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Non-surgical treatment of adults with chronic diffuse sclerosing osteomyelitis/tendoperiostitis of the mandible

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ABSTRACT

Non-surgical therapy has proved to be effective in chronic diffuse sclerosing osteomyelitis (DSO) of the mandible in children. Therefore we aimed to investigate the effect of non-surgical therapy in adult DSO patients.

We included consecutive patients with DSO who received non-surgical therapy in our center. They all received occlusal splint therapy, counselling about the disease, and/or physiotherapy by a specialised team. The use of analgesics, preferably nonsteroidal anti-inflammatory drugs, was advised for symptomatic control during periods of exacerbation.

Sixteen patients (11/5 female/male) aged 39.9 ± 15.0 years with DSO of the mandible were included. The mean duration of symptoms was 39.7 ± 26.3 months before referral to our center. Patients were treated with a broad range of treatments before referral. All patients underwent non-surgical treatment. In 12 patients this led to remission. Four patients still had complaints after 12 months of non-surgical therapy and started with intravenous bisphosphonate therapy.

In our center, DSO of the mandible was successfully treated with non-surgical therapy, despite a long duration before referral and extensive pre-treatment. Considering this high success rate, we recommend this non-surgical approach as the first treatment option for DSO of the mandible. In case of persistence, alternative treatments such as bisphosphonates should be explored.

1. Introduction

Chronic diffuse sclerosing osteomyelitis (DSO) of the mandible is a chronic non-infectious osteomyelitis, with recurrent episodes of pain and swelling of the cheek, often accompanied by trismus and progressive mandibular deformity (Jacobsson, 1984; van Merkesteyn et al., 1988). No age prevalence is described, although, a subclassification into adolescent and adult onset of the disease can be distinguished (Baltensperger et al., 2004). The diagnosis of DSO is made on a combination of specific clinical and radiological aspects possibly supported by histopathological examination. The exact etiology of DSO of the mandible is unclear, which results in many different treatment strategies, with variable clinical outcomes (Jacobsson, 1984; van Merkesteyn et al., 1988, 1990; Groot et al., 1992; 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; Mari et al., 2014; Idahosa et al., 2015; Otto et al., 2015, 2018; Patel et al., 2015; van de Meent et al., 2017).

It has been suggested that DSO of the mandible could be part of a syndrome, such as sternocostoclavicular hyperostosis (SCCH), chronic recurrent multifocal osteomyelitis (CRMO), or synovitis, acne, pustulosis, hyperostosis, or osteitis (SAPHO) syndrome (Kahn et al., 1994; Suei et al., 1995; Mari et al., 2014).

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It has also been postulated that DSO of the mandible could be caused by overuse of the masticatory muscles, leading to a chronic tendoperiostitis (TP), which can be treated with muscle relaxation therapy (van Merkesteyn et al., 1990). Therefore, in our center, the first line of treatment is non-surgical treatment. Non-surgical therapy consists of physiotherapy with relaxation therapy, counseling about the disease, occlusal splint therapy and, in the case of exacerbations, preferably nonsteroidal anti-inflammatory drugs (NSAIDs) or other painkillers. Recently, we have reported our successful results in children with DSO, and therefore we aimed to explore the effect of non-surgical therapy in adult patients with DSO of the mandible (van de Meent et al., 2017).

2. Material and Methods

In this retrospective study, all consecutive adult patients (≥18 years of age) diagnosed with DSO of the mandible between November 2011 and May 2017 in the Department of Oral and Maxillofacial Surgery and the Center for Special Dental Care, Leiden University Medical Center (LUMC), the Netherlands, were included. Patients were excluded from the study if they were previously treated with bisphosphonates and/or were not treated by our dentist specialized in temporomandibular disorders.

The following data were retrospectively retrieved from the electronic medical files; medical history, clinical symptoms, radiographic images (panoramic radiograph, computed tomography [CT] scan, magnetic resonance imaging [MRI] scan, bone scintigraphy), and histological and microbiological results of obtained specimens.

The LUMC institutional review board agreed with the present collection and analyses of the data (G18.033).

2.1. Treatment protocol

All patients received a standardized non-surgical therapy and were treated according to a standard of care protocol, which was implemented in November 2011 (Fig. 1). The standard of care protocol allowed for the diagnosis of DSO based on clinical and radiological findings. However, if the diagnosis was not clear on the basis of the clinical and radiological findings, a bone biopsy and subsequent histological examination were performed to exclude other disorders (i.e. bacterial osteomyelitis or malignancy).

