

## CASE REPORT

# The treatment of diffuse sclerosing osteomyelitis with oral bisphosphonates

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**Key words:**

alendronic acid, bisphosphonate, diffuse sclerosing osteomyelitis

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**Abstract**

Diffuse sclerosing osteomyelitis (DSO) is a rare inflammatory disease of bone. The underlying cause is poorly understood and traditional management techniques have struggled to provide patients with adequate relief. A number of reports in the literature have described the use of bisphosphonates to manage DSO; however, these have predominantly been associated with the intravenous formulation. Understandably, there is an element of angst due to its underlying and well-recognised risk of osteonecrosis of the jaw. In this article, we review the literature for the management of DSO including the novel approach of using bisphosphonates. As an example, we present a case of a 56-year-old female with DSO where conventional therapies failed to manage her symptoms; however, treatment with oral alendronic acid led to complete and sustained resolution. This case in conjunction with additional reported cases provides further evidence of the value of bisphosphonates in DSO and highlights that the use of oral bisphosphonates can be successful and could be a viable consideration prior to the use of intravenous versions.

**Introduction**

Diffuse sclerosing osteomyelitis (DSO) is a rare inflammatory disease of bone, which affects the mandible and other long bones. Reported symptoms include intermittent pain, swelling, trismus, paraesthesia and occasionally lymphadenopathy<sup>1,2</sup>. Its occurrence can burden patients for many years with the condition recognised for its refractory nature. Recent evidence has shown bisphosphonates can be useful in the long-term management of this debilitating disease. Two small studies and multiple case reports and mini-series have suggested that the use of intravenous (IV) bisphosphonates can help improve patient symptoms, and decrease disease activity<sup>3-5</sup>. In addition to these few cases, we present a patient with DSO who has had symptom resolution following the commencement of oral alendronic acid.

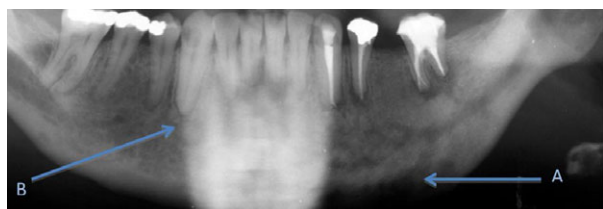
**Case report**

A 56-year-old female was referred to Guys Dental Hospital in 1997 regarding persistent jaw pain and swelling. On attendance, she reported having pain and swelling on the left side of her jaw which had been present for 14 months. She had presented having previously had root canal treatment of her lower left canine, 1<sup>st</sup> premolar and 1<sup>st</sup> molar and extraction of her lower left 2<sup>nd</sup> premolar and 2<sup>nd</sup> molar. In addition, the lower left canine and 1<sup>st</sup> molar has undergone re-root canal treatment by the endodontic department. All of the proposed and completed treatment had failed to resolve her symptoms and she continued to experience pain, swelling and infection that required continuing antibiotic therapy. At this stage, she was referred to the oral surgery department for assessment and management.

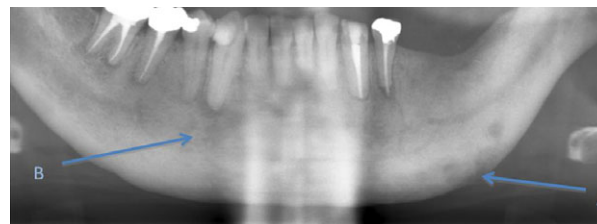
On examination, extra oral palpation revealed bowing of the left lower border of the mandible. Intraoral examination showed buccal expansion in the left body of the mandible extending to the mid-line. There was no lingual expansion or draining sinuses. A dental panoramic tomograph showed the lower left canine, 1<sup>st</sup> premolar and 1<sup>st</sup> molar were root filled and had periapical radiolucencies; however, clinically, they were not tender to percussion (Fig. 1). A lower standard occlusal radiograph showed the soft tissue outline to be pronounced in a buccal position. A diagnosis of osteomyelitis was made and the patient was commenced on antimicrobial therapy. Over the course of 2 years, she required repeat prescriptions for cyclic infections of differing intensity.

