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Bisphosphonate therapy in chronic diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible: Retrospective case series

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ABSTRACT

This study aims to evaluate short-term and long-term results of bisphosphonate therapy in patients with diffuse sclerosing osteomyelitis/tendoperiostitis (DSO/TP) of the mandible.

Eighteen patients (12 female, 6 male) aged 34.8 ± 22.2 years with DSO/TP of the mandible that were treated with bisphosphonates were included. In 16 patients, the bisphosphonate treatment led to remission with decrease of symptoms (pain, swelling of the cheek, trismus, tenderness of masticatory muscles) with a follow-up period of 4.5 (0.8–11.9) years between start of bisphosphonate treatment and latest follow-up consult. Of these, three patients were still in need of regular bisphosphonate therapy. Two patients were lost to follow-up.

Bisphosphonate therapy is a treatment option for DSO/TP of the mandible that is associated with a high chance of remission of symptoms. Within the limitations of the study it seems that this treatment might be an effective second step in DSO/TP refractory to conservative treatment.

1. Introduction

Chronic diffuse sclerosing osteomyelitis/tendoperiostitis (DSO/TP) of the mandible is characterised by recurrent pain and swelling of the cheek, combined with radiographic signs of diffuse sclerosis or a mixed sclerotic and lytic lesion with subperiosteal bone formation (Jacobsson and Hollender, 1980; Jacobsson, 1984; van Merkesteyn et al., 1988; Suei et al., 2005; Theologie-Lygidakis et al., 2011; van de Meent et al., 2018; Li et al., 2020). In addition, there is an absence of pus, fistulae or other signs of bacterial infection and some cases present with trismus and progressive mandibular deformity.

Conservative treatment with muscle relaxation therapy has proven to be successful in patients with DSO/TP of the mandible (van de Meent et al., 2017, 2019). This therapy is based on the hypothesis that DSO/TP is caused by overuse of the masticatory muscles, leading to chronic tendoperiostitis (TP). However, treatment with bisphosphonates is the second-line treatment for patients with DSO/TP refractory to the (first-line) conservative therapy. It is hypothesised that bisphosphonates inhibit osteoclast-mediated bone remodelling, which decreases the inflammatory response, resulting in a reduction of pain and swelling of the cheek (Montonen et al., 2001; Soubrier et al., 2001; Montonen and Lindqvist, 2003; Hino et al., 2005; Yamazaki et al., 2007; Urade et al., 2012; Berglund et al., 2015; Otto et al., 2015; van de Meent et al., 2017). Some authors suggest that DSO/TP of the mandible is part of a systemic spectrum with syndromes such as SCCH (sternocostoclavicular hyperostosis), CRMO (chronic recurrent multifocal osteomyelitis) or SAPHO-syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis) (Kahn et al., 1994; Suei et al., 1995; Mari et al., 2014). Therapy with bisphosphonates is already a more common additional treatment in these syndromes, when refractory to anti-inflammatory medication (Aljuhani et al., 2015; Cianci et al., 2017; Hofmann et al., 2017; Yachoui et al., 2017; Li et al., 2020).

To date, several case descriptions and a few small clinical cohort studies are reported in the literature concerning the treatment of

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DSO/TP with bisphosphonates (Montonen et al., 2001; Soubrier et al., 2001; Eyrich et al., 2003; Baltensperger et al., 2004; Hino et al., 2005; Compeyrot-Lacassagne et al., 2007; Kuijpers et al., 2011; Urade et al., 2012; Otto et al., 2015, 2018; van de Meent et al., 2017; Li et al., 2020). No reports are available that report short-term and long-term evaluation of bisphosphonate therapy as a treatment for DSO/TP in a large group of patients. Therefore, the aim of the study was to evaluate the long-term effect of bisphosphonate treatment in a large group of patients with DSO/TP of the mandible.

2. Case series

In this retrospective case series, 38 consecutive patients presenting for evaluation and treatment of DSO/TP between August 1991 and April 2018 at the Department of Oral and Maxillofacial Surgery and the Department of Internal Medicine, division of Endocrinology of the Leiden University Medical Center, the Netherlands, were reviewed. Eighteen patients were included in the study on the criteria that they were diagnosed with DSO/TP of the mandible and were treated with bisphosphonate therapy.