The non-surgical treatment consisted of occlusal splint therapy, disease counseling and/or physiotherapy with habit reversal training, myofeedback and/or relaxation therapy. The treatment protocol was executed by one DSO/TP-specialized Oral and Maxillofacial Surgeon (R.M.) and one dentist specialised in temporomandibular disorders (M.W.).

During the first visit, the use of analgesics was accentuated, preferably NSAIDs, including ibuprofen, naproxen, diclofenac, and etoricoxib.

Patients were referred to the endocrinologist for screening for bisphosphonate therapy if they still experienced insufficient response after 12 months. Insufficient response was defined as patients reporting persistent or recurrent pain and/or deterioration of the radiological appearances (e.g. extension of the radiological abnormality, more lysis on the panoramic radiograph, or increase in uptake of the radiopharmacon on the bone scintigraphy). Deviating laboratory results, pregnancies and/or lactation were ruled out before the start of bisphosphonate therapy.

2.2. Outcomes

Patient characteristics and disease characteristics were recorded from the patients' medical files and radiographs. These characteristics included the patient's sex, age, location of DSO, time from the start of symptoms until the first visit to our center, previous treatments, treatments in our center, and symptoms during first consultation (including swelling of the cheek, trismus, tenderness of masticatory muscles). Furthermore, patients were asked about parafunctional habits (bruxism, nail-biting, co-contraction, and/or inability to relax the masticatory muscles). Tooth wear was assessed, and an association between complaints and stress was evaluated.

The primary outcome in this study was a pain assessment as reported by the patient. Pain assessment was performed at baseline

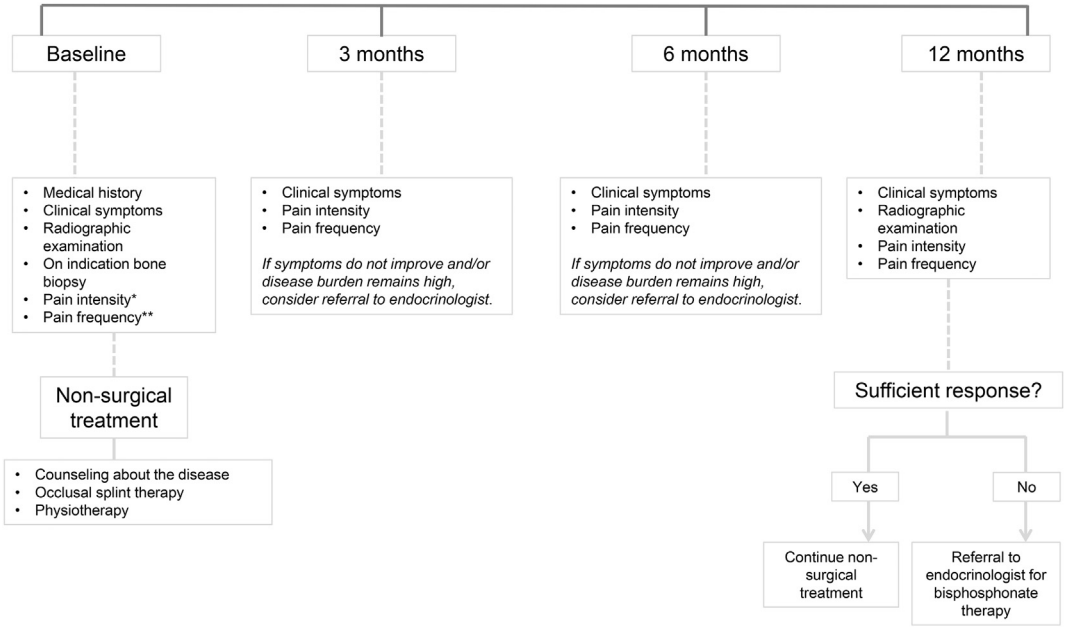

Fig. 1. Standard of care protocol. *Pain intensity in Visual Analogue Scale. **Pain frequency in days/3 months.

(before the start of non-surgical therapy), at 3, 6, and 12 months. The pain assessment consisted of rating pain intensity, objectified with a visual analogue scale (VAS) ranging from 0 to 10; and the frequency of pain complaints, objectified as the number of days per 3 months that pain was experienced.