Due to recurring symptomatic episodes, treatment with salmon calcitonin was commenced in January 2000. A varying dose based on symptoms (25–100 units weekly via subcutaneous injection) was prescribed and treatment lasted for 5 years. In 2005, she was changed to the nasal spray version for ease of administration. She remained on calcitonin nasal spray for a further 8 years reporting sporadic symptomatic events treated with either antimicrobials alone (erythromycin and metronidazole) or in combination with diclofenac. Between 1997 until 2013, radiographic evidence confirmed further progression of DSO extending across to the right body of the mandible (Fig 2). It was at this juncture, alendronic acid (70 mg, once weekly) was started.

Following the commencement of alendronic acid, the patient reported symptom improvement in comparison to the previous treatments attempts. At 5 months, the patient's symptoms had completely resolved. She was maintained on alendronic acid and the overall duration of the medication was 20 months with no acute episodes of pain, swelling or infection. She reported no side effects from alendronic acid and at the 2-year review from commencement radiographically the mandibular lesions were seen to have almost fully resolved, there was



**Figure 1** DPT Dec 1998. Arrow A shows loss of cortical bone. Arrow B shows generalised diffuse sclerosis throughout the mandible.



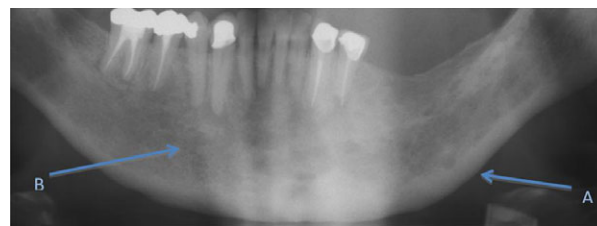
**Figure 2** DPT Jan 2010. During management phase of calcitonin, anti-inflammatories and antibiotics. Arrow A shows an osteolytic area of the cortex at the lower border of left mandible. Arrow B shows generalised sclerotic areas throughout the body of the mandible.

no evidence of further expansion or periosteal reaction (Fig. 3).

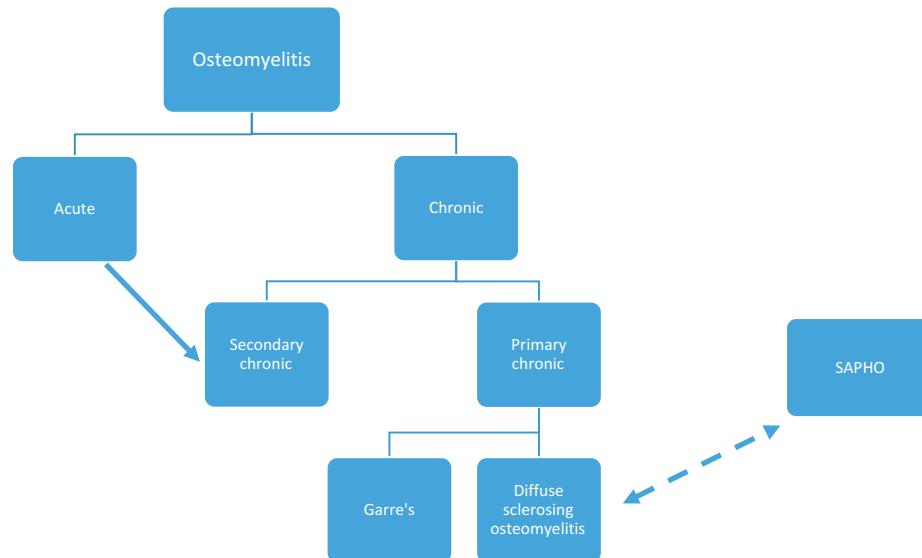
## Discussion

The basic definition for osteomyelitis is well recognised as infection of the medullary cavity of bone and the disease is seen in various bones of the skeleton. In the jaws, various sub-categories of osteomyelitis have been proposed; however, no internationally agreed classification has been agreed which has led to some confusion in the literature as to which terminology to use. The Zurich classification<sup>6</sup> has gained popularity and sub-divides osteomyelitis into three areas: acute osteomyelitis, secondary chronic osteomyelitis (suppurative) and primary chronic osteomyelitis (non-suppurative)<sup>7</sup>. Figure 4 shows the flow diagram outlining the various sub-categories of osteomyelitis.

