Medication Management of Selected Pathological Jaw Lesions

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KEYWORDS

• Jaw lesions • Nonsurgical • Oral surgery • ABC • CGCG • Fibrous dysplasia
• Paget's disease of bone • MRONJ

KEY POINTS

- Most jaw lesions are treated surgically, but there is evidence for treating select jaw lesions pharmaceutically.
- Most jaw lesions are osteolytic, so drugs that target the physiology of bone turnover are effective.
- Bisphosphonates and denosumab are a common group of drugs that can be used to treat select bone lesions, but they can also cause medication-related osteonecrosis of the jaw.
- Necrosis of the jaw either owing to medications or radiation can also be treated pharmaceutically.

INTRODUCTION

Most jaw lesions are treated by surgical removal. Minimizing or eliminating surgical trauma is beneficial to patients whenever possible. Interest is growing in nonsurgical treatment alternatives, especially in pharmaceutical therapy, for surgery refractory or surgery contraindicated patients. Some of the evidence is taken from orthopedic literature studying extragnathic lesions that also occur in the jaw. Some drugs work by targeting a cellular mechanism antithetical to the pathophysiology of a specific lesion. Other drugs work by promoting bone fill through global mechanisms because jaw lesions are predominantly osteolytic. Drugs that target the osteoblast–osteoclast relationship to build bone or prevent bone resorption are especially common. Select jaw lesions with well-studied pharmaceutical treatments are presented.

CENTRAL GIANT CELL GRANULOMA

Nonsurgical treatments for central giant cell granulomas (CGCG) are the most studied in jaw lesions. CGCGs are benign, locally destructive intraosseous lesions predominantly found in the anterior mandible but can occur anywhere in the jaw bones.[1,2] First described by Jaffe in 1953 as a reparative non-neoplastic lesion, it has a female predilection and occurs most commonly in young people between 10 and 25 years of age.[3] It is characterized microscopically by proliferating giant cells in a stroma of oval and spindle mesenchymal cells, especially around areas of hemorrhage.[2,4] Radiographically, CGCGs are osteolytic or radiolucent, with the ability to displace teeth and expand or perforate gnathic contours, and may be unilocular or multilocular. In 1986, Chuong distinguished between 2 types of CGCGs, namely, nonaggressive and aggressive.[5] The former describes an indolent lesion that usually presents with painless asymptomatic swelling of the jaw but aggressive lesions were described as showing more neoplastic characteristics including presence of pain, paresthesia, root resorption, rapid growth, cortical perforation, and high recurrence after curettage. Histologically, however, the 2 types of CGCGs were indistinguishable.[2,4] Multiple lesions are rare but possible, and have bene associated

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with genetic syndromes especially Noonan syndrome, which is associated with growth deformities, cardiac problems, and coagulopathies.[6] The recognition of the aggressive variant and syndromic links call into question if CGCGs are entirely reparative in nature. Although the exact etiology of CGCG is unclear, it is hypothesized that the actual proliferating cells in CGCGs are spindle cells in the stroma, which act to recruit giant cells from adjacent vasculature. Although abundant, giant cells seem to be histologically non-neoplastic under a microscope. Nevertheless, the abundant giant cells are reactive to RANKL, and when activated promote osteoclastogenesis, thereby producing a lysis of regional bone.[2]

The most common treatment modality is surgery. Enucleation alone has been shown to exhibit up to 72% recurrence.[4] Resection had much high long-term success, but still can have recurrence.[7] Nonsurgical treatment modalities are well studied for CGCGs.