The LUMC institutional review board (IRB) agreed with the present retrieval and analyses of the data. Because of the retrospective nature of the study, no IRB approval was necessary and the study was granted a written exemption (G18.034).

2.1. Clinical characteristics

The group consisted of 6 men and 12 women, with a mean age of 34.8 ± 22.2 years. In 9 patients DSO/TP was located in the right mandible, in 7 patients in the left mandible, and 2 patients had bilateral complaints (Table 1). Three patients showed extra-oral manifestations of the disease diagnosed on bone scintigraphy, two patients were diagnosed with SAPHO syndrome, and one patient was diagnosed with SCCH.

At first consultation 16 out of the 18 included patients presented with swelling of the cheek and 17 out of the 18 patients showed painful palpation of the masticatory muscles. During clinical examination, 11 patients showed trismus, and 13 patients showed signs of parafunctional habits, such as tooth wear or on the oral soft tissues (cheek, tongue and/or lips). In total, 12 patients reported a relation with stress and 11 patients reported parafunctional habits, such as the inability to relax the masticatory muscles, nail biting, and/or co-contraction.

Panoramic radiographs and a bone scintigraphy were available in all patients, a (CB)CT scan was performed in 15 patients, and a MRI scan in 4 patients. Histopathological results of bone biopsies were available in 12 patients. In the other patients a biopsy was not performed, because of obvious clinical and radiological characteristics.

2.2. Previous treatment and treatment after referral

All patients received many different therapies in other centers – medical and surgical –, which did not result in long-term improvement of their complaints (Table 1). As our (previously published) treatment protocol dictates, conservative treatment is the treatment of choice in most patients. Nine patients described in this case series were treated conservatively according to a standard of care protocol, which was implemented in November 2011 (van de Meent et al., 2017, 2019). The other 9/18 patients described in this case series were not included in previous studies. The conservative treatment protocol started with occlusal splint therapy, disease counselling and/or physiotherapy with habit reversal training, myofeedback and/or relaxation therapy. After 12 months of continuing or increasing complaints this group of patients were considered refractory to conservative therapy and started with additional therapy with second-line intravenous bisphosphonates. Eight other patients also received conservative therapy, but not according to the standard of care protocol, because they started with treatment prior to November 2011. One patient was not treated conservatively, because the patient started with bisphosphonate therapy shortly after referral due to already long-standing serious complaints (6 years).

Sixteen of the eighteen included patients received anti-inflammatory medication, such as non-steroidal anti-

Table 1
Characteristics of included patients with chronic diffuse sclerosing osteomyelitis (DSO/TP) of the mandible.

Category	No of patients	Mean (SD)
Gender		
Male	6	
Female	12	
Age (years)[a]		34.8 (22..2)
Location of DSO		
Right mandible	9	
Left mandible	7	
Both sides	2	
Time from start of symptoms until first intravenous bisphosphonate administration (in months)		73 (41)
Previous treatment		
Dental treatment	5	
Antibiotics	13	
Analgesics	8	
Physiotherapy	5	
Occlusal splint therapy	2	
Anti-inflammatory medication	8	
Surgery	7	
Treatment after referral		
Physiotherapy	17	
Occlusal splint therapy	11	
Counselling	15	
Antiresorptive medication	18	
Anti-inflammatory medication	16	
Muscle relaxants	6	
Surgery	1	

[a] Age at first visit.

inflammatory drugs (NSAIDs) or corticosteroids and six patients received muscle relaxants. One patient received explorative (diagnostic) surgery, because of persistent complaints.

2.3. Treatment protocol

If the prespecified treatment protocol with occlusal splint therapy, physiotherapy, and/or disease counselling was not successful enough, patients were referred to the department of Endocrinology for treatment with bisphosphonates.