Acute osteomyelitis of the jaws is rarely seen these days due to the availability of antibiotics. Infection tends to be odontogenic in origin and often results in intense pain, swelling, lymphadenopathy and pyrexia lasting less than 4 weeks. Non-resolution or progression beyond this time frame leads to secondary chronic osteomyelitis, which is also often referred to as 'chronic suppurative osteomyelitis' as



**Figure 3** DPT Jan 2017. After treatment with alendronic acid. Arrow A shows bony healing, the lower border of the mandible has well-defined cortex. Arrow B shows the bony pattern throughout the mandible appears near normal.



**Figure 4** Summary diagram of osteomyelitis.

an interchangeable term. In this type of osteomyelitis pus, sinuses and sequestrate are seen clinically. Pain tends to be dull in character and with firm swelling due to the periosteal reaction. Radiographically, it can vary from osteolytic to osteosclerotic in appearance. Primary chronic osteomyelitis (PCO) or 'chronic non-suppurative osteomyelitis' describes a group of osteomyelitis conditions where there is no pus or fistulae. Unlike the acute or secondary chronic forms of osteomyelitis where a bacterial source is the aetiological factor, in PCO the aetiology is unknown. The lack of pus, sequestra or fistulae clearly distinguishes PCO from acute or secondary chronic osteomyelitis. The symptoms tend to be insidious in onset, be long lasting and fluctuate in intensity<sup>7</sup>. The terminology used to describe PCO and its various forms has changed over the years with DSO being the most commonly used alternative term. Garré's osteomyelitis is a term that has been used to describe PCO where predominantly periosteal reaction is seen both radiographically and histologically. It is characterised by periosteal sclerosis and peripheral deposition of bone, rather than the diffuse endosteal reaction seen in DSO<sup>2</sup>.

### Sapho

SAPHO (skin, acne, pustulosis, hyperostosis, osteitis) syndrome was first reported by Chamot *et al.* in 1987 and describes a condition where patients suffer with synovitis, acne, pustulosis, hyperostosis and/or osteitis<sup>8</sup>. A recognised link between SAPHO and PCO

exists. Hayem *et al.* reported 13/120 (11%) patients with SAPHO had clinical and radiological manifestations resembling DSO of the mandible while Khan *et al.* showed the incidence at 8% (7/85 patients)<sup>9,10</sup>. Many authors have also described DSO as the mandibular presentation of SAPHO<sup>8-11</sup>.

### Diffuse sclerosing osteomyelitis

The pathogenesis of DSO is poorly understood and no aetiological factor has been confirmed; however, various causes have been suggested, including infective, autoimmune and genetic. Clinically, there is pain and swelling without suppuration.

Most commonly, the mandible is affected, usually unilaterally, although it is acknowledged that other long bones can be affected with reports of DSO in the femur, tibia and humerus<sup>12,13</sup>. This involvement of other long bones of the skeleton supports an aetiological factor beyond dental infection alone<sup>12,13</sup>.

Diagnosis of DSO is made from clinical and radiographic findings. In addition, histopathology and Technetium (Tc) scintigraphy are also used to investigate and aid diagnosis. Radiographically, sclerosing radio-opaque and radio-dense mixed areas can be seen. Overtime, these become increasingly sclerotic. Destruction of the cortical bone is seen in later stages of the disease and in older patients<sup>14</sup>. In the past decade, cone beam CT has become a valuable investigatory and monitoring adjunct with its ability to provide high-resolution images of the jaws where these changes can be seen in much better detail.

These changes histopathologically are seen as non-specific inflammation and sclerotic changes within the bone<sup>1,15</sup>.

### Traditional therapies

The management of DSO has always been challenging and this is seen in the various strategies employed, all of which have had limited success. Treatments include the use of analgesics, long-term antimicrobials, calcitonin, corticosteroids, hyperbaric oxygen or surgical interventions, including decortication<sup>1,4,16</sup>. As evident in the current case, often patients will have tried a number of these treatments with some approaches simultaneously.

The use of long-term antibiotics has been the primary and most popular form of treatment for patients with DSO. No antibiotic has been found to cure DSO, but most patients find that without continual antibiotics their symptoms recur or worsen. This is less than ideal, as sustained antibiotic therapy risks resistance. In addition, most patients also require regular NSAIDs for pain relief, often taken daily for several years which has its own side effects and complications. The use of long-term corticosteroids is also non-ideal due to the long-term side effects and well-recognised consequences on general health. The introduction of calcitonin was promising due to the positive effect it had on osteoclast activity as well as the analgesic benefits; however, in 2012, evidence arose which found that patients on long-term use were at increased risk of cancer<sup>17</sup>. It was essentially discontinued understandably for DSO. Hyperbaric oxygen therapy has been suggested as a potential therapy; however, the evidence and outcomes behind its use are poor. The treatment is both costly and time-consuming with no proven benefits. Surgery has been reserved for refractive DSO and has shown variable results and in some cases exacerbated the condition. The lack of success and confidence in these proposed treatments over the past 50 years has led to other therapies being investigated, including bisphosphonates.