Secondary outcome variables included subjective improvement of complaints and radiological improvement. Subjective improvement of complaints was defined as improvement of mouth opening/function, decrease in pain and decrease in swelling of the cheek. Radiological improvement was defined as less lysis and more sclerosis of panoramic radiographs and/or reduction in uptake of the radiopharmacon in bone scintigraphy.

If patients were treated with antiresorptive medication after non-surgical treatment, this was also recorded, combined with the reason why they started with antiresorptive treatment. The type of bisphosphonate, the amount of cycles of bisphosphonate treatment, subjective improvement of complaints, and adverse events were recorded.

2.3. Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences (IBM SPSS Statistics for Mac, version 25, IBM SPSS Inc., Armonk, NY). Descriptive statistics were used to illustrate relevant patient characteristics. Due to the presence of repeated measurements to study the effect of non-surgical therapy on the pain intensity and pain frequency, a generalized linear mixed model (GLMM) was estimated. A p-value of <0.05 indicated statistical significance. Data are presented as mean ± standard deviation, unless stated otherwise.

3. Results

A total of 27 adults with DSO of the mandible were identified. Eleven patients were excluded, of whom five, due to organizational reasons, were not treated by our dentist specialized in temporomandibular disorders, and five already received bisphosphonate therapy previous to non-surgical treatment. One patient was started on bisphosphonate- and non-surgical therapy simultaneously, due to the duration (53 months) and the seriousness of complaints (VAS 4–8 daily). Therefore, a total of 16 patients (5 males, 11 females) aged 39.9 ± 15.0 years were included in the present analyses (Table 1).

In seven patients, DSO was located in the right mandible, in eight patients in the left mandible, and one patient had bilateral complaints. Patients were referred from other hospitals, with a mean period from the start of symptoms until the first visit to our hospital of 39.7 ± 26.3 months (Table 1).

In 14 of 16 patients, swelling of the cheek was observed at first presentation. In our center, 12 patients had trismus observed during clinical examination. Palpation of the masticatory muscles revealed tenderness in 15 patients. All patients had parafunctional habits, and 15 showed signs of bruxism on their dentition (i.e. tooth wear) and the oral soft tissues (cheek, tongue and/or lips). Thirteen patients noticed a relation between stress and exacerbations of their complaints.

A panoramic radiograph was available in all patients. In 15 patients, an additional cone beam computed tomogram was available, and in five an additional MRI scan was performed. Bone scintigraphy performed before the start of non-surgical therapy was available in 13 patients. Histopathological results from bone biopsies or surgery material were available in seven patients. In the other patients, a biopsy was not performed, because of obvious clinical and radiological characteristics.

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

Category	No of patients (%)	Mean (SD)
Gender, Nr (%)		
Male	5 (31.3)	
Female	11 (68.8)	
Age (years)[a]		39.9 (15.0)
Location of DSO, Nr (%)		
Right mandible	7 (43.8)	
Left mandible	8 (50.0)	
Both sides	1 (6.3)	
Time from start of symptoms until first visit to our institute (in months)		39.7 (26.3)
Previous treatment, Nr (%)		
Dental treatment	3 (18.8)	
Antibiotics	13 (81.3)	
Analgesics	5 (31.3)	
Physiotherapy	9 (56.3)	
Occlusal splint therapy	7 (43.8)	
Anti-inflammatory medication	6 (37.5)	
Anti-rheumatics	1 (6.3)	
Muscle relaxants	2 (12.5)	
Surgery	2 (12.5)	
Treatment in our institute, Nr (%)		
Physiotherapy	15 (93.8)	
Occlusal splint therapy	16 (100)	
Counselling	16 (100)	
Antiresorptive medication	4 (25)	
Anti-inflammatory medication	14 (87.5)	
Muscle relaxants	2 (12.5)	
Stress, Nr (%)		
Yes	13 (81.3)	
Unknown	3 (18.8)	
Parafunctional habits, Nr (%)		
Yes	16 (100)	

[a] Age at first visit.

After 12 months of non-surgical treatment, both pain intensity (pre-treatment VAS score of 7.4 ± 1.8 vs 3.5 ± 3.3, $p = 0.004$) and pain frequency (pre-treatment 61.3 ± 23.4 vs 11.4 ± 17.5 days/3 months, $p = 0.000$) decreased significantly (Fig. 2).