Intralesional Steroid Injections in Central Giant Cell Granulomas

In 1988, Jacoway was the first to report treatment of CGCG with corticosteroids. Since then, numerous investigators have reported success with intralesional steroid injections as monotherapy or in combination with surgery.[2] Osterne and associates[8] reviewed 41 cases of CGCG treated with intralesional steroid between 1994 and 2011. The patients were split 20:21 male:female, with an average age of 15.9 years. There were 12 lesions in the maxilla and 29 lesions in the mandible. On follow-up (range, 7 months to 7 years), 32 (78%) were considered good responses, 6 (15%) were considered moderate responses, and 3 (7%) were considered negative responses. Seventeen patients (41%) did require additional surgical treatment; 9 (22%) underwent further osteoplasty, 5 (12%) underwent further curettage, and 3 (7%) required resection. Additionally, 3 patients (7%) received additional steroid injections on follow-up, although they did not require surgery. Predictably, when the data were stratified, nonaggressive lesions (18 [44%]) were more responsive to steroid injections. No cases had negative responses. Sixteen patients (89%) reported good response to therapy versus 2 (11%) who reported moderate response to therapy. Four patients (22%) required additional osteoplasty, 3 (17%) required additional curettage, and 2 cases required additional injections; no cases resulted in resection. Aggressive lesions (23 [56%]) showed less overall but significant response to steroid injections. Sixteen patients (70%) reported a good response, 4 (17%) reported a moderate response, and 3 (13%) reported a negative response. Four patients (17%) required additional osteoplasty, 2 (9%) required additional curettage, and 3 (13%) ultimately needed resection, but it is useful to note that 14 (61%) did not require surgical treatment after corticosteroid therapy.[8] From these data, it can be inferred that there may be a clinical benefit to use of corticosteroid intralesional injections in both aggressive and nonaggressive lesions.

The mechanism of corticosteroids' therapeutic effect is not well-understood. All CGCG lesions seem to express receptors for glucocorticoids to some degree.[9] On one hand, dexamethasone was shown in vitro to stimulate osteoclast precursor differentiation and proliferation.[10] On the other hand, it seems like corticosteroids induce apoptosis of osteoclastlike cells.[11] The net effect clinically sees to be the inhibition of bone resorption.[1,2,11]

Most commonly, the steroid used for injection was triamcinolone acetonide (10 mg/mL) or triamcinolone hexacetonide (20 mg/mL), diluted with equal parts lidocaine or marcaine, and injected weekly or biweekly for 6 weeks. Two milliliters of injection fluid was generally injected for every 2 cm of radiolucency, with 1 mL of fluid for every 1 cm^3 of lesion was used reported. Common side effects include injection site pain, bleeding, bruising, infection, contact dermatitis (generally only if there is a preservative), and impaired wound healing. Systemic side effects are unlikely due to the localized route of delivery, but can potentially include allergic reactions, glucose intolerance, Cushing syndrome, hirsutism, osteoporosis, muscle weakness, tendon rupture, and cardiac and neurologic problems.[1,12]

Calcitonin in Central Giant Cell Granulomas

Calcitonin is a peptide hormone produced primarily by the thyroid parafollicular cells that regulate blood calcium levels by directly inhibiting the activity of osteoclasts and decreasing the activity of calcium resorption in the kidneys.[13] Calcitonin has also been demonstrated to interfere with osteoclast precursor differentiation. Calcitonin receptors are found in osteoclast cells and the giant cells in CGCG have been shown to be osteoclasts.[2,14] Therefore, calcitonin should have a direct inhibitive effect in decreasing bone resorptive activity of CGCG giant cells. Both human and salmon calcitonin have been implicated in CGCG therapy, with the latter being approximately 1.5× as potent, but with the former being potentially less immunogenic. In vitro studies showed