Before treatment initiation patients underwent a full screening, including markers of bone- and calcium/phosphate metabolism, such as parathyroid hormone (PTH), procollagen type 1 N-terminal propeptide (P1NP), β-crosslaps (Ctx), and alkaline phosphatase (ALP). In addition, renal function, C-reactive protein, erythrocyte sedimentation rate, and full blood count were determined. In twelve patients, deficiencies in calcium and/or vitamin D-levels had to be corrected before or during bisphosphonate therapy. The use of contraception was emphasised in female patients, because of possible teratogenicity of bisphosphonate therapy. All patients underwent bone scintigraphy prior to bisphosphonate therapy to assess bone activity and to assess possible extra-oral manifestations of the disease, to eventually diagnose CRMO/SCCH/SAPHO-syndrome.

2.4. Outcomes

Three (1/2 F/M, aged 34 ± 22.8 years) of the eighteen included patients were free of complaints after treatment with bisphosphonates and no longer in need of analgesic medication with more than two years of follow-up (2.3 ± 0.2 years). Their mean amount of cycles of bisphosphonate therapy was 5.3 ± 3.3. Post-bisphosphonate panoramic radiograph showed an almost normal bone architecture in two patients, and improvement in one patient (Fig. 1). In two patients a post-bisphosphonate (CB)CT-scan was made and showed normalisation in one patient, and improvement in the other patient. In one patient a post-bisphosphonate bone scintigraphy was performed and showed reduction in activity.

Another three patients (3/0 F/M, aged 25 ± 4.9 years) were complaint-free after bisphosphonate therapy as well with less than two years of follow-up (0.8 ± 0.5 years). They were no longer in need of analgesic medication. Their mean amount of cycles of bisphosphonate therapy was 2 ± 1.4. In one patient a post-bisphosphonate bone scintigraphy was performed and showed a reduction in radiopharmaceutical uptake.

Seven (6/1 F/M, aged 43 ± 26.3 years) of the eighteen patients reported a substantial reduction of pain intensity and frequency, but still used intermittently paracetamol or NSAIDs for pain relief with a follow-up of 4.0 ± 3.7 years. Varying swelling of the cheek was reported in three patients. None of the patients reported complaints of trismus. Two patients reported varying tenderness of the masticatory muscles. Their mean amount of cycles of bisphosphonate therapy was 6.3 ± 3.2. In six patients a post-bisphosphonate panoramic radiograph was performed; in one patient the panoramic radiograph showed normalisation, in three patients it showed improvement (less lysis), and in two patients it showed deterioration (more lysis and/or extension of the disease). In three patients a post-bisphosphonate (CB)CT-scan was performed and showed improvement in two patients and deterioration in the other patient. In six patients a post-bisphosphonate bone scintigraphy was performed and showed no activity in two patients, reduction in activity in two patients, the same activity in one patient, and more activity in the last patient (Fig. 2).

Three patients (2/1 F/M, 24 ± 14.6 years) were still in need for regular bisphosphonate therapy, with a mean amount of cycles of bisphosphonate therapy of 14.3 ± 15.4 and their follow-up time was 5.9 ± 5.4 years. One of these patients reported no complaints of the mandible after bisphosphonate therapy, but still received intravenous bisphosphonates based on extra-oral complaints of SAPHO syndrome. The other two patients showed varying recurrent pain, and one patient reported recurrent swelling of the cheek and tenderness of the masticatory muscles as well. All three patients showed improvement on panoramic radiograph and (CB)CT-scan (Fig. 3), they showed a reduction in uptake of radiopharmacon on the bone scintigraphy as well.

Two patients were lost to follow-up, one patient stopped treatment because of pancreatic cancer, and the other patient did not appear for follow-up consults for unknown reasons.