Four patients were completely pain free after 12 months of non-surgical therapy; eight patients showed less pain and less frequent swelling of the mandible, and no additional bisphosphonate treatment was necessary. In these 12 patients, pain intensity decreased significantly in time (pre-treatment VAS score of 7.3 ± 2.0 vs 3.4 ± 3.4 after treatment, $p = 0.008$). Patients showed a significant decrease of pain frequency in time (pre-treatment 60.7 ± 24.1 days/3 months vs 11.6 days/3 months ± 18.6 after treatment, $p = 0.000$). In 11 patients, improvement of radiographic examination was seen, in nine patients on the panoramic radiograph, and two patients showed decreased activity in the diseased area on the bone scintigraphy taken after 1 year of non-surgical therapy (Figs. 3 and 4).

After 15 ± 5.8 months, three patients still had persistent disease complaints, and one patient had progressive complaints of the sternocostoclavicular joint in the context of sternocostoclavicular hyperostosis (SCCH); these four patients were started on bisphosphonates. Two of these patients were already referred to the endocrinologist for bisphosphonate therapy at the start of non-surgical therapy, because of intense pain and prolonged duration of symptoms. However, the bisphosphonate treatment was postponed, because of a vitamin D deficiency in one patient, and the other patient was still lactating, which is contra-indicated with bisphosphonate therapy. On non-surgical therapy, these four patients did show a decrease in pain intensity and frequency, albeit not significant (VAS score of 7.8 ± 1.0 to 3.7 ± 3.2, $p = 0.146$

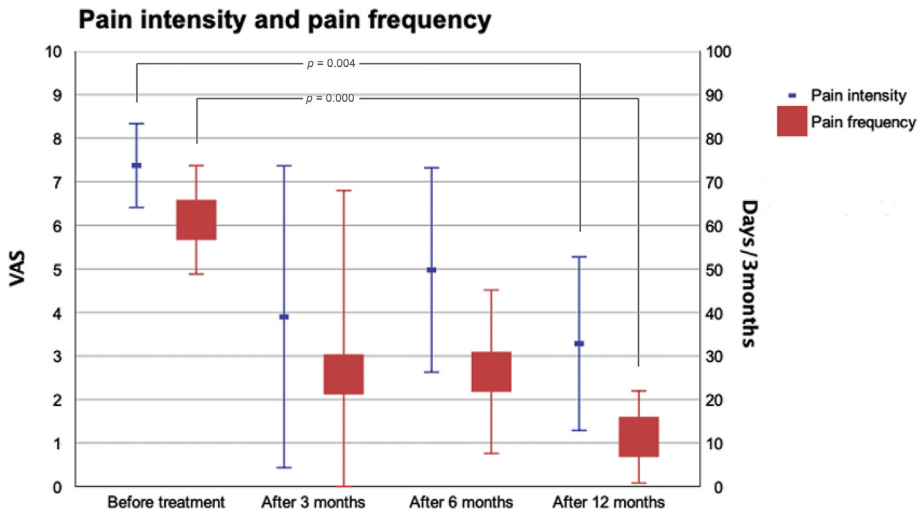

Fig. 2. The mean pain intensity according to VAS score and the mean pain frequency in days/3 months over time. VAS = Visual Analogue Scale.

and 63.0 ± 24.2 to 10.5 ± 14.8 days/3 months, $p = 0.450$). In all but one patient, intravenous pamidronate was administered for 1–5 days. One patient was free of pain after a single infusion of pamidronate. For patient convenience, one patient received a single course of intravenous zoledronic acid. All patients reported improvement of their symptoms of pain and swelling of the mandible after bisphosphonate infusion. One patient reported adverse events with fever, headache, and flu-like symptoms, the so-called acute phase reaction present in approximately 40% of patients at the first cycle.

Patients who were started on bisphosphonates did not differ from those with successful non-surgical mono-therapy in baseline characteristics including pain scores, except for duration of symptoms upon referral, 63 ± 43 months in the bisphosphonate group vs 32 ± 13 months in the mono-therapy group.

