated with 6 mg ibandronate for three years and developed a regression of symptoms. The patient remained free of MRONJ and disease-free recurrence after 3-years-follow-up (Troeltzsch et al., 2012). Fig. 2 shows panoramic radiography after three years.

In 2012 Locke and Morgan already argued that osteoclastic lesions associated with MM requiring therapy in patients lacking bone disease can be treated successfully with bisphosphonates (Then et al., 2012).

However, in MM patients who are treated with high-dose chemotherapy and autologous stem cell transplantation, the risk of MRONJ development is elevated (Berenson et al., 1996). In those patients, preventive measurements such as profound dental hygiene and regular dental examinations to reduce the risk of MRONJ are of utmost importance (Ward et al., 2024).

Fig. 4 shows panoramic radiography of a patient suffering from plasmocytoma infiltration of the mandible.

2.3.2. Tumor infiltration of jaw bone/metastasis in jaw

The most common tumor of the head and neck region is squamous cell carcinoma (SCC). Starting as a mutation of epithelial cells, it spreads fast into surrounding tissue and jaw bone. Treatment options range from radio-over chemotherapy to surgery. Most often, the treatment of choice includes resection and reconstruction.

Surgical interventions in the head and neck region are frequently accompanied by substantial side effects and can adversely impact quality of life, given the potential compromise of numerous vital functions.The question remains whether a non-surgical approach might be an alternative.

For multiple oncologic diseases that can infiltrate bone or cause bone metastasis such as breast or prostate cancer, ARD are a standard treatment when bone is affected. They decrease bone resorption and new osteoclastic lesions, significantly prevent fractures and other skeletal related events and improve quality of life of those patients by alleviating pain (Black et al., 2006; Fleisch et al., 2002; Mizuta et al., 2023).

As treatment with ARD in MM patients showed promising results, it should also be considered in other oncological diseases that infiltrate the jaw such as SCC. Wypij et al., 2008 showed in an in vivo and in vitro study the efficiacy of zoledronate for treating OSCC in cats. They