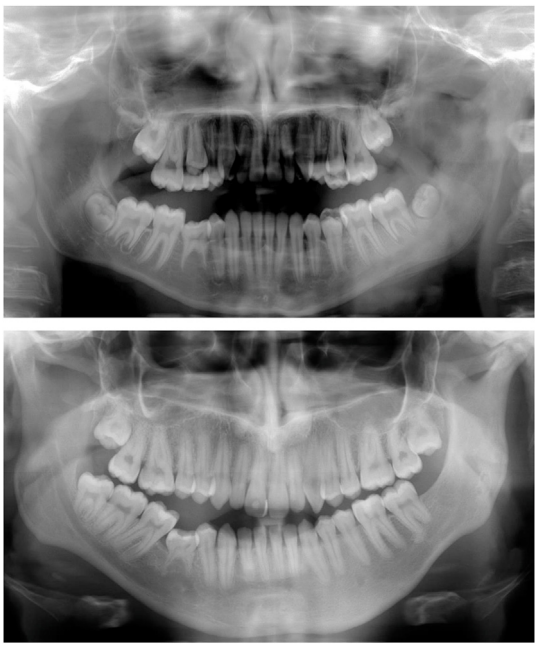

Fig. 1. Pre- and post-treatment panoramic radiography of a 12-year-old patient with DSO/TP of the left mandible. The upper panoramic radiography is taken before the start of bisphosphonate therapy. The panoramic radiograph shows mixed lysis and sclerosis of the left mandibular ramus. The lowest panoramic radiography is taken 5,5 years after the first administration with bisphosphonates. It shows normalisation of the bone structures of the left mandibular bone.

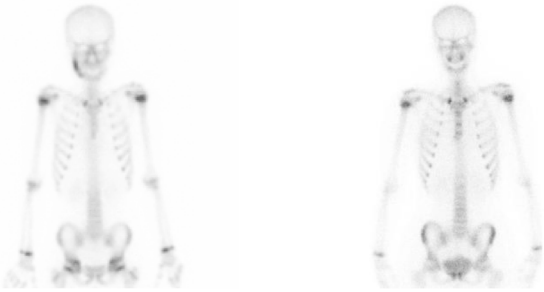

Fig. 2. Pre- and post-treatment bone scintigraphy of a 10-year-old patient with DSO/TP of the mandible. The left bone scintigraphy is taken before start of bisphosphonate treatment, which shows increased uptake of radiopharmaceutical in the right mandible and physiological uptake of the radiopharmaceutical in the epiphyseal discs, according to age. The right bone scintigraphy is taken 3,5 years after the first administration with bisphosphonates, which shows no increased activity in the right mandible, without any residual defects.

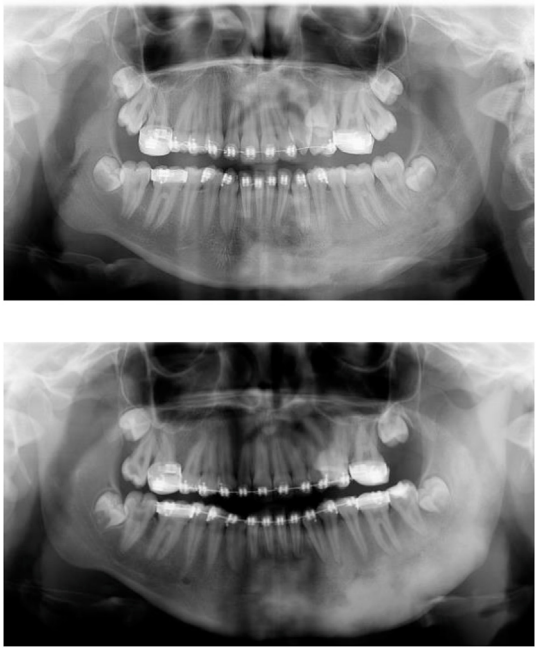

Fig. 3. Pre- and post-treatment panoramic radiography of a 13-year-old patient with DSO/TP of the left mandible. The upper panoramic radiography is taken before the start of bisphosphonate therapy, it shows lysis and subperiosteal bone formation of the left mandible. The lowest panoramic radiography is taken three months after bisphosphonate treatment. It shows sclerosis of the left mandible.