4. Discussion

Our data show that in 16 patients with DSO of the mandible, 75% had a complete or partial response to non-surgical therapy. This therapy consisted of a combination of physiotherapy, occlusal splint therapy and counselling. This non-surgical treatment was effective and did not require additional bisphosphonate therapy, despite already long-term complaints. The remaining four patients received additional therapy with second-line intravenous bisphosphonates, after consultation with an endocrinologist. Patients requiring

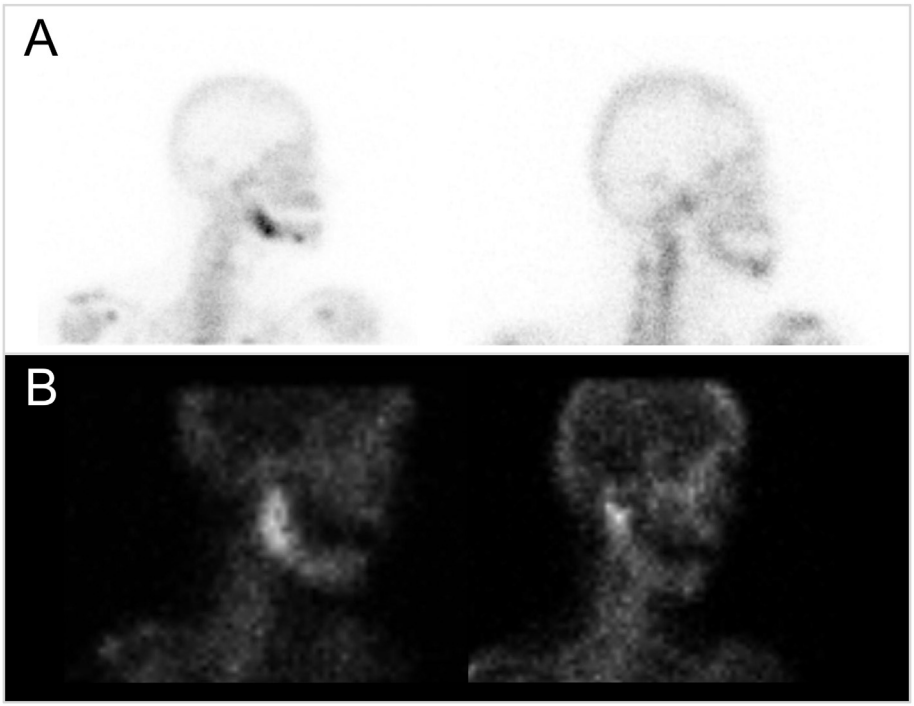

Fig. 3. Pre- and post-treatment Tc-scans of two patients with DSO of the mandible. A: Left Tc-scan is taken before start of non-surgical treatment, the right Tc-scan is taken after 18 months of non-surgical therapy, showing decreased disease activity in the right mandible. B: Left Tc-scan is taken before start of non-surgical treatment, the right Tc-scan is taken after 13 months of non-surgical therapy, also showing decreased disease activity in the right mandible.