### Bisphosphonates

Bisphosphonates are pyrophosphate analogues that share a common phosphorous-carbon-phosphorous chemical core, and inhibit the resorption of bone<sup>18</sup>. They aim to reduce bone turnover through a decrease in osteoclast activity, leading to increased bone density and are well established for the management of various bone diseases.

Bisphosphonates bind to bone mineral and build up in high concentrations particularly in areas of high bone turnover. They are then taken in by the surrounding osteoclasts, and disrupt their function in multiple ways; by reducing the lifespan of each osteoclast, reducing the recruitment of new osteoclasts, and reducing the effectiveness of osteoclast activity on the bone<sup>19,20</sup>. Several studies have shown bisphosphonates to be effective at reducing pain as well as increasing the density of bone although the exact mechanism for this is not known<sup>21,22</sup>.

Bisphosphonates are often categorised by the absence or presence of the nitrogen side arm, which also relates to their potency with the latter group being more potent. The first-generation non-nitrogen-containing bisphosphonates (e.g. etidronate, clodronate and tiludronate) are metabolised within the osteoclast resulting in a build-up of adenosine triphosphate (ATP) analogues, which becomes cytotoxic and causes apoptosis of the osteoclast. The second and third generation are nitrogen-containing bisphosphonates (e.g. alendronate, risedronate, ibandronate, pamidronate, zoledronate) which work by inhibiting farnesyl pyrophosphate synthase which is a key enzyme in cholesterol production, ultimately leading to cell apoptosis.

Bisphosphonates are well recognised for their potential to cause medication related osteonecrosis of the jaw (MRONJ) which has no guaranteed cure and is of concern for the dental and surgical community. This risk is heightened with the intravenous formulations of these drugs compared to the oral type. The American Association of Oral & Maxillofacial Surgery (AAOMS) 2014 guidance<sup>23</sup> advises that the risk of developing MRONJ for patients taking long-term oral bisphosphonates can be estimated at ~0.5% after a single tooth extraction. This is significantly lower than the estimate for cancer patients who had received IV bisphosphonates, which was estimated to be between 1.6% and 14.8%. Importantly, it is recognised that the oral bisphosphonate risk for MRONJ still remains very low even with continuous use after 4 years which is seen as the threshold for when true risk occurs<sup>23</sup>.

### Bisphosphates in the management of DSO

The use of bisphosphonates in DSO is a novel approach. In light of this and the rarity of DSO, a limited number of cases are present in the literature. Two studies, two cases series and nine case reports totalling 36 patients discuss the use of bisphosphonates in managing DSO (Table 1). Of these 36