Four types of bisphosphonates were administered in this group of patients (Table 2). The type, dose and frequency of bisphosphonates depended on age and preference of the patient and the treating physician and has changed throughout the years. The majority of the patients were started on pamidronate, in this study sixteen patients received intravenous pamidronate with a mean amount of 4.5 ± 3.1 cycles, spread over 1–5 days with a total dose of 45–120mg. Three patients received intravenous olpadronate with a mean amount of 9.3 ± 9.7 cycles, spread over 3–5 days with a total dose of 6–20mg. One patient received oral olpadronate 50–100mg daily for two years and started with 5mg oral risedronate afterwards, mainly because of extra-oral complaints of SAPHO syndrome. Reasons to choose for the bisphosphonate olpadronate was the potential intention to start a patient on an oral drug in the future, as olpadronate was locally produced by our pharymacy of which intravenous and oral preparations were available. Two patients received 4–5mg intravenous zoledronic acid administered in one day. Reasons for choosing the bisphosphonate zoledronate and risedronate were patient preference (less frequent dosing) or availability.

After bisphosphonate treatment, six patients reported an acute phase reaction, with transient complaints of headache, fever, and flu-like symptoms. In this group of patients, no long-term adverse effects, such as medication-related osteonecrosis of the jaw, were reported.

3. Discussion

Chronic diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible is difficult to treat and many different treatment options have been reported in literature (van de Meent et al., 2020). During the last decades, bisphosphonate therapy seems to be a promising treatment option for DSO/TP of the mandible, next to conservative treatment (Montonen et al., 2001; Soubrier et al., 2001; Eyrich et al., 2003; Baltensperger et al., 2004; Hino et al., 2005; Compeyrot-Lacassagne et al., 2007; Kuijpers et al., 2011; Urade et al., 2012; Otto et al., 2015, 2018; van de Meent et al., 2017; Li et al., 2020). This study shows that bisphosphonate therapy resulted in a clinical decrease in disease activity in 16/18 of the patients, with a mean follow-up of 27 ± 34 months. The other 2/18 patients were lost to follow-up.

DSO/TP is characterised by recurrent pain, swelling and trismus of the cheek and local inflammatory changes in the mandible (Soubrier et al., 2001; Hino et al., 2005; Urade et al., 2012; Berglund et al., 2015; Otto et al., 2015; van de Meent et al., 2017; Li et al., 2020). With antiresorptive medication, such as bisphosphonates, this bone resorption, -turnover, and -renewal can be decreased by inhibition of involved osteoclasts and will lead to a reduction in complaints, such as pain and swelling (Soubrier et al., 2001; Hino et al., 2005; Urade et al., 2012; Otto et al., 2015). In most cases the analgesic effect takes several weeks to months, because bone turnover starts again after the efficacy of the administered bisphosphonate has expired. Therefore, multiple cycles of bisphosphonates are often required.

Bisphosphonates can be administered orally or intravenously in different dosages. Two types of bisphosphonates are registered, nitrogen-containing (pamidronate, olpadronate, alendronate, ibandronate, zoledronic acid, risedronate) and non-nitrogen-containing (disodium clodronate) bisphosphonates (Montonen et al., 2001; Soubrier et al., 2001; Eyrich et al., 2003; Baltensperger et al., 2004; Hino et al., 2005; Compeyrot-Lacassagne et al., 2007; Kuijpers et al., 2011; Urade et al., 2012; Otto et al., 2015). Nitrogen-containing bisphosphonates are more common in the treatment for DSO/TP of the mandible, because they have a higher affinity for bone, a higher bioavailability and a possible longer duration of action than non-nitrogen-containing bisphosphonates (Otto et al., 2015; van de Meent et al., 2020).

In literature, one randomized, placebo-controlled, double blinded trial has been reported about bisphosphonate treatment in patients with DSO/TP of the mandible (Montonen et al., 2001). In this article, ten patients were enrolled who received disodium clodronate (a non-nitrogen containing bisphosphonate) or a placebo intravenously. Pain reduced significantly in the first 6 months in the bisphosphonate-group, but there were no differences in pain reduction at 12 months between the groups. Seven patients needed a second infusion, because of persistent or recurrent pain, 5/6 patients in the bisphosphonate-group, and 2/4 patients in the placebo-group. These results could be different if a nitrogen-containing bisphosphonate would have been used as these have a higher affinity for bone and therefore act longer (Otto et al., 2015).

Table 2
Bisphosphonates administered in this group of 18 patients.