no difference in bone-resorptive effects between human and salmon calcitonin.[15] Calcitonin can be injected subcutaneously 50 to 100 IU/d or sprayed nasally 100 to 200 IU/d. There is no consensus regarding the efficacy injection versus nasal spray, but bioavailability is estimated to be approximately 70% for injections and 3% to 25% for nasal spray.[2] Harris[16] was the first to suggest the use of human and salmon calcitonin via injection (100 IU/d) and nasal spray (200 IU/d) in 4 patients with CGCG. He claimed complete remission, but 2 patients had to undergo additional surgery. Studies following Harris generally showed partial to complete remission with varying calcitonin regimen.[2] However, in the largest of such studies by De Lange,[2] 14 patients with CGCG treated by salmon nasal spray 200 IU/d showed no response to only partial remission. The inconsistency in the clinical efficacy of calcitonin therapy for CGCG may be related to varying expressions of calcitonin receptors in CGCG lesions. Vered and coworkers[9] observed that only 23 of 41 CGCG lesions stained positive for calcitonin receptors, and of the lesions that were positive, the intensity of staining varied. Side effects can be inferred from the use of calcitonin subcutaneous injections for osteoporosis, which include nausea, abdominal pain, diarrhea, vomiting, flushing, injection site swelling or redness, salty taste in the mouth, increased urination, or loss of appetite.[17]

Interferon in Central Giant Cell Granulomas

Interferon (IFN) is a cellular mediator that has antiviral and antiangiogenic effects.[2] Some investigators have observed that CGCG are associated with high vascularity and have speculated that decreasing vascular growth to the lesions may act to suppress lesion proliferation. An in vitro study with porcine mesenchymal stem cells also showed that IFN stimulated differentiation of precursors to osteoblasts. The efficacy of IFN in literature is promising. De Lange[2] and associates presented 6 studies totaling 32 patients in 2006. All showed arrest or slowing of lesion growth; however, only 2 of 6 studies claimed complete remission. Three of the 6 studies had patients undergo additional surgery after IFN therapy. It is hypothesized that IFN's antiangiogenic and bone-forming effects can terminate rapid growth in CGCG, but because there are no direct effects on the proliferating cells, complete remission is unlikely in most cases. IFN is given as a subcutaneous injection 1×10^6 to 9×10^6 IU per day for 2 to 14 months.

The use of IFN is also limited by its well-known side effects, including headache, fatigue, diarrhea, upset stomach, appetite loss, dizziness, xerostomia, dysgeusia, nausea/vomiting, and, most important, pancytopenia. Blood counts should be monitored regularly during therapy. Liver damage has also been reported. IFN is contraindicated in patients with autoimmune or decompensated liver disease, pregnancy, and known hypersensitivity reactions.[1] Therefore, surgery is preferred over or used in combination with IFN. IFN has rarely been used as monotherapy.

Bisphosphonates and Denosumab in Central Giant Cell Granulomas

Antiresorptives are medications that prevent bone resorption and include bisphosphonates (eg, zoledronate) and monoclonal antibodies that inhibit the osteoclast activator RANKL (eg, denosumab). It is intuitively sound that lytic lesions such as CGCG should respond to antiresorptive therapy, and in fact bisphosphonates will be making multiple appearances throughout this write up. Bisphosphonates being the older of the 2 are also used to strengthen bone in a myriad of destructive bone diseases such as osteoporosis and metastatic bone disease. Bisphosphonates are small molecules with a structure similar to inorganic phosphate and they work in 2 main ways. First, bisphosphonates bind strongly to the mineral component of bone thereby disrupting the normal process of conversion between amorphous calcium and phosphate molecules and crystal hydroxyapatite. Second, they disrupt osteoclasts intracellularly, eventually inducing programmed cell death. There is also evidence to suggest that they downregulate osteoclast precursors. Their strong binding affinity to bone allows them to stay embedded in bone, being effective years after administration.[18] Denosumab on the other hand was created after discovery of the RANK/RANKL system between stromal cells and osteoclast precursors to activate osteoclasts. Denosumab is a monoclonal antibody that disrupts this interaction, thereby downregulating the availability of activated osteoclasts. The effect of denosumab is much shorter and also stronger compared with bisphosphonates.[18]