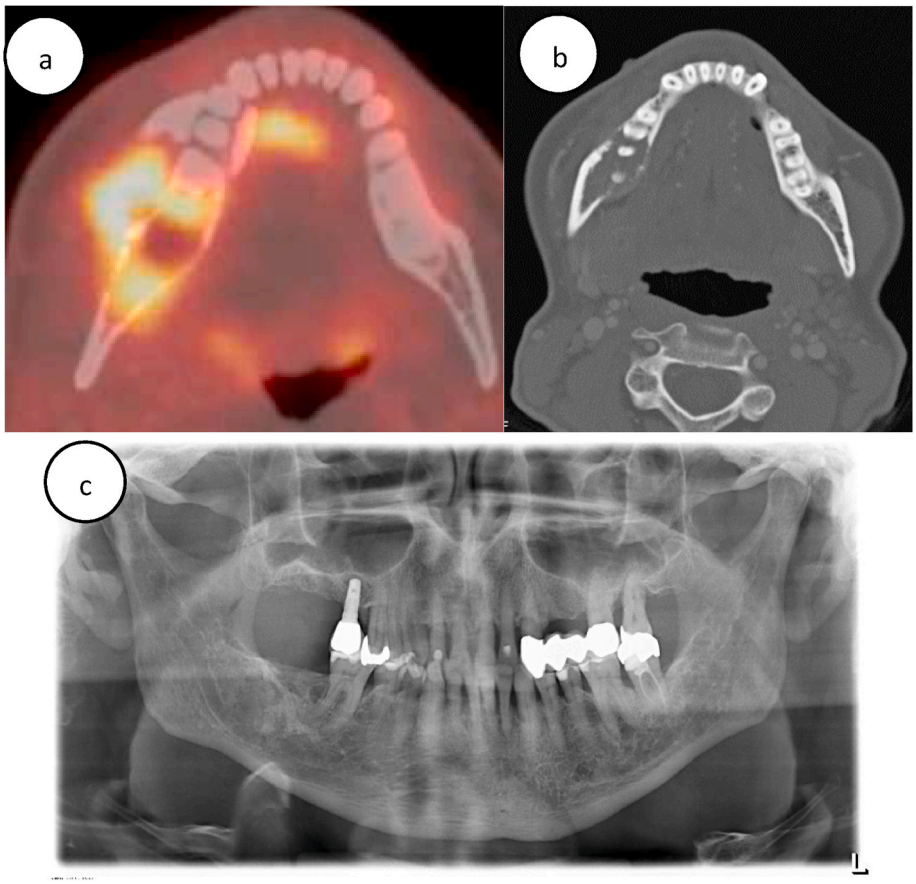

Fig. 4. Panoramic radiographic and PET-(FDG)-CT of a 82-year old patient with osteolytic MM lesion of the mandible a) FDG-emission computed tomography of MM lesion of the jaw b) native computed tomography of MM lesion c) Three-year follow up after applying ibandronate.

reported that zoledronate decelerated tumor growth as well as pathological bone turn over associated with OSCC (Wypij et al., 2008).

From a surgical perspective, the administration of ARD increases the risk of potentially fatal complications such as MRONJ. On the other hand, from an oncological perspective, ARD might offer a non-surgical treatment approach on oncologic bone diseases in the head and neck region. They possibly could stop or slow down tumor growth and spreading until surgery is performed. Especially in older patients or severe cases where risks and consequences of surgery outweigh potential benefits, alternatives to classical surgical approaches will be needed in the future.

Different tumor-entities like breast cancer, prostate cancer, multiple myeloma and lung cancer can develop osseous metastases. Typically, they metastasize in the long bones, skull bone, pelvic bone or spine. In rare cases they can metastasize into the jaw bone and can cause symptoms like hypesthesia of the trigeminal nerve there (Lorange et al., 2023).

The option to treat bone infiltration tumors with ARD should be carefully pondered as following surgical interventions such as resections or reconstructions might be complicated due to the risk of MRONJ. Until now, no case reports are available for such a treatment complication. However, as reconstructions are also possible following MRONJ, there should not be a major limiting factor for surgery. The use of ARD is not recommended outside specialist centers, preferably in the context of a clinical study or trial.

Fig. 5 shows am intraoperative situs of a patient suffering from jaw metastasis of an osseous metastasized breast cancer. This patient was treated by removal of tooth 48 and administration of ARD, resulting in regression of symptoms.

3. Discussion

Antiresorptive drugs, particularly bisphosphonates and denosumab, have demonstrated substantial benefits in the management of osteoporosis, metastatic bone disease, and selected maxillofacial pathologies (Black et al., 2007). They significantly reduce fracture incidence and improve quality of life, but their potential to induce medication-related osteonecrosis of the jaw (MRONJ) has created concern among oral and maxillofacial surgeons. This narrative review highlights both the therapeutic opportunities and the risks associated with antiresorptive treatment in the craniofacial region. Ultimately, the decision to prescribe these medications must balance their proven systemic benefits with the rare but severe complications that may affect the jaw. Preventive measures, early diagnosis, and interdisciplinary collaboration remain the cornerstones of safe and effective patient care. Recent syntheses refine both benefit–risk appraisal and procedural decision-making with antiresorptives. Across mixed real-world cohorts, a 2025 population-based analysis found MRONJ incidences of ~0.3 % with low-dose (osteoporosis) versus ~9 % with high-dose (oncology) antiresorptives, underscoring dose and indication as major risk drivers. In cancer populations, a 2025 study reported higher cumulative MRONJ incidence with denosumab compared with bisphosphonates (11.6 % vs. 2.8 %), and the highest with sequential/combined exposure (16.3 %), which is pertinent to long-term skeletal management pathways (Kujanpää et al., 2025; Brunner et al., 2025). For maxillofacial indications, a 2024 systematic review of central giant cell granuloma (CGCG) supports denosumab's clinical activity but highlights heterogeneity in dosing, recurrence risk, and adverse events—calling for standardized regimens (Hassing et al., 2025a,b). Emerging strategies such as monthly low-dose intralesional denosumab (≥8 injections) achieved 78 % complete remissions with low early recurrence in a 2025 phase II study, though confirmatory randomized trials are needed. For aneurysmal bone cysts (ABC), contemporary reviews corroborate symptomatic and volumetric responses to denosumab but emphasize post-discontinuation rebound (notably hypercalcemia in children), arguing for great caution and "sealing" strategies when therapy is stopped (Sandhu et al., 2024).