**Table 1** Management of diffuse sclerosing osteomyelitis with bisphosphonates

Citation	Author & year published	No. patients	Diagnostic criteria	Previous treatment	Method of bisphosphonate administration	Length of clinical follow-up	Clinical outcome	Radiographic outcome
<b>IV bisphosphonates in DSO mandible – Studies</b>								
Ibandronate treatment of diffuse sclerosing osteomyelitis of the mandible: Pain relief and insight into pathogenesis. <sup>5</sup>	Otto 2015	11 (9F, 2M)	1 Patient history 2 Clinical 3 Radiographic 4 Histopathology	1 Analgesics 2 Antibiotics 3 Corticosteroids 4 Hyperbaric oxygen 5 Surgery, including corticotomies	IV Ibandronate single infusion 6 mg	17–39 months	10 out of 11 patients had distinct improvement in pain scores	1 Less pronounced sclerosis 2 clearer visibility of the inferior alveolar channel
Disodium clodronate in the treatment of diffuse sclerosing osteomyelitis (DSO) of the mandible. <sup>3</sup>	Montonen 2001	6 (6F)	1 Clinical 2 Radiographic 3 Histopathology		Disodium clodronate (a non-nitrogen-containing bisphosphonate)	12 months	Median VAS scores less for bisphos. group. At 6 months pain is less for bisphos. group. At 12 months - fewer exacerbations of pain, in bisphos. group, but not statistically significant.	At 12 months – no difference between placebo and bisphosphonate group
<b>IV bisphosphonates in DSO mandible – Case Series/Case Reports</b>								
Initial results of the treatment of diffuse sclerosing osteomyelitis of the mandible with bisphosphonates. <sup>4</sup>	Kuijpers 2011	7 (6F, 1M) (2–78 years)	1 History 2 Clinical 3 Radiographic 4 Histopathology 5 Tc scans	1 Analgesics 2 Antibiotics 3 Physiotherapy 4 Corticosteroids 5 Surgery	IV Pamidronate 15 mg/day 3–5 days (total 45–75 mg) Repeated every 3 months dependent on pt response	30 months	7 out of 7 patients had a decrease in pain	Tc scans of all patients showed a decrease in uptake in DSO area at 1 year
Diffuse sclerosing osteomyelitis of the mandible successfully treated with pamidronate: a long-term follow-up report. <sup>25</sup>	Urade 2012	1 (61yo F)	1 Clinical 2 Radiographic 3 Histopathology 4 99mTc scintigraphy	1 Anti-inflammatory agents 2 Antibiotics 3 Curettage 4 Decortication of the mandible	IV pamidronate single infusion 45 mg	6 years	Pain resolved 3 days after infusion. Trismus improved. Symptom free at 6 year follow-up	Near normal appearance of bone trabeculae at 3 years. 99mTc scintigraphy showed decreased accumulation at 2 months, almost disappeared at 3 years

Table 1 (Continued)

Citation	Author & year published	No. patients	Diagnostic criteria	Previous treatment	Method of bisphosphonate administration	Length of clinical follow-up	Clinical outcome	Radiographic outcome
Remarkable response of juvenile diffuse sclerosing osteomyelitis of mandible to pamidronate. <sup>26</sup>	Yamazaki 2007	1 (9yo M)	1 Clinical 2 Radiological CT 3 Tc scintigram 4 Histological	1 Extraction of tooth 2 Antibiotics 3 Curettage 4 Decortication of the mandible 5 Hyperbaric oxygen 6 NSAIDs	IV Pamidronate 30 mg+ 30 mg at 3 months+ 30 mg at 10 months (for humerus lesion)		Reduction in pain	Reappearance of lamina dura and alveolar bone with normal density. Scintigraphy at 5 months showed reduction in uptake in the mandible.
Response of diffuse sclerosing osteomyelitis of the mandible to alendronate: follow-up study by 99mTc scintigraphy <sup>27</sup>	Hino 2005	1 (44yo)	1 History 2 Clinical 3 Radiographic + CT 4 99mTc Scintigraphy 5 Histology	1 Extraction of tooth 2 Antibiotics 3 Curettage 4 Decortication of the mandible	IV Alendronate 10 mg	12 months	Pain resolved within 24 hours	Tc uptake considerably reduced at 3 months
Successful management of severe facial pain in patients with diffuse sclerosing osteomyelitis (DSO) of the mandible using disodium clodronate. <sup>28</sup>	Sugata, 2003	1 (60yo F)	1 History 2 Clinical 3 Radiographic 4 CT 5 99mTc Scintigraphy	1 Antibiotics 2 Decortication of the mandible (x8) 3 NSAIDs	IV Pamidronate 30 mg	6 months	Pain resolved within 72 hours	
Pamidronate in the treatment of diffuse sclerosing osteomyelitis of the mandible. <sup>29</sup>	Soubrier 2001	1 (67yo F)	1 Clinical 2 99mTc Scintigraphy 3 Histology 4 Radiographic + CT	1 Antibiotics 2 NSAIDs	IV Pamidronate 2 x 60 mg		Pain resolved within 72 hours	