Landesberg and colleagues[19] reported 3 cases of use of intravenous bisphosphonate therapy with varying degree of success. One patient was treated with a single treatment of 4 mg zoledronic acid and lesion showed complete regression after 6 months. The second patient was treated by 2 treatments of 90 mg pamidronate at 6 months intervals, which resulted in a 30% decrease in lesion size on a computed tomography scan. The patient was then lost to follow-up. The third patient

received 3 doses of 4 mg zoledronic acid at yearly intervals. The lesion stabilized but did not regress. The patient ended up requiring surgical excision. In the pediatric population, alternatives to surgery are preferred when possible; however, antiresorptives are not often used owing to concerns of skeletal growth disruption. However, in cases where the initial surgery failed to achieve adequate resolution, Chien and associates[20] were able to describe 4 pediatric patients with CGCG treated with zoledronic acid, 3 of whom had resolution of lesions without need for additional therapy. Chien and associates reported that there were instances of flulike symptoms and phosphate depletion after treatment, but the therapy was generally well-tolerated without evidence of long term effects on projected anthropometric growth parameters. Choe and coworkers[21] also reported that CGCG in children can be treated by denosumab. Choe and coworkers described 2 cases where denosumab was used successfully to achieve a positive response in lesions, indicated by bone fill on CBCT and histopathologic evaluation showing viable in lieu of giant cells. One of the 2 cases also received intralesoinal corticosteroid injections. Facial deformity was also reduced for each patient. Denosumab was given monthly by 120 mg subcutaneous injections.

The most common side effects of antiresorptives include extremity pain, back pain, and headache. More serious side effects include hypocalcemia, hypophosphatemia, anemia, and osteonecrosis of the jaw. There is also concern of disruption of linear growth when used in pediatric patients. However, this is difficult to study owing to long-term follow-up and we have found no reports in literature.

In this author's opinion, the role of antiresorptives in the treatment of CGCG is supported by case studies, albeit with limited evidence. Surgery remains the first-line treatment, and in surgery-refractory cases or pediatric cases indicated for a more conservative approach, there are other pharmaceutical treatments such as intralesional steroid injections that do not have the potential to cause stunted growth or osteonecrosis of the jaw. Medication related osteonecrosis of the jaw in the dental and oral surgery community has been an active topic and its relationship to antiresorptive use before trauma to the jaw bones is well-documented. Osteonecrosis of the jaw is a rare but chronic complication that can cause prolonged morbidity to the patient, sometimes requiring extensive invasive surgery. In fact, many of the cases in literature supporting use of antiresorptives were in patients with other prior or concurrent non–antiresorptive pharmaceutical therapy.

ANEURYSMAL BONE CYST

The aneurysmal bone cyst (ABC) is, despite its name, a pseudocyst of the skeleton that occurs in the jaw in approximately 2% of cases. It is a non-neoplastic bony lytic lesion filled with blood.[22] ABCs occur mostly in the pediatric population. The etiology is unclear. Some investigators have hypothesized that ABCs are secondary lesions arising from other primary lesions of the jaw because microcysts and cysts filled with blood are also found in many other jaw lesions such as the aforementioned CGCG, Paget's disease of bone (PDOB), fibrous dysplasia (FD), and so on.[23] ABCs occur more in the mandible compared with the maxilla, with the condyle and ramus being the most common areas of occurrence.[24] In literature, the majority of cases were treated by surgical curettage or resection. Successful cryotherapy and spontaneous healing have also been observed.[24] Estimated recurrence ranges from 13.3% to 59.0% and, owing to its vascular nature and increased risk of perioperative hemorrhage, nonsurgical pharmaceutical agents have been proposed as surgical alternatives or adjuncts.[24,25]