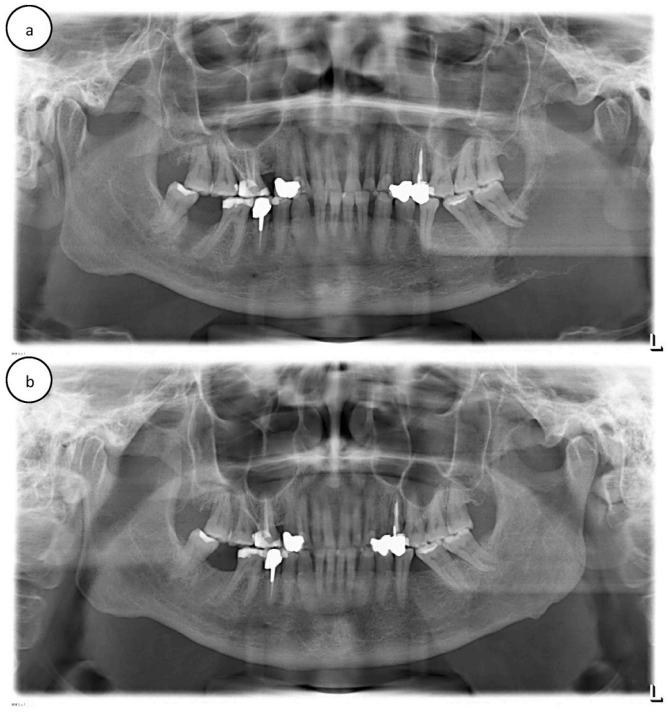

Fig. 5. Panoramic radiograph of a 64-year old female patient with osseous metastatic breast cancer and bone metastasis in the left mandible jaw a) Extensive osteolytic metastasis in the left mandible jaw angle b) Panoramic radiograph 3 years after administration of denosumab (120 mg).

3.1. Limitations

This review is limited by its narrative design and the predominance of case reports and small series in the available literature on rare maxillofacial diseases. High-quality randomized controlled trials are scarce, and much of the evidence stems from retrospective or observational studies. Consequently, the conclusions drawn should be interpreted with caution, and further prospective studies are needed to confirm efficacy and safety of antiresorptive therapy in maxillofacial indications.

4. Conclusion

While many osteologists and oncologists appreciate the value of ARD, they can show serious adverse reaction in maxillofacial region known as MRONJ.

On the other hand, lately many different treatment strategies, especially for rare chronic diseases such as SAPHO, DSO, FD and others use the enormous anti-osteoclastic potential of ARD and show promising results.

In various studies they led to pain reduction, reduced the extension of bone lesions, and thereby both improved patients' quality of life and often superseded the necessity of surgical intervention.

We conclude that ARD offer the possibility of effective new treatment strategies, especially for patients with rare diseases who formerly lack the proper treatment for such diseases.

As a matter of course, the risk of development of MRONJ should be carefully pondered for each patient individually. Patients must be informed about risks and concerns associated with ARD treatment and should undergo dental evaluation prior to treatment. The better understanding of the etiology of MRONJ lately led to promising preventive measurements, which should always be part of treatment protocols as soon as the use of AR drugs becomes even likely.

4.1. Recommendations for practice

The use of antiresorptive therapy should be considered carefully and individually in every patient. Prior to initiation of treatment, dental evaluation and optimization of oral health are strongly advised. Patients should be informed about both the benefits and risks, including the possibility of MRONJ, to support shared decision-making. This review also demonstrates that patients with rare bone diseases may benefit from antiresorptive drugs in terms of quality of life. Thus, antiresorptive agents are not only an essential component of therapy in osteoporosis and in osseous metastatic malignancies, but they may also play an important therapeutic role in the management of rare conditions within oral and maxillofacial surgery. Close interdisciplinary communication between prescribers and dental or maxillofacial specialists is recommended throughout therapy. In high-risk patients, management should ideally be coordinated in specialized centers.

Informed consent

Written informed consent was obtained from the patients for the publication of case details and clinical images.

Funding

No funding was received for this work.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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