**Table 1** (Continued)

Citation	Author & year published	No. patients	Diagnostic criteria	Previous treatment	Method of bisphosphonate administration	Length of clinical follow-up	Clinical outcome	Radiographic outcome
Implication of bisphosphonate use in the treatment of SAPHO syndrome: Case report and discussion of current literature <sup>24</sup>	Gorecki 2015	1 (39yo F)	1 History 2 Clinical 3 Radiographic 4 Histology 5 Pain and Thermal Sensitivity Test 6 Scintigraphy 7 MRI	1 Antibiotics 2 NSAIDs 3 Apicectomy 4 Splint therapy 5 Corticosteroids	IV Zoledronate 5 mg	1 month	Initial fever + pain (side effect) Relief of pain, no relapse at 1 month	No changes to MRI 3 weeks post bisphosphonate
A case of SAPHO syndrome initially diagnosed as diffuse sclerosing osteomyelitis of the mandible and effectively treated by bisphosphonate. <sup>30</sup>	Suzuki 2015	1 (32yo M)		1 Antibiotics 2 NSAIDs 3 Hyperbaric oxygen	IV Pamidronate	10 years	Pain disappeared	CT improvement at 5 months.
Oral Bisphosphonates DSO mandible – Case Reports								
A case of SAPHO syndrome with diffuse sclerosing osteomyelitis of the mandible treated successfully with prednisolone and bisphosphonate. <sup>31</sup>	Hatano 2012	1 (61yo M)	1 History 2 Clinical findings 3 Radiographic findings 4 99mTc scintigram 5 MRI	1 Antibiotics 2 Decortication of the mandible 3 Hyperbaric oxygen 4 Corticosteroids	Oral Risendronate 17.5 mg/day+ prednisolone (60 mg·2 mg/day) for 12 months	12 months	Resolution of pain/swelling. No sign of recurrence	Tc Scan showed decrease in level and range of uptake in mandible after 12 months
The treatment of diffuse sclerosing osteomyelitis with oral bisphosphonates.	Taylor 2017	1 (56yo F)	1 History 2 Clinical findings 3 Radiographic findings	1 Analgesics 2 Antibiotics 3 Calcitonin	Oral Alendronic Acid 70 mg/week 20 months	24 months	Resolution of pain/swelling at 5 month review. No sign of recurrence after 2 years	Radiographically resolution of mandibular lesion seen at 2 year review

**Table 1** (Continued)

Citation	Author & year published	No. patients	Diagnostic criteria	Previous treatment	Method of bisphosphonate administration	Length of clinical follow-up	Clinical outcome	Radiographic outcome
IV bisphosphonates for DSO in other bones								
Bone marker response in chronic diffuse sclerosing osteomyelitis treated with intravenous ibandronate. <sup>12</sup>	Armstrong 2005	3 (27yo F femur, 38yo F tibia + femur, 21yo F tibia + femur)	<ol style="list-style-type: none"> <li>History</li> <li>Clinical</li> <li>Radiographic</li> <li>MRI</li> <li>Scintigraphy</li> <li>Histology</li> </ol>	<ol style="list-style-type: none"> <li>Excision</li> <li>Bone grafting</li> <li>External fixation of tibia</li> </ol>	<ol style="list-style-type: none"> <li>Oral Risedronate 2 months, IV ibandronate 3 x 2 mg over 3 months</li> <li>IV Pamidronate 6 infusions + oral risedronate + IV ibandronate 2 mg, 3 mg, 3 mg</li> <li>IV pamidronate 4 x 2 mg</li> </ol>	<ol style="list-style-type: none"> <li>1 Risedronate = rapid but temporary improvement, Ibandronate = Immediate symptomatic relief</li> <li>2 Pamidronate + risedronate = temporary improvement in symptoms. Ibandronate = rapid + persistent improvement in symptoms</li> </ol>	<ol style="list-style-type: none"> <li>2 decrease in activity on Tc Scan</li> <li>3 No changes with Pamidronate.</li> </ol>	
Chronic diffuse sclerosing osteomyelitis treated with risedronate. <sup>13</sup>	Wright SA, Millar AM	1 (21yo FFemur)	<ol style="list-style-type: none"> <li>History</li> <li>Radiology</li> <li>Histopathology</li> </ol>	<ol style="list-style-type: none"> <li>Analgesia</li> </ol>	Risedronate		Dramatic improvement in symptoms + biochemical markers of bone turnover	



patients, 33 had mandibular lesions and four had lesions affecting the femur or tibia. They had all previously undergone various treatments outlined earlier unsuccessfully. In all the cases reported, bisphosphonate treatment had a beneficial effect on the patients' pain, often within a few days of commencing treatment. One case reported fever lasting 2 days related to IV zoledronate, which is a recognised side effect of the drug<sup>24</sup>. The follow-up periods ranged from 1 month to 10 years. Radiographically, the bony appearance improved, and Tc scintigraphy showed a reduction in uptake in all cases that were scanned. Twenty out of 36 patients required repeat bisphosphonate infusion. To date, there appears to be no reported MRONJ in patients who have had treatment with bisphosphonates for DSO.