Sclerosing Agents (Percutaneous Embolization) in Aneurysmal Bone Cysts

Sclerosing agents disable a vascular source or lesion, traditionally endovascularly. Percutaneous embolization of an ABC introduces the sclerosing agent directly into the bony cavity of the ABC. Alcoholic zein (Ethibloc) is one of the most widely used sclerosing agents. Zein is a storage protein found in corn and is thrombogenic. Dissolved in alcohol as Ethibloc, the zein component causes a local inflammatory reaction.[25] Harvey George studied patients with ABCs treated with 4.0 to 7.5 mL of alcoholic zein via direct intralesional injections. He found that 58% of patients exhibited complete resolution and 35% exhibited partial healing (with asymptomatic residual nonprogressive lytic areas) at 22 to 90 months follow-ups on a postprocedural computed tomography scan. Harvey's review did not, however, include cases of ABC in the jaw. Baldo and colleagues[26] reported a case of a 7 year old with ABC in the left mandible being treated with histoacryl. Histoacryl is *n*-butyl-2-cyanoacrylate, a resin based sclerosing agent that polymerizes upon contact with blood thereby sealing the area of the bleed. Histoacryl is used 1:1 with a lipiodol carrier to prevent premature polymerization. In the case that Baldo and associates treated, the lesion showed no sign of recurrence and the patient also underwent successful orthodontic treatment involving movement of teeth in the area of the lesion with

preservation of teeth vitality. The biggest risk of using sclerosing agents is venous drainage. Contrast or dye is injected before introducing the sclerosing agent to the control risk of unwanted sclerosing of the downstream vasculature or the creation of an embolus. Other complications reported included aseptic fistulation, infection of the bone and soft tissue, and systemic immune reactions such as fever.

Aqueous Calcium Sulfate in Aneurysmal Bone Cyst

Some consider ABCs as not only secondary lesions, but reparative lesions. Delloye and associates[27] reported healing of ABCs treated with nothing but demineralized bone and bone marrow to facilitate the reparative process. Ossification was seen in the within 3 months postoperatively. However, this procedure required surgical access that was not so different from a curettage procedure. Clayer[28] advanced this concept by injecting aqueous calcium sulfate directly into the cyst, which he hypothesized has the same osteoconductive properties within the lesion without the surgical trauma. In his pool of 15 patients, Clayer noted a 90% response rate in increased ossification of lesions by 8 weeks without surgical morbidity. He also reported a decrease in preoperative pain around the lesions in all but 1 patient. The report had a recurrence rate of 2 patients among 15 and pathologic fracture despite radiographic signs of healing. On a spectrum of treatment options, aqueous calcium sulfate is one of the more conservative treatment options.

PAGET'S DISEASE OF BONE AND CRANIOFACIAL FIBROUS DYSPLASIA

PDOB and craniofacial FD are 2 fibro-osseous conditions that have similar skeletal phenotypic presentations and have similar treatments. PDOB was first described by James Paget in 1877 and is predominantly polyostotic and predominantly in people over the age of 30.[29] It is a rare disease of bone turnover characterized by 3 distinct phases. Phase I (early) is a period of osteolysis. It is the most aggressive time of the PDOB and appears and behaves like other lytic lesions of the jaw. It is thought of as an imbalance of osteoclastic to osteoblastic activity. Phase II (intermediate) is a period of disordered bone growth. It is the most dominant phase in PDOB, where diseased phase I bone is interspersed with immature woven bone resulting in a net gain but weaker stock of bone. In phase III (late), the disease burns out. Previously late immature bone is remodeled to sclerotic hard bone, clinically presenting as multiple abnormal bone overgrowths. The etiology is not clear, with possible genetic and/or environmental factors such as bony reactions or low-grade viral infections. FD also compromises the integrity of the skeleton, but tends to be mono-ostotic rather than polyostotic. It has a well-characterized genetic basis in mutations involving the GNAS1 gene, a component of the ubiquitous G protein involved in intracellular secondary messaging. This factor explains that FD is associated with McCune–Albright syndrome, a multisystem syndromic condition with endocrine dysfunction, somatic lesions, and polyostotic FD. Similar to PDOB, normal bone architecture is disrupted by proliferation of GNAS1 mutated osteoblasts creating soft spongy bone that is predisposed to fractures. All of these patients have weakened and sometimes abnormally shaped bone, which can lead to facial deformities, pathologic fractures, and impingement of nearby nerves. Surgery is not always indicated, except for severe cases; for example, if the bony expansion is invading nearby vital structures such as the first and seventh cranial nerves, possibly leading to blindness or deafness, surgery is indicated. Without surgery, these patients are treated pharmacologically when needed.[29]