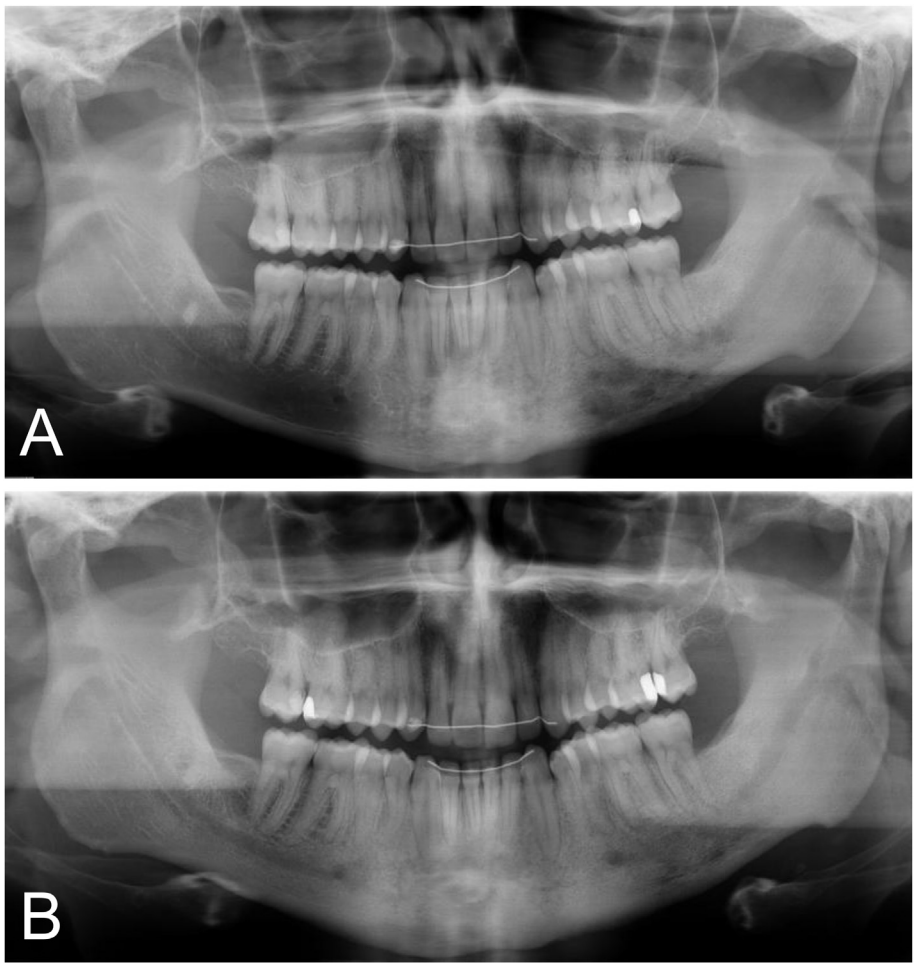

Fig. 4. Pre- and post-treatment panoramic radiography of a patient with DSO of the left mandible. A: Before start of non-surgical treatment, the panoramic radiograph revealed mixed sclerosis and osteolysis of the left mandibular bone. B: The panoramic radiograph, taken approximately 2,5 years after the start of non-surgical treatment, showed an almost normal bone architecture.

bisphosphonate therapy did have a longer duration of complaints before referral to our center compared with patients with a complete or partial response to non-surgical treatment alone.

Since the pathophysiology of DSO of the mandible is unknown, DSO has been treated with several different modalities with variable outcome (Jacobsson, 1984; van Merkesteyn et al., 1988, 1990; Groot et al., 1992; 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; Mari et al., 2014; Idahosa et al., 2015; Otto et al., 2015, 2018; Patel et al., 2015; van de Meent et al., 2017). Many of these treatments, however, are not capable of inducing long-term disease remission.

DSO of the mandible has a chronic recurrent character. Furthermore, it has a strong predilection for the posterior part of the mandibular body and angle, and the cuspid-premolar region, which corresponds with the attachment of the masticatory muscles. The presence of parafunctional activities during clinical examination and a positive relation of exacerbations to stress in most patients suggest that DSO of the mandible could partially be a reactive hyperplasia of the mandible caused by chronic tendoperiostitis due to overuse of the masticatory muscles, as proposed by van Merkesteyn et al. (van Merkesteyn et al., 1990; Groot et al., 1992). In this retrospective study of 27 patients with DSO of the mandible, 13 received relaxation therapy of the muscles, leading to complete disappearance of symptoms in 4 of 13 patients. Another study also showed complete recovery of a patient with DSO of the mandible treated with relaxation of the musculature, occlusal splint therapy and myofeedback training, supported by muscle relaxant medication (Groot et al., 1992). Based on these publications, our standard of care protocol was developed and implemented (Fig. 1) (van de Meent et al., 2017).

Only 25% of the patients in our study needed additional treatment with intravenous bisphosphonates. Three patients started with bisphosphonate therapy due to lack of improvement with non-surgical therapy. Two of the patients were already referred to the endocrinologist to start with bisphosphonates simultaneously with non-surgical therapy at first presentation in our center, because of the intense pain (VAS $\geq$6.5 almost every day) and the prolonged duration of symptoms (36–120 months). In one patient, intravenous bisphosphonate therapy was postponed due to vitamin D deficiency. Vitamin D and calcium concentrations should be determined, and a deficiency must always be corrected before treatment initiation with bisphosphonates, because a vitamin D deficiency is associated with an increased risk of hypocalcemia after intravenous bisphosphonate therapy (Rosen and Brown, 2003; Body et al., 2018). Another patient was still lactating and therefore the intravenous bisphosphonate therapy was postponed, since bisphosphonates are contraindicated during lactation (Suresh et al., 2014). The fourth patient was diagnosed with a combination

of DSO of the mandible and sternocostoclavicular hyperostosis (SCCH). This patient showed complete remission of the complaints of the mandible, but started with bisphosphonates because of the progressive disease activity on the sternocostoclavicular joint. In the patients who received bisphosphonates, the therapy was effective after the first administration of intravenous treatment.