Almost all published reports on bisphosphonates for the management of DSO have used IV formulations. In the case presented, we found that the same benefits and resolution of symptoms can be achieved with oral alendronic acid. There are a number of benefits of using oral alendronic acid over the IV infusions. Firstly, the risk of developing MRONJ is extremely unlikely with oral bisphosphonates. Secondly, the annual cost of treatment with oral bisphosphonate in the United Kingdom is a fraction of that for IV infusions with oral alendronic acid costing approximately £13/annum compared to £215/infusion of zoledronic acid. Finally, oral alendronic acid can be taken at home while IV bisphosphonates require hospital attendance.

## Conclusion

The exact mechanism of DSO is not understood, but the fact that bisphosphonates have been successful in managing the disease has led authors to believe that osteoclasts could play an important role in the pathogenesis. This could be due to a discrepancy in balance between the osteoblast–osteoclast activity or through the effect they have on the local tissue environment possibly causing a change in pH or through the release of pain causing factors<sup>5</sup>. In the current case, the use of oral alendronic acid at a dose of 70 mg weekly for 20 months provided the patient with complete resolution of symptoms. Furthermore, at this dose for this length of time, the risk of MRONJ remains extremely low<sup>23</sup>. It is therefore worth considering the use of alendronic acid as a first-line treatment for the management of DSO. Failure to achieve adequate symptom control with this method would still allow prescription of more potent intravenous bisphosphonate versions if necessary.

Ultimately, more research is required regarding the regime and dose of bisphosphonates in the management of DSO ideally through a randomised control trial; however, due to the rarity of this disease, sufficiently populating such a study is likely to be difficult. Until then, we are reliant on case reports such as this to build evidence.

## Declaration

No ethical approval required.

## References

1. Ontonen M, Lindqvist C. Diagnosis and treatment of diffuse sclerosing osteomyelitis of the jaws. *Oral Maxillofac Surg Clin* 2003;15:69–78.
2. Jacobsson S. Diffuse sclerosing osteomyelitis of the mandible. *Int J Oral Surg* 1984;13:363–85.
3. Montonen M, Kalso E, Pylkkären L, Lindström BM, Lindqvist C. Disodium clodronate in the treatment of diffuse sclerosing osteomyelitis (DSO) of the mandible. *Int J Oral Maxillofac Surg* 2001;30:313–17.
4. Kuijpers SC, de Jong E, Hamdy NA, van Merkesteyn JR. Initial results of the treatment of diffuse sclerosing osteomyelitis of the mandible with bisphosphonates. *J Craniomaxillofac Surg* 2011;39:65–8.
5. Otto S, Troeltzsch M, Burian E, Mahaini S, Probst F, Pautke C *et al.* Ibandronate treatment of diffuse sclerosing osteomyelitis of the mandible: pain relief and insight into pathogenesis. *J Craniomaxillofac Surg* 2015;43:1837–42.
6. Baltensperger MM. A retrospective analysis of 290 osteomyelitis cases treated in the past 30 years at the Department of Cranio-Maxillofacial Surgery Zurich with special recognition of the classification (Doctoral dissertation).
7. Marx RE. *Osteomyelitis of the Jaws*: Springer Science & Business Media, 2008.
8. Chamot AM, Benhamou CL, Kahn MF, Beranek L, Kaplan G, Prost A. Acne-pustulosis-hyperostosis-osteitis syndrome. Results of a national survey. 85 cases. *Rev Rhum Mal Ostéoartic* 1987;54:187–96.
9. Hayem G, Bouchaud-Chabot A, Benali K, Roux S, Palazzo E, Silbermann-Hoffman O *et al.* SAPHO Syndrome: A Long-Term Follow-Up Study of 120 Cases. In *Seminars in Arthritis and Rheumatism*: WB Saunders, 1999:159–71.
10. Kahn MF, Khan MA. The SAPHO syndrome. *Baillière's Clin Rheumatol* 1994;8:333–62.
11. Eyrych GK, Harder C, Sailer HF, Langenegger T, Bruder E, Michel BA. Primary chronic osteomyelitis associated with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO syndrome). *J Oral Pathol Med* 1999;28:456–64.