Bisphosphonates in Paget's Disease of Bone

Bisphosphonates are commonly used in conditions that weaken the skeleton such as osteoporosis and metastatic bone disease. PDOB and FD both have clinically weakened bone prone to fracture. Bisphosphonates are the mainstay for treatment of PDOB before surgery. Ralston and associates[30] conducted a systematic review of the literature on the diagnosis and treatments of Paget's disease, including the use of bisphosphonates. One meta-analysis of 418 patients showed that predominately bisphosphonate-treated patients achieved a decrease in bone pain at 45% versus 23% in placebo. Intravenous zoledronate was inferred to be the preferred agent for bone pain. Zoledronic acid (4 mg) for bone pain was found to be superior to 30 mg IV pamidronate when given on 2 consecutive days every 3 months. One other study also found that 5 mg zoledronic acid provided more pain relief than 30 mg risedronate given orally. The same study found that bone pain relapsed a lot more (10 times more with zoledronic acid and 25% more with risedronate) than biochemical relapse, suggesting there are separate mechanisms dictating the 2 entities. Ralston and coworker's review also showed that quality of life (as surrogated by the Short Form 36 physical summary score) consistently was slightly elevated

when using zoledronic acid. However, the effect was not statistically significant in any of the included articles that studied this parameter. On the effect of bisphosphonates on the incidence of pathologic fractures, Ralston and colleagues reported that there was insufficient evidence to recommend bisphosphonates for fracture prophylaxis. Similarly, insufficient evidence was found to recommend bisphosphonates for limiting the progression of osteoarthritis or for limiting progression of hearing loss. One study in Ralston and associate's data reported that 7 of 8 patients treated with etidronate or clodronate for between 1 and 6 years developed less facial deformity, as measured by facial or skull volume. For limiting neurologic symptoms, Ralston and colleagues stated that bisphosphonates may be considered, but there was no conclusive evidence. Work that studied this parameter studied bisphosphonates in conjunction with calcitonin, which has been shown independently to improve neurologic symptoms in patients with PDOB. Last, Ralston and colleagues reported that bisphosphonates are highly effective in reducing metabolic activity in PDOB, as evidenced by decreased serum alkaline phosphatase (ALP) levels. In a Cochrane review, bisphosphonates achieved a 50% greater decrease in ALP versus placebo. The same review showed that nitrogen containing bisphosphonates such as zoledronic acid was more effective than non-nitrogen–containing bisphosphonates. One study showed that the healing of lytic lesions was achieved in 47.8% of patients treated with alendronic acid. Histopathology showed lower turnover in these patients versus placebo.[30]

Adverse events for bisphosphonate use for PDOB is similar to those reported for bisphosphonate use for CGCG in the previous section, and includes atypical femoral fractures, uveitis, osteonecrosis of the jaw, hypocalcemia, and kidney damage. The estimated medication-related osteonecrosis of the jaw (MRONJ) incidence rate is estimated to be 0.06%, lower than in osteoporosis. The risk of adverse events was not found to be lower after discontinuation of bisphosphonates. This finding is consistent with the long functional half-life of bisphosphonates from embedding in bone matrices. Zoledronic acid being the most efficacious for control of PDOB symptoms also was reported as having an increased risk of adverse effects versus placebo. The most common adverse event reported with zoledronic acid was flulike symptoms.[30]

Commonly, zoledronic acid is given as a single dose 5 mg intravenously. Pamidronate is given 30 mg intravenously for 3 consecutive days. Alendronate is given 40 mg orally daily for 6 months. Risedronate is give 30 mg orally once daily for 2 months.[29]

Calcitonin in Paget's Disease of Bone

Similar to its use for CGCG described elsewhere in this article, calcitonin is used in PDOB for its inhibitory effects on osteoclast activity. Ralston and associates[30] reported on a case series of 38 patients with active PDOB who received porcine calcitonin therapy (80 units/d). Bone pain improved in 82% of the patients. The serum ALP decreased from 899 to 579 in the pretreatment and post-treatment groups. Six patients developed side effects such as nausea and diarrhea. Calcitonin, when used in combination with etidronate, was more effective at decreasing ALP than etidronate alone. In 2 independent studies, calcitonin was found to have improved neurologic dysfunction in 20 of 21 patients.[30] A common regimen for calcitonin for PDOB is 100 IU subcutaneous or intramuscular once daily for 6 to 18 months.[30]

Denosumab in Paget's Disease of Bone

Denosumab, as discussed elsewhere in this article. is an antiresorptive that has a similar effect on bone integrity as bisphosphonates but a shorter clinical half-life. Two case reports using 60 mg by subcutaneous injection every 6 months in PDOB patients resulted in decreased ALP serum concentrations.[30] Although intuitively the use of denosumab is logical, there is a scarcity of evidence in literature to support the use of denosumab for PDOB at this time.

FIBROUS DYSPLASIA

Bisphosphonates in Fibrous Dysplasia

The rationale for bisphosphonate therapy in FDOB is similar to the rationale for bisphosphonate therapy in Paget's disease in that the end goal of therapy is the same, namely, to strengthen pathologically weakened bone through inhibition of osteoclasts. Numerous reports of bisphosphonates used in FDOB can be found. Liens and coworkers[31] reported 9 patients with FDOB with 60 mg pamidronate infusions every 6 months. At 4 years of follow-up, bone density increased, although serum ALP and bone pain decreased. Chapurlat and colleagues[32] also treated 20 patients with the same pamidronate regimen ,except the subjects were also given calcium and vitamin D supplements. Again, lesions resolved in approximately one-half of the patients. Kos and colleagues[33] treated 6 children with progressive cranial facial monostotic FD with 1 mg/kg IV pamidronate every 4 to 6 months because they

believed the children could ill tolerate major surgery. Pain relief was achieved in all cases. Increases in bone density and a decrease in lesion size was also noted. The only side effects reported were flulike symptoms in a report by Egner-Höbarth and coworkers.[34] However, given what we know about bisphosphonates, MRONJ and increased bone brittleness is expected.

Denosumab in Fibrous Dysplasia

Raborn and colleagues[35] presented a case of a 13-year-old female patient, who developed a biopsy confirmed FD of the left maxilla at 6 years of age. Owing to progressive increases in lesion size, including encroachment on the nasal cavity, she underwent surgical debulking. However, 1 year later, her symptoms returned. She would continue to undergo 3 more debulking surgeries and was treated with both pamidronate and zoledronate. These treatments relieved her symptoms temporarily each time, with bisphosphonates especially effective for her bone pain, but her lesion remained active. Raborn and associates treated her with 1 mg/kg denosumab every 4 weeks for 18 months followed by 70 mg every 4 weeks for 3.5 years. She reported resolution of pain. She was noted to have progressive an increase in bone density and stabilization of her lesion. Her therapy was discontinued and she remained in remission at 2 years of follow-up.[35]