Type	No. of patients	Dosage	Days of administration	Administration route	Amount of cycles
Pamidronate	16	45–120 mg	1–5	Intravenous	72
Olpadronate[a]	3	6–20 mg/50–100 mg	3-5/daily	Intravenous/oral	28
Zoledronic acid	2	4–5 mg	1	Intravenous	5
Risedronate[a]	1	5 mg	Daily	Oral	–

[a] Olpadronate (50–100mg daily) and risedronate (5mg daily) can be given orally for longer periods of time.

Before starting with bisphosphonate therapy, correction of any disturbances in mineral metabolism need to be corrected since a vitamin D deficiency is associated with an increased risk for hypocalcaemia after bisphosphonate therapy (Rosen and Brown, 2003; Body et al., 2018; van de Meent et al., 2019). Also markers of bone turnover might be of use for follow-up on therapy. In our study, in 12 patients calcium or vitamin D-level deficiencies had to be corrected before or during bisphosphonate therapy.

When bisphosphonates are initiated, patients need to be informed about the so-called acute phase reaction with transient complaints of fever, headache, and flu-like symptoms, present in 6 patients in our study (33%). Also other more rare complications need to be mentioned, such as medication-related osteonecrosis of the jaw, and atypical femoral fractures, although we did not expect and observe any in our study, since bisphosphonates in DSO/TP are usually effective within a couple of cycles, and no long-term treatment is necessary (Kuijpers et al., 2011). Also, three out of eighteen patients (17%) in this study group showed an extra-oral manifestation of DSO/TP, with two patients diagnosed with SAPHO syndrome, and one patient with SCCH. And, since DSO/TP of the mandible regularly manifests as part of CRMO, SCCH, or SAPHO syndrome, it is advised to screen patients on extra-oral lesions (in particular extra-oral bone lesions, and skin lesions). For this reason and to evaluate disease activity bone scintigraphy is advised.

More recently, studies about treatment of DSO/TP of the mandible with subcutaneous injections of denosumab have been published (Hallmer et al., 2018; Otto et al., 2018). Denosumab is a human monoclonal antibody, which also inhibits differentiation, function, and survival of osteoclasts. The symptoms of these patients were well controlled with regular injections. The advantage of denosumab compared to bisphosphonates is the shorter half-life in bone. However, treatment cessation is more challenging considering the rebound phenomenon which has shown to be associated with vertebral fractures and in other metabolic bone diseases even with catch up tumour growth and hypercalcemia, especially in children (Cummings et al., 2018; Collins et al., 2020).

Standard treatment protocol or guidelines are lacking for DSO/TP of the mandible. Non-surgical strategies with analgesic drugs, NSAIDs, antibiotics, corticosteroids, hyperbaric oxygen treatment, bisphosphonates and conservative therapy have been reported (van de Meent et al., 2020). Also, different surgical strategies with local resections, but also invasive segmental resections and hemimandibulectomy have been reported in literature. Excessive mandibular surgery is not recommended, because of its high morbidity and remission can be achieved with conservative- and drug therapy. A standard of care protocol was proposed in 2019 by our center, which starts with non-surgical treatment with occlusal splint therapy, disease counselling, and/or physiotherapy with habit reversal training, myofeedback and/or relaxation therapy (van de Meent et al., 2019). Analgesics, preferably NSAIDs, are prescribed for exacerbations of symptoms. If patients experience insufficient response after 12 months of this non-surgical therapy, they should be referred for additional bisphosphonate therapy.

This study is limited by its retrospective nature, causing less objective parameters for performing research. Patients' complaints as pain and swelling of the cheek are the main reason to treat patients. These subjective parameters were analysed to evaluate treatment with bisphosphonates. However, statistical analyses were not possible with regard to these parameters. This report is the largest to date evaluating bisphosphonate therapy in DSO/TP of the mandible. Nevertheless, it is still a relatively small sample size, since DSO/TP of the mandible is a rare disease and therefore larger, joined studies are necessary.

4. Conclusion

Whithin the limitations of the study it seems that if patients are refractory to conservative therapy, the administration of bisphosphonates might be an alternative treatment option.

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