12. Armstrong DJ, Wright SA, Coward SM, Finch MB. Bone marker response in chronic diffuse sclerosing osteomyelitis treated with intravenous ibandronate. *Ann Rheum Dis* 2006;65:976–7.
13. Wright SA, Millar AM, Coward SM, Finch MB. Chronic diffuse sclerosing osteomyelitis treated with risedronate. *J Rheumatol* 2005;32:1376–8.
14. Swei Y, Taguchi A, Tanimoto K. Radiographic evaluation of possible etiology of diffuse sclerosing osteomyelitis of the mandible. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontology* 1997;84:571–7.
15. van Merkesteyn JP, Groot RH, Bras J, Bakker DJ. Diffuse sclerosing osteomyelitis of the mandible: clinical radiographic and histologic findings in twenty-seven patients. *J Oral Maxillofac Surg* 1988;46:825–9.
16. Jones J, Amess TR, Robinson PD. Treatment of chronic sclerosing osteomyelitis of the mandible with calcitonin: a report of two cases. *Br J Oral Maxillofac Surg* 2005;43:173–6.
17. Medicines and Healthcare products Regulatory Agency. Drug Safety Update 2012 <https://www.gov.uk/drug-safety-update/calcitonin-miacalcic-increased-risk-of-cancer-with-long-term-use#further-information> Calcitonin (Miacalcic): increased risk of cancer with long-term use. [accessed 20 August 2012]
18. McLeod NM, Davies BJ, Brennan PA. Bisphosphonate osteonecrosis of the jaws; an increasing problem for the dental practitioner. *Br Dent J* 2007;203:641–4.
19. Rodan GA, Fleisch HA. Bisphosphonates: mechanisms of action. *J Clin Invest* 1996;97:2692.
20. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 2004;62:527–34.
21. Wong RK, Wiffen PJ. Bisphosphonates for the Relief of Pain Secondary to Bone Metastases: The Cochrane Library. 2002.
22. Fulfarò F, Casuccio A, Ticozzi C, Ripamonti C. The role of bisphosphonates in the treatment of painful metastatic bone disease: a review of phase III trials. *Pain* 1998;78:157–69.
23. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B. Medication-related osteonecrosis of the jaw—2014 update. American association of oral and maxillofacial surgeons position paper (AAOMS). *J Oral Maxillofac Surg* 2014;72:1938–56.
24. Gorecki P, Stockmann P, Distler JH, Wuest W, Schmidt D, Neukam FW *et al.* Implication of bisphosphonate use in the treatment of SAPHO syndrome: case report and discussion of current literature. *J Med Hypotheses Ideas* 2015;9:72–8.
25. Urade M, Noguchi K, Takaoka K, Moridera K, Kishimoto H. Diffuse sclerosing osteomyelitis of the mandible successfully treated with pamidronate: a long-term follow-up report. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012;114:e9–12.
26. Yamazaki Y, Satoh C, Ishikawa M, Notani KI, Nomura K, Kitagawa Y. Remarkable response of juvenile diffuse sclerosing osteomyelitis of mandible to pamidronate. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontology* 2007;104:67–71.
27. Hino S, Murase R, Terakado N, Shintani S, Hamakawa H. Response of diffuse sclerosing osteomyelitis of the mandible to alendronate: follow-up study by 99m Tc scintigraphy. *Int J Oral Maxillofac Surg* 2005;34:576–8.
28. Sugata T, Fujita Y, Myoken Y *et al.* Successful management of severe facial pain in patients with diffuse sclerosing osteomyelitis (DSO) of the mandible using disodium clodronate. *Int J Oral Maxillofac Surg* 2003;32:574–5.
29. Soubrier M, Dubost JJ, Ristori JM, Sauvezie B, Busière JL. Pamidronate in the treatment of diffuse sclerosing osteomyelitis of the mandible. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontology* 2001;92:637–40.
30. Suzuki K, Kobayashi M, Ozawa S *et al.* A case of SAPHO syndrome initially diagnosed as diffuse sclerosing osteomyelitis of the mandible and effectively treated by bisphosphonate. *Oral Ther Pharmacol* 2015;34:16–22.
31. Hatano H *et al.* A case of SAPHO syndrome with diffuse sclerosing osteomyelitis of the mandible treated successfully with prednisolone and bisphosphonate. *J Oral Maxillofac Surg* 2012;3:626–31.