MEDICATION-RELATED OSTEONECROSIS OF THE JAW AND OSTEORADIONECROSIS OF THE JAW

MRONJ and osteoradionecrosis of the jaw (ORN) are 2 conditions of the jaw whereby a jaw bone with a decreased capacity to heal develops necrosis after a traumatic injury, most commonly after dental extractions. In ORN, the offending insult is from radiation damage for the treatment of head and neck cancers to bone marrow and soft tissue supplying blood to the bone. The resulting bone becomes hypovascular, hypoxic, and hypocellular[36] and has a decreased capacity to heal in response to stress, resulting in necrosis. In MRONJ, the compromised bony healing is from antiresorptive medications, including bisphosphonates and denosumab.[37] The strengthened bone resulting from decreased osteoclastic activity also limits bone turnover in response to trauma, which results in a chronic nonhealing wound and then develops necrosis. The treatment of the necrotic jaw is difficult and without consensus.[36,37] Marx[38] has been at the forefront of understanding and treating both conditions. Marx[38] (1983) proposed a treatment protocol that recommends hyperbaric oxygen (30 preoperative dives and 10 postoperative dives) to all ORN patients and surgery corresponding with the staging of the disease. The hyperbaric oxygen acts to promote vascular infiltration and angiogenesis to the hypovascular, hypoxic jaw and surgery removes necrotic bone. Marx[39] (2003) was also the first to describe osteonecrosis related to bisphosphonate use. He recommended avoiding tooth removals when possible and to treat established cases with palliation and control of overlying osteomyelitis. Unlike ORN, there is no hypoxic state, and hyperbaric oxygen has not been shown to be effective in treatment of MRONJ.[40] In both conditions, the role of surgery must be evaluated judiciously because it is difficult to obtain healthy bony margins in an unhealthy bone. Surgical trauma has the potential to create more osteonecrosis, the same condition it aims to address. This factor creates a need to a find nonsurgical treatment in the management of necrosis of the jaw.

Pentoxifylline, Tocopherol, and Clodronate for Osteoradionecrosis of the Jaw

After Marx described ORN, it was proposed that radiation causes vascular damage by inducing fibrosis of the bone marrow.[36] Pentoxifylline, tocopherol, and clodronate (PENTOCLO) was proposed to treat ORN medically without surgery. Pentoxifylline is a xanthine derivative used for the management of peripheral vascular disease.[41] It increases red blood cell deformability through second messenger cascades, thereby promoting flow of blood to the tissues, in the case of ORN, necrotic bone. Tocopherol is a free radical scavenger that limits oxidative stress damage in necrotic bone. Clodronate is a bisphosphonate that acted to strengthen irradiated bone. Patel and associates[36] showed in a large cohort of 169 cases that this triple therapy achieved an overall healing rate of 54.4% and achieved a stabilization and healing rate of 85.8%. Severe ORN cases that presented with pathologic fractures, extraoral fistulas, or full-thickness soft tissue defects responded less favorably with a stabilization rate of 53.7%. In this subpopulation, Patel and colleagues recommended surgery, although some were not surgical candidates for other reasons. The mean time to achieve healing was 13 months. The PENTOCLO regimen described by Patel and associates started with treating any active infection before initiating PENTOCLO with broad spectrum antibiotics followed by 30 days of doxycycline 100 mg/d. Pentoxifylline was given 400 mg twice daily with 1000 IU tocopherol daily. Clodronate was given 800 mg twice daily.

Common adverse events include nausea and vomiting. PENTOCLO is contraindicated in patients who have an increased bleeding risk, have a known allergy to xanthine (eg, caffeine, theophylline), severe kidney or liver disease, and acute myocardial infarction or severe coronary artery disease owing to risk of increased myocardial demand.[41]

Pentoxifylline and Tocopherol for Medication-Related Osteonecrosis of the Jaw

Owing to the success of PENTOCLO therapy in ORN, the same formulation has been adopted to MRONJ, with the modification to omit the bisphosphonate clodronate. Cavalcante and Tomasetti[37] reviewed 23 patients from 4 studies. All 23 patients developed MRONJ after dental extractions. After PENTO treatment, bone lesion size was reported to be smaller in all patients. Sixty-one percent had completed eliminated bone exposure. Thirty percent had partially eliminated bone exposure. Fifty-two percent had medical therapy only. The remaining patients had some form of surgery including saucerization or sequestrectomy. No patients required resection. The mean follow-up was 10.6 months. All patients before therapy had pain; none of the patients after therapy had pain. From these data, it seems that PENTO therapy has clinical and measurable benefits in MRONJ patients with or without surgery.

DISCLOSURE

The authors have nothing to disclose.

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