Antiresorptive therapy has been reported to be an effective treatment for DSO of the mandible; this is our second line of therapy in patients refractory to non-surgical therapy (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). Soubrier et al. was the first to publish about a patient successfully treated with intravenous pamidronate (Soubrier et al., 2001). Bisphosphonates inhibit osteoclast-mediated bone resorption, resulting in a decrease in bone remodelling. This decrease in bone remodelling leads to a reduction in pain in patients with DSO of the mandible (Montonen et al., 2001; Hino et al., 2005; Urade et al., 2012; Otto et al., 2015). Bisphosphonates can be administered intravenously or orally in different dosages, and the use of various types of bisphosphonates has been reported (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; van de Meent et al., 2017). The use of bisphosphonates is, when properly administrated, safe. About 40% of patients experience the so-called acute phase reaction, in which there are transient complaints of fever, headache, and flu-like symptoms, which were observed in one patient in our patient group.

Treatment of DSO of the mandible with another antiresorptive drug, subcutaneous injections of denosumab, has recently been described in three cases, in which the symptoms were well controlled with regular injections (Hallmer et al., 2018; Otto et al., 2018). Denosumab initiates apoptosis of osteoclasts, which inhibits excretion of osteoclastic pain mediators. It has a shorter half-life than bisphosphonates, which could result in less long-term adverse events. However, improvement of symptoms after injection seems to take longer than with bisphosphonate treatment (Otto et al., 2018).

One patient who benefited from non-surgical treatment had been treated for a long time with methotrexate, an anti-rheumatic, for psoriatic arthritis. Anti-rheumatics have also been used experimentally as therapy for DSO, with symptomatic improvement in a small patient group (Idahosa et al., 2015; Patel et al., 2015). However, anti-rheumatics are not yet a standard treatment in DSO of the mandible.

In this group of patients, the use of analgesics was accentuated simultaneously with non-surgical therapy, preferably with NSAIDs, which could suppress the inflammatory responses and could lead to an analgesic effect (Heggie et al., 2003; Montonen and Lindqvist, 2003). Treatment with corticosteroids has already been reported by Jacobsson and could also be used to stabilise and improve symptoms (Jacobsson, 1984).

In the treatment of CRMO, SCCH, and SAPHO syndrome, the use of a tumor necrosis factor–alpha (TNF-α) inhibitor, such as infliximab or adalimumab, is already a more common additional treatment (Aljuhani et al., 2015; Cianci et al., 2017; Hofmann et al., 2017; Taddio et al., 2017; Yachoui et al., 2017). In the literature, only one case has been described of a patient with DSO of the mandible treated with a TNF-α inhibitor combined with methotrexate, which resulted in improvement of symptoms (Idahosa et al., 2015).

One limitation of the study is that the subjective nature of patient-reported outcomes complicates scientific analysis. Since the patients' complaints are the main factor treated in DSO patients, we focused our analysis on the outcome of treatment as experienced by the patient. Also, extraoral manifestations of DSO (as possible signs of SCCH, CRMO, or SAPHO syndrome) were not consistently evaluated, since this study focused mainly on DSO as it presents in a maxillofacial clinic. Our study was furthermore limited by a relatively small sample size, since DSO of the mandible is a rare disease. Due to the retrospective nature of this study, some data regarding the pain assessment were missing. Unfortunately, this makes the series of results too small to have enough statistical power to detect a possible effect of non-surgical treatment in adult patients with DSO of the mandible. We nevertheless suggest that this non-invasive therapy should be the first step in treating DSO of the mandible.

5. Conclusion

In DSO of the mandible, non-surgical treatment has been successful in children. This study shows that non-surgical therapy might also be effective in adult patients with DSO of the mandible. These results strengthen the hypothesis that DSO of the mandible is partly due to masticatory muscle overuse, also known as chronic tendoperiostitis. Therefore a non-surgically approach, with physiotherapy, occlusal splint therapy, and counseling about the disease, should be first-line treatment in both children and adult patients with DSO of the mandible. Bisphosphonate therapy could be an effective second step in patients who have complaints even after non-surgical treatment. However, due to the rarity of the disease, samples are small, and larger studies are warranted.

